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Risk factors for antibiotic resistance development in healthcare settings in China: a systematic review

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Abstract

Antibiotic resistance (ABR) threatens the effectiveness of infectious disease treatments and contributes to increasing global morbidity and mortality. In this study, we systematically reviewed the identified risk factors for ABR among people in the healthcare system of mainland China. Five databases were systematically searched to identify relevant articles published in either English and Chinese between 1 January 2003 and 30 June 2019. A total of 176 facility-based references were reviewed for this study, ranging across 31 provinces in mainland China and reporting information from over 50 000 patients. Four major ABR risk factor domains were identified: (1) sociodemographic factors (includes migrant status, low income and urban residence), (2) patient clinical information (includes disease status and certain laboratory results), (3) admission to healthcare settings (includes length of hospitalisation and performance of invasive procedures) and (4) drug exposure (includes current or prior antibiotic therapy). ABR constitutes an ongoing major public health challenge in China. The healthcare sector-associated risk factors was the most important aspect identified in this review and need to be addressed. Primary health care system and ABR surveillance networks need to be further strengthened to prevent and control the communicable diseases, over-prescription and overuse of antibiotics.

Introduction

Antimicrobial resistance (AMR) has risen on the global agenda across various sectors [1]. Drug-resistant infections cause more than 700 000 deaths worldwide each year, and are projected to rise to 10 million per year by 2050 [2]. AMR may threaten patient safety by changing the outcome of infectious disease treatment, which in turn may lead to prolonged illness and hospital admissions, disabilities or even increased mortality [3, 4]. Further, the impact of AMR may result in a reduction of the annual global gross domestic product, which according to current estimates could cost the world up to 100 trillion US dollars by 2050 [5].

Antibiotic resistance (ABR) is defined as the ability of bacteria to resist antibiotic agents [6]. As part of AMR, ABR is also a global health crisis [7], and increases the global burden of infectious diseases [2, 8]. Thus, alongside the continuous development of new antibiotics, a comprehensive strategy to minimise further development of ABR is critical [9].

In human health, inappropriate medical prescribing practices, poor patient adherence to antibiotic therapies, and insufficient oversight and regulation are associated with the development and spread of ABR [2]. According to the US Centers for Disease Control and Prevention (CDC), despite the proportion of unnecessary prescribed antibiotics reducing from 50% to 30% in 2019, there are still over 2.8 million ABR-related infections each year in the US, resulting in more than 35 000 deaths annually [10]. Insufficient oversight and regulation on antibiotics include easy access these agents which are frequently available over-the-counter in many countries [11].

China is among the world's leading countries in terms of serious problems with AMR and ABR [12, 13]. Despite a slight decline over time, the prevalence of ABR of organisms such as carbapenem-resistant *Pseudomonas aeruginosa* has remained at *c.* 20% while carbapenem-resistant *Acinetobacter baumannii* has continuously risen to *c.* 60% [14]. China has more than five times the per capita use of antibiotics compared to Europe or the US [15], and the country is one of the largest consumers of agricultural antibiotics worldwide [16]. An important driving factor of the high rates of ABR is the inappropriate use of antibiotics in healthcare settings, where strong incentives are provided for overprescribing. This trend underlines the importance of antibiotic policies to restrict their overuse [17–20]. In China, national

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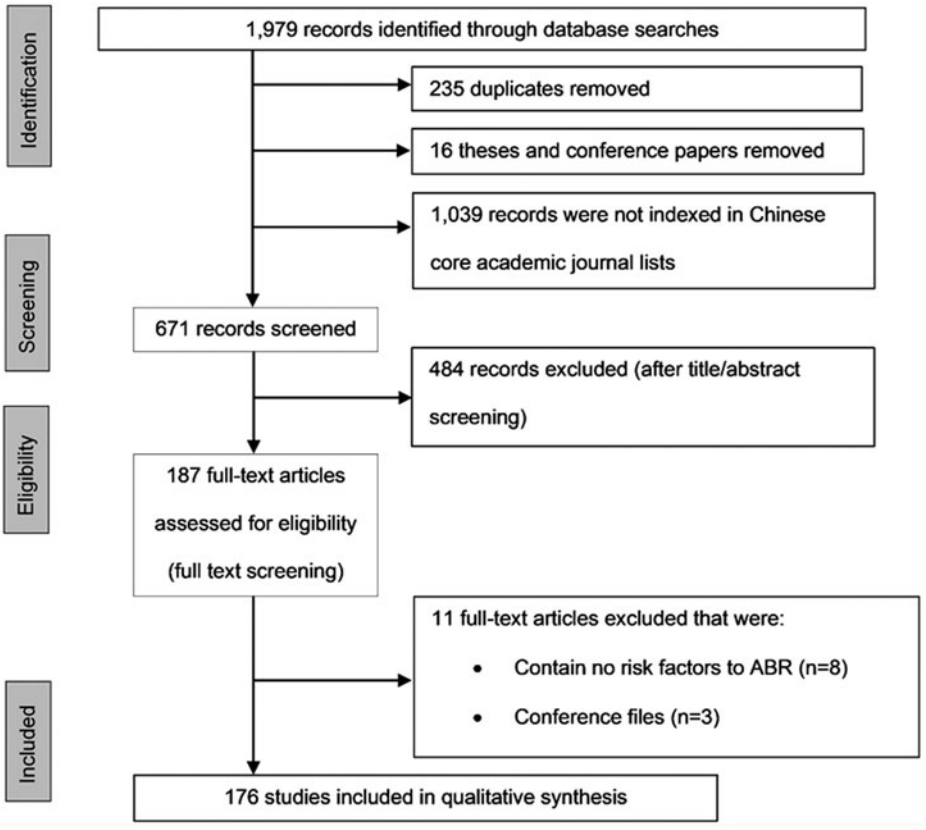

Fig. 1. Process of study selection for systematic review based on PRISMA flow diagram.

guidelines for antimicrobial therapy were developed in 2012, and a decree for country-wide monitoring of ABR was released [21]; these were revised in 2017 [14]. China's recent health system reform suggested a pharmaceutical policy including a strategy for the rational use of medication [22], but the aim of reducing overuse of antibiotics remains a significant challenge for the country [23–25].

For this paper, we systematically reviewed publications on ABR in China with the aim of identifying modifiable risk factors within healthcare settings.

Methods

Search strategy

This study aimed to systematically review research on ABR in humans and the related healthcare-associated risk factors in mainland China. The literature search was conducted using the Cochrane Library (CENTRAL), PubMed, The China National Knowledge Infrastructure (CNKI), Wanfang and VIP. The search terms were defined over the course of discussions between the authors and included controlled vocabulary (Medical Subject Headings (MeSH)). Search strategies were developed by the main researcher (QC) and three experts (CB, GL, BM) (online Supplementary Table S1).

Inclusion and exclusion criteria

Studies were included that were published between 1 January 2003 and 30 June 2019 and in either English or Chinese. Articles were included that presented original data focusing on ABR among patients in hospital settings. Reviews, opinion papers, commentaries, communications, theses and conference reports were excluded, as well as studies that did not focus on humans. There were no exclusion criteria regarding study methodology. Articles on viral, parasite and fungal drug resistance were also excluded.

Chinese academic journals are evaluated and ranked according to different criteria and institutions and are summarised in so-called 'core academic journal lists' [26]. CNKI offers the possibility to search only papers from journals which are part of these lists, and we selected core academic journal lists for our study. Only the Chinese articles that appeared in the lists were included to ensure that high quality studies were included.

Study selection

The initial screening of papers was done independently by two researchers (QC, DL) who also conducted full-text screenings a random sample of which were rechecked by GL. Disagreements were resolved through joint discussion. The study selection process followed the 'Preferred Reporting Items for Systematic Review and Meta-Analysis' (PRISMA) guidelines and is shown in the PRISMA flow diagram (Fig. 1) [27].

Quality assessment

The quality assessment of the selected studies was done according to the Methodological Index for Non-Randomized Studies (MINORS) [28]. Accordingly, 12 methodological domains were evaluated and each was scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). A 'not applicable' category was added in case the domain did not apply to the respective study design. The risk of bias assessment was

Fig. 2. Geographical distribution of included studies (adapted from Wikimedia Commons contributors) [31].

performed by QC, with a random sample of paper assessments rechecked by DL (Chinese papers) and CB (English papers).

Data extraction and analysis

Due to the heterogeneity of research in the included papers, a quantitative analysis of the data was not appropriate. Study characteristics (design and setting) were extracted, and distributions of drug-resistant bacteria, antibiotic treatment and risk factors were summarised. Identified bacterial strains and their antibiotic susceptibility test results via standard microbiological methods based on laboratory guidelines such as the Clinical and Laboratory Standards Institute were described.

The type of ABR was classified into single drug resistance (DR), multidrug resistance (MDR), extended drug resistance (XDR), and pan-drug resistance (PDR). MDR was defined as non-susceptibility of an isolate to at least one agent in three or more antimicrobial categories [29]; XDR, as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories [29], and PDR, as non-susceptibility to all agents in all categories of antimicrobials [29].

As a benchmark for data extraction and analysis, we adopted a method from the systematic review conducted by Chatterjee *et al.* [30]. Building on this review, we summarised risk factors that were identified by the papers as statistically significant (*P*-values <0.05 among univariate or multivariate analyses) into four domains: (1) sociodemographic factors, (2) patient clinical information, (3) admission in healthcare settings and (4) drug exposure. Reported sociodemographic risk factors included age, sex, education level, patient residence (local or migrant) and annual income. Risk factors within the patient clinical information category included assessments for the severity of underlying disease (i.e. high scores in certain clinical assessments performed – for a detailed list of the assessments, see online Supplementary Table S3), abnormal laboratory test results (e.g. haemoglobin level, TB sputum smear-positivity and drug susceptibility of bacteria), underlying diseases (non-communicable diseases (NCDs)], infectious diseases (IDs) and other predispositions) and bacteria-related risk factors (including production of extended beta-lactamases, presence of virulence associated genes, i.e. *esp*, etc.). Admission in healthcare settings risk factors included previous and current hospital stay, the type of hospital facility (e.g. general department or intensive care unit (ICU)), length of hospital stay and exposure to surgery and other invasive procedures. Drug exposure risk factors included the risks of prior and current medications (especially antibiotics), monotherapy, combination therapy and longer duration of treatment or drug exposure. Prior medication refers to the medication history of the investigated patients within the past 3 months, such as prescriptions from clinical staff before having been transferred to another hospital or clinical department, or self-medication by patients.

Studies included in the review were managed in EndNote (Version X9, Philadelphia, USA, for Windows & Mac). The

Table 1. Information on included papers ($n = 176$)

Information category			No. of papers
Study design	Case–control		125 (71.0%)
	Cohort	Retrospective cohort study	21 (11.9%)
		Prospective cohort study	7 (3.9%)
	Cross-sectional		17 (9.7%)
	Case series		4 (2.3%)
	Other methodologies[a]		
Healthcare setting	General hospital		140 (79.5%)
	Specialty hospital	Children's hospital	4 (2.3%)
		Tuberculosis (TB) hospital	20 (11.4%)
		Other specialty hospitals[b]	12 (6.8%)
General information[b]			No. of participants/isolates
Participants[c]	Total participants		53 056
	Sex (male/female)		23 762/13 062
	Resistant participants		17 083
Isolates from participants[c]	Total isolates		63 075
	Resistant isolates		26 383

[a]Two papers applied their methodologies including one case report (0.6%) and one clinical trial (0.6%).
[b]A total of 12 other specialty hospitals including: cancer hospital ($n = 2$, 1.1%), Chinese medical hospital ($n = 2$, 1.1%), eye, ear, nose, and throat hospital ($n = 1$, 0.6%), geriatric hospital ($n = 1$, 0.6%), maternity and child health hospital ($n = 2$, 1.1%), metabolic disease hospital ($n = 2$, 1.1%), pulmonary hospital ($n = 1$, 0.6%), and sexually transmitted infection and skin disease hospital ($n = 1$, 0.6%).
[c]Not every paper reported all general information (for example, the numbers of males and females do not add up to the total number of participants).

quality assessment was conducted in Review Manager (Version 5.3, Copenhagen, Denmark, for Windows). A data extraction table was developed in Microsoft Excel (Version 2016, Washington, USA, for Windows), and results were analysed and described accordingly. Scalable Vector Graphics (Version 1.1 Second Edition, Cambridge, USA, for Windows) was used to draw Figure 2 [31].

Results

Search results and study description

The search yielded a total of 1979 results (Fig. 1). After removing duplicates ($n = 253$), theses and conference papers ($n = 16$), and papers that were not indexed in Chinese core academic journal lists ($n = 1039$), a total of 671 papers remained for title and abstract screening; of these 484 were excluded during title and abstract screening, resulting in 187 articles for full-text screening. From the latter, 11 papers were excluded for specific reasons (Fig. 1). Finally, 176 studies were included in this review for synthesis (Supplementary List 1). Of these, 116 (65.9%) were written in Chinese and 60 (34.1%) in English. Table 1 details the studies included in the review. Almost all were observational, with case-control studies dominating, and all studies were facility-based. Most papers reported the number of patients included, totalling $n = 53\,056$. Information on the number of resistant patients, isolates and resistant isolates was also reported by most papers.

Study quality

The quality assessment graded the studies as overall low risk for bias in most domains (online Supplementary Figure S1). High risk of bias was found only in 8/176 (4.5%) in the domain of *adequate statistical analyses* and 11/176 (6.3%) in the domain of the *prospective calculation of the study size*. The domains *follow-up period appropriate to the aim of the study* and *loss to follow-up less than 5%* were not applicable to case–control and cross-sectional studies, hence the high proportions of 'not applicable.'

Study regions

The studies took place in all regions of China (Fig. 2). In addition to the 168 regional studies, five (2.8%) targeted the whole of mainland China, two (1.1%) were conducted in the east and southwest regions, and one focused on a total of six provinces, covering north, northeast, east, south-central and southwest regions of the country.

Characteristics of antibiotic-resistant bacteria

Of the 176 included papers, 159 (90.3%) studied either DR resistance phenotypes ($n = 64$, 36.4%), MDR ($n = 87$, 49.4%), XDR ($n = 3$, 1.7%), or PDR ($n = 5$, 2.8%). Another 14 (8.0%) reported both DR and MDR pathogens; two, both MDR and XDR bacteria and one, both MDR and PDR phenotypes (0.6%).

An overview of the bacterial species reported is given in Table 2; the majority ($n = 107$, 60.8%) of papers documented single *species*, and the remainder reported on more than one. Some papers provided information about the studied bacteria at genus level only or as *species pluralis* (spp.), without further species definition. More reports concerned Gram-negative antibiotic-resistant bacteria than their Gram-positive counterparts.

Table 2. Antibiotic-resistant species as reported by studies ($n = 176$)

Genus	Species	No. of papers
Klebsiella	77 (43.8%)	
	Klebsiella pneumoniae	68 (38.6%)
	Other *Klebsiella* species	9 (5.4%)
Staphylococcus	73 (41.5%)	
	Staphylococcus aureus	46 (26.1%)
	Staphylococcus epidermidis	12 (6.8%)
	Other *Staphylococcus* species	15 (8.5%)
Pseudomonas	68 (38.6%)	
	Pseudomonas aeruginosa	60 (34.1%)
	Other *Pseudomonas* species	8 (4.5%)
Acinetobacter	62 (35.2%)	
	Acinetobacter baumannii	52 (29.5%)
	Other *Acinetobacter* species	10 (5.7%)
Escherichia	*Escherichia coli*	57 (32.4%)
Enterobacter	44 (25.0%)	
	Enterobacter cloacae	22 (12.5%)
	Enterobacter spp.[a]	14 (8.0%)
	Enterobacter aerogenes	7 (15.91%)
	Other *Enterobacter* species	1 (0.6%)
Enterococcus	36 (20.5%)	
	Enterococcus[a]	14 (8.0%)
	Enterococcus faecium	12 (6.8%)
	Enterococcus faecalis	10 (5.7%)
Mycobacterium tuberculosis	20 (11.4%)	
Proteus mirabilis		13 (7.4%)
Stenotrophomonas	13 (7.4%)	
Streptococcus		9 (5.1%)
	Streptococcus[a]	5 (2.8)
	Streptococcus pneumoniae	4 (2.3)
Others		32 (18.2%)

[a]No further details given by the paper.

Risk factors for ABR in healthcare settings

Applying the risk categories used by Chatterjee *et al.* [30], we identified 62/176 (35.2%) papers with significant risk factors by univariate analysis, 60 (34.1%) by multivariate analysis, and 54 (30.7%) from both analyses.

An overview of the risk factors reported by the 122 (69.3%) studies analysed through univariate analysis is given in Figure 3. The percentages in the figure are the proportions of papers that reported significant effects of respective risk factor categories; frequently more than one significant effect occurred in the individual studies (i.e. adding up to more than 100%).

Sociodemographic risk factors were mentioned in 31% of the papers, with age (either very young and new-borns, or older age) being the most prominent (28%). **Patient clinical information** was reported as a risk factor by 67% of papers, with underlying diseases the most cited (64%). **Admission to healthcare settings** was found to be a risk factor in 81% of the papers, with hospital stay (65%) and the performance of invasive procedures (66%) the dominant factors. **Drug exposure** was found to be equally important as admission to healthcare settings, particularly current or previous antibiotic therapy.

Risk factors from papers reporting on multivariate analyses ($n = 114$) were summarised into the same four broad risk categories. To analyse the strength of the reported evidence, odds ratios (ORs) showing significant effects were grouped into 10 different ranges, adopted from Chatterjee *et al.* [30] (Table 3 and online Supplementary Table S2). The ORs were generally between 1 and 5. In the four risk categories, the following factors were identified as important independent risk factors for ABR.

(1) **Sociodemographic risk factors:** Older people (45–60 years, >60 years), patients with a low annual income, migrants (people who moved from another area within 6 months and were not registered in the current living area), and residents living in urban environments were all identified to be at risk of ABR infection.
(2) **Patient clinical information risk factors:** Higher levels in clinical scores such as APACHE II (for a detailed list, see online Supplementary Table S3) as well as a number of abnormal laboratory findings (e.g. low haemoglobin levels, positive TB sputum smear) and bacteria-related risk factors (for a detailed list, see online Supplementary Table S3) were associated with ABR. Moreover, infections (including osteomyelitis, pneumonia, and tuberculosis), NCDs (including chronic respiratory diseases, diabetes, cardiovascular diseases, and malignancies), and some other specific underlying conditions (e.g. injuries) were identified as risk factors contributing to ABR.
(3) **Admission in healthcare settings risk factors**: Prolonged hospitalisation was associated with ABR. Surgery and other invasive procedures were also identified as risk factors. In particular, invasive procedures in the respiratory system (e.g. artificial respiration) and urogenital system (e.g. dialysis), as well as any kind of catheter application, were associated with ABR in many papers; prolonged length of invasive procedures was also identified as a risk factor.
(4) **Drug exposure risk factors:** Current and prior antibiotic medication was identified as a risk factor for ABR with monotherapy being more often mentioned than combination therapy. Longer duration of antibiotic therapy was also recognised as a risk factor for ABR during both current and prior medication, but only two papers reported associations between exposure to other drugs but these were not specifically listed. Table 4 specifies the OR distribution for drug classes used for antibiotic monotherapy in current and prior medications, that were identified by multivariate analyses as risk factors. Carbapenems and cephalosporins were widely cited as risk factors in many papers.

Discussion

This narrative systematic review provides information on the healthcare-associated risk factors contributing to ABR in China from papers published over 16 years in English and Chinese. The relevant predominant risk factors identified from the papers

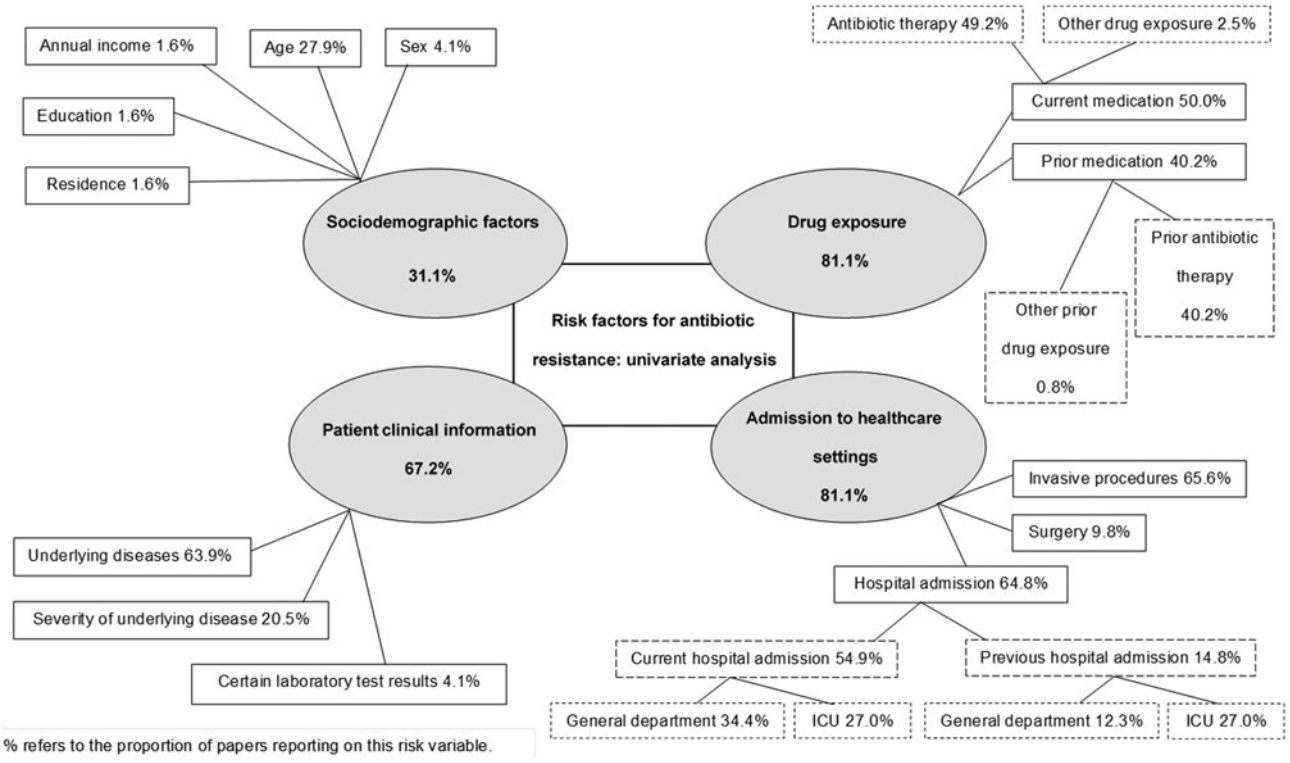

Fig. 3. Significant healthcare sector-associated risk factors from univariate analyses ($n = 122$).

included current or previous hospital stay, underlying diseases, invasive procedures, laboratory test results, age and current or prior medication.

The East Region was the most common location for the studies included in this review, followed by the South-Central and North Regions of China. These regions also have the highest populations, economic development, agricultural economies and healthcare service densities [32]. The tendency towards irrational use and consumption of antibiotics may explain the status and trends of ABR in these regions compared to others in China [33]. Correspondingly, the highest prevalence of resistance for certain species of bacteria and antibiotics was reported from the East Region, followed by the North and South-Central Regions [34, 35]. This is comparable to other countries such as India, where a higher prevalence of ABR is reported from highly populated and economically productive regions [34, 36].

ABR was more frequently associated with Gram-negative than Gram-positive bacterial species which accords with observations worldwide [30], with an increase in ABR among Gram-negative species, and often progressing to the development of MDR [10, 34, 37, 38].

In terms of demographic characteristics, older age, male sex, a migration background, and living in an urban environment were all reported as risk factors. The literature on these factors, however, is often inconsistent; some reports have suggested that age and sex are risk factors for ABR [39, 40] while others have not found such an association [41, 42]. Moreover, ABR among patients is associated with both poor adherence to therapies and high consumption of clinically inappropriate antibiotics [2, 43, 44]. Our review recognised that the social situation of migrants may play a role in poor compliance to antibiotic treatment, while urban populations seem to consume antibiotics more frequently. The latter factors along with ease of access to antibiotics at an individual level are well documented contributors to resistance development [25, 45], either at the household level [30], among village doctors, in community pharmacies [46], and even among medical students [47].

Patients with a weaker health status are more likely to develop ABR [48], and in our category of patient clinical information, abnormal laboratory test results, underlying diseases, and advanced disease status were frequently reported as risk factors. It is well known that more sick patients are predisposed to carry resistant bacteria primarily because they are more likely to have had previous exposure to antibiotic treatment [7]. This is sometimes exemplified by the emergence of hetero-resistance in the pathogen defined as 'a phenotype in which a bacterial isolate contains subpopulations that show a substantial reduction in antibiotic susceptibility compared with the main population' [49], which may lead to failure of antibiotic treatment. The linkage between some specific bacteria (i.e. *Enterococcus* spp., *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp., termed 'ESKAPE') and their tendency to progress towards MDR has recently gained global attention [38, 50, 51]. Accordingly, infections due to this group, which are at high risk of developing resistance, necessitate improvements in routine screening and prevention measures [50]. Underlying conditions such as NCDs and certain infections associated with ABR in China have also been identified as risk factors in other countries [10, 34, 37, 38].

Much ABR development is well known to occur in healthcare settings such as hospitals where extended stays and ICU admission increase the risk for the development of resistant organisms in patients [38, 52], other contributors to their spread are poor hygiene standards and inadequate infection control practice [2].

Table 3. Simplified table for OR ranges reported by risk factor domain from 114 papers applying multivariate analyses[a]

Risk factor[b]		OR >1 to ⩽2	OR >2 to ⩽3	OR >3 to ⩽4	OR >4 to ⩽5	OR >5 to ⩽6	OR >6 to ⩽7	OR >7 to ⩽8	OR >8 to ⩽9	OR >9 to ⩽10	OR >10
Sociodemographic factors (*n* = 17)		11 (64.7%)	7 (41.2%)	2 (11.8%)	2 (11.8%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.9%)	0 (0)
Patient clinical information (*n* = 55)		17 (30.9%)	16 (29.1%)	12 (21.8%)	19 (34.5%)	3 (5.5%)	6 (10.9%)	4 (7.3%)	1 (1.8%)	1 (1.8%)	8 (14.5%)
Severity of underlying disease (*n* = 12)		5 (41.7%)	3 (25.0%)	1 (8.3%)	2 (16.7%)	0 (0)	0 (0)	1 (8.3%)	1 (8.3%)	0 (0)	0 (0)
Underlying diseases (*n* = 38)	NCDs[c] (*n* = 12)	2 (16.7%)	1 (8.3%)	1 (8.3%)	5 (41.7%)	0 (0)	2 (16.7%)	1 (8.3%)	0 (0)	1 (8.3%)	2 (16.7%)
	IDs (*n* = 20)	2 (10.0%)	10 (50.0%)	6 (30.0%)	5 (25.0%)	2 (10.0%)	0 (0)	0 (0)	0 (0)	0 (0)	2 (10.0%)
	Other conditions (*n* = 17)	4 (23.5%)	4 (23.5%)	3 (17.6%)	4 (23.5%)	0 (0)	1 (5.9%)	1 (5.9%)	0 (0)	0 (0)	2 (11.8%)
Bacteria-related risk factors (*n* = 7)		2 (28.6%)	0 (0)	1 (14.3%)	3 (42.9%)	1 (14.3%)	2 (28.6%)	1 (14.3%)	0 (0)	0 (0)	2 (28.6%)
Admission in healthcare settings (*n* = 71)		61 (85.9%)	44 (62.0%)	51 (71.8%)	22 (31.0%)	17 (23.9%)	18 (25.4%)	8 (11.3%)	8 (11.3%)	6 (8.5%)	25 (35.2%)
Hospital stay (*n* = 45)		15 (33.3%)	9 (20.0%)	9 (20.0%)	5 (11.1%)	4 (8.9%)	3 (6.7%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	5 (11.1%)
Invasive procedures (*n* = 48)		0 (0)	8 (32.0%)	7 (28.0%)	2 (8.0%)	2 (8.0%)	0 (0)	1 (4.0%)	2 (8.0%)	0 (0)	5 (20.0%)
Drug exposure (*n* = 84)		43 (51.2%)	44 (52.4%)	35 (41.7%)	35 (41.7%)	17 (20.2%)	23 (27.4%)	4 (4.8%)	12 (14.3%)	6 (7.1%)	49 (58.3%)
Current medication (*n* = 33)		10 (30.3%)	9 (27.3%)	9 (27.3%)	6 (18.2%)	0 (0)	4 (12.2%)	0 (0)	1 (3.0%)	0 (0)	9 (27.3%)
Prior medication[d] (*n* = 57)		11 (19.3%)	14 (24.6%)	9 (15.8%)	9 (15.8%)	9 (15.8%)	7 (12.3%)	2 (3.5%)	5 (8.8%)	3 (5.3%)	15 (26.3%)

[a]The exact OR values and ranges is listed in the Supplementary Table S2.
[b]Risk factors are reported as mentioned in the papers (*n* = number of papers). Because some papers reported multiple ORs for multiple factors within each domain, the individual rows add up to more than 100%.
[c]Abbreviations: Non-communicable diseases, NCD; infectious diseases, IDs.
[d]Prior medication refers to the medication history of the investigated patients within the past 3 months, such as prescriptions from clinical workers before they transferred from another hospital or clinical department, or self-medication by patients.

Table 4. OR distribution for drug classes used during antibiotic monotherapies from 114 papers applying multivariate analyses

Risk factor	OR >1 to ⩽2	OR >2 to ⩽3	OR >3 to ⩽4	OR >4 to ⩽5	OR >5 to ⩽6	OR >6 to ⩽7	OR >7 to ⩽8	OR >8 to ⩽9	OR >9 to ⩽10	OR >10
Monotherapies, current medication[a]										
Carbapenems ($n = 10$)	1 (10.0%)	1 (10.0%)	2 (20.0%)	2 (20.0%)	0 (0%)	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)	3 (30.0%)
Cephalosporins ($n = 6$)	2 (33.3%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)
Other antibiotics ($n = 3$)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0%)	0 (0%)	1 (25.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No clear information ($n = 4$)	1 (25.0%)	0 (0%)	0 (0%)	1 (25.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (50.0%)
Monotherapies, prior medication[a]										
Carbapenems ($n = 16$)	2 (12.5%)	2 (12.5%)	1 (6.3%)	1 (6.3%)	3 (18.8%)	4 (25.0%)	0 (0%)	2 (12.5%)	1 (6.3%)	2 (12.5%)
Cephalosporins ($n = 9$)	1 (11.1%)	2 (22.2%)	0 (0%)	3 (33.3%)	0 (0%)	0 (0%)	2 (22.2%)	0 (0%)	0 (0%)	2 (22.2%)
Glycopeptides ($n = 5$)	0 (0%)	0 (0%)	1 (20.0)	1 (20.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (60.0%)
Other antibiotics ($n = 7$)	0 (0%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	3 (42.9%)	0 (0%)	0 (0%)	0 (0%)	2 (28.6%)	1 (14.3%)
No clear information ($n = 22$)	5 (22.7%)	4 (18.2%)	3 (13.6%)	1 (4.6%)	2 (9.1%)	4 (18.2%)	0 (0%)	3 (13.6%)	0 (0%)	6 (27.3%)

[a]20/51 papers reported monotherapy in current or prior medication as a significant risk factor in multivariate analyses (see Table 3 and online Supplementary Table S2) respectively; among these, different and multiple drugs could have been in use – hence, the numbers of papers citing the specific drug adds up to more than 20/51.

Among invasive procedures, those concerning the respiratory system were most frequently reported as significant risk factors by the papers included in this review, in agreement with a number of other investigations and reports [2, 10, 52]. This observation thus underlines the need for efficient sterilisation of instruments and maintaining a clean environment to aid prevention of ABR [53].

Drug exposure plays a major role in the development of ABR because resistance is associated with high levels of antibiotic use [10, 30, 33, 44, 54]. This is supported by our findings that prior antibiotic therapy is a common risk factor for the emergence of ABR, and more often a consequence of monotherapy than combination therapy. Carbapenem and cephalosporin treatment were strongly associated with ABR development in China, which threatens the effectiveness of these essential life-saving antibiotics. This is explained by the fact that these agents are widely prescribed and frequently misused in China [14, 21, 22, 45]. Interestingly, the use of glycopeptides has been cited as a factor promoting the increase of carbapenem resistance rates [55].

Periodic reviews of antibiotic susceptibility patterns for commonly used antibiotics and improved diagnosis of IDs have been recognised as effective measures for preventing ABR, alongside better training of healthcare workers and more dispersal of information to the population [54–57]. The establishment of an early warning system flagging increased rates of ABR in healthcare settings is currently in preparation in China [14]. This approach combined with well-developed national and local guidelines for the management of antibiotics at different levels of the health system have also been proposed as valuable instruments for better control of ABR [58, 59]. Such surveillance networks, including monitoring of resistance trends, are under continuous development in China and other parts of the world [1, 10, 33, 35, 38]. For China, multifaceted approaches to improving antibiotic use in the health system have been identified as effective tools to minimise the rise in ABR, including pharmacist-on-duty regulations, specific training of pharmacy staff, and general education of the public [2, 46, 60].

This review has some strengths and limitations. One strength is that it considered not only English but also Chinese literature, and for the latter only the highest-quality papers published in core academic journals over more than 16 years were considered. A possible limitation is that information on certain parameters might have been lost through exclusion of the Chinese language papers which did not pass the quality check.

Conclusion

ABR constitutes an ongoing major public health challenge in China. The healthcare sector-associated risk factors was the most important aspect identified in this review and such factors need to be addressed through a reduction of antibiotic exposures, long hospital stays and invasive procedures, within the hospital setting. The findings also point to a need to strengthen primary health care to prevent and control NCDs, over-prescription and overuse of antibiotics through better training of healthcare workers and pharmacists, as well as strengthening of health promotion and health literacy among the general population. Finally, AMR surveillance networks would benefit from being linked to other sectors, such as agriculture and veterinary practice, to further adopt the One Health Approach.

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Authors' contributions. The study was designed by OM and GL. The development of the search terms and search strategy was done by QC together with OM, CB, GL and BM. The quality check for the Chinese literature was performed by QC and GL. The risk of bias assessment was performed by QC. The assessment of Chinese papers was rechecked by DL. QC, DL and CB were involved in resolving disagreements. Title, abstract and full-text screening were done independently by QC and DL. Data extraction and synthesis were performed by QC. QC and CB wrote the first draft of the manuscript. All authors contributed to writing the manuscript.

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