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Risk Factors for the Healthcare-associated Antibiotic Resistance in China

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DEDICATION

To my parents, loving me and giving me the motivation to "make it to the end". To my friends, Claudia Beiersmann, Guangyu Lu and Chao Hu, supporting me with being my side.

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ABR	Antibiotic resistance
AMR	Antimicrobial resistance
AST	Antibiotic susceptibility test
CDC	The Center for Disease Control
DDD	Defined Daily Doses
DR	Drug resistance
DRI	Drug Resistance Index
EARSS	European Antimicrobial Resistance Surveillance System
EARS-Net	European Antimicrobial Resistance Surveillance Network
E. coli	*Escherichia coli*
ESBL	Extended-spectrum beta-lactamase
EU	The European Union
GLASS	The Global Antimicrobial Resistance Surveillance System
GN	Gram negative
GP	Gram positive
HAI	Hospital-associated infection
ICU	Intensive care unit
ID	Infectious disease
LMIC	Low- and middle-income country
MDR	Multidrug-resistance

MDR-TB	Multi-drug resistant *tuberculosis*
MINORS	Methodological Index for Non-Randomized Studies
MRSA	Methicillin-resistant *Staphylococcus aureus*
NCD	Non-communicable disease
NDM	New Delhi Metallo-beta-lactamase
PDR	Pandrug-resistance
PHC	Primary healthcare center
OECD	The Organization for Economic Co-operation and Development
Spp.	Species
XDR	Extensively drug-resistance

1 INTRODUCTION

1.1 History of antibiotic resistance

1.1.1 Global history

Ancient outbreaks of bacterial infections among humans in Egypt, China, and some other countries are well-documented (Sengupta et al. 2013). As one of the most prominent examples, the Plague of Justinian in the 6th century marked the “first pandemic”, killing 25-50 million people— nearly half of the European population at that time (Cohn 2008).

Antibiotics can be used to inhibit bacterial growth or kill bacteria, thereby decreasing morbidity and mortality from bacterial infections (Milic et al. 2013). One way to classify antibiotics is according to their chemical structure. Table 1 shows an example list of chemical classes of antibiotics (Aminov 2017; Brown and Wright 2016).

Table 1: Examples of chemical classes of antibiotics and examples for each antibiotic class (Aminov 2017; Brown and Wright 2016)

Antibiotic class	**Examples of antibiotics at the current class**
Aminoglycosides	Amikacin, Kanamycin, neomycin, spectinomycin

Beta-lactams	Amoxicillin, carbapenems, cephalosporins, penicillins
Chloramphenicols	Chloramphenicol
Glycopeptides	Teicoplanin, telavancin, vancomycin
Macrolides	Azithromycin, clarithromycin, erythromycin
Oxazolidinones	Linezolid, tedizolid
Quinolones	Ciprofloxacin, fluoroquinolones
Streptogramins	Pristinamycin, quinupristin
Sulfonamides	Sulfadimidine, sulfamethoxazole, sulfanilamide
Tetracyclines	Tetracycline, doxycycline

The first antibiotic, penicillin, was discovered by Sir Alexander Fleming in 1928 (Sengupta et al. 2013). In the 1940s, antibiotics were first prescribed for the treatment of serious infections (Ventola 2015). Antibiotic treatment was later used to combat infections on a large scale, and became an essential approach of modern medicine (Aslam et al. 2018). The mortality from communicable diseases and endogenous infections was reduced through the application of

antibiotic therapy and prophylaxis (Woolhouse et al. 2016). For example, approximately 1 million children under age five are killed by pneumonia annually worldwide, and antibiotic therapy could be used to combat community-acquired pneumococcal infections and save an estimated 445,000 of these lives (Gandra et al. 2016). Further, infectious disease and infection-related long-term consequences critically impact the quality of human lives (Colzani 2019),with an estimated total burden of 1.38 million disability-adjusted life years among European inhabitants (Cassini et al. 2018). Hence, antibiotic treatments play an important role in human health, as well as other applications such as agriculture.

As early as 1945, Alexander Fleming warned of antibiotic resistance (ABR) (Podolsky 2018). Bacteria develop resistance to antibiotics as they are exposed to these drugs (Centers for Disease Control and Prevention 2018; O'Neill 2016; World Health Organization 2018a). ABR is an important subtype of antimicrobial resistance (AMR), which describes the resistance of microbes (such as bacteria, viruses, fungi, and parasites) to antimicrobial drugs used to cure these infections (World Health Organization 2001). ABR has often quickly developed after an antibiotic has begun to be used. A famous example is the resistance to penicillin, which was widely available by 1946, but the first sign of penicillin resistance was reported by Abraham and Chain in 1940 (Abraham and Chain 1988; Lobanovska and Pilla 2017). Ceftaroline was introduced in 2010 for the treatment of bacterial skin infections and already methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia (Lounsbury et al. 2019). Resistance was soon identified, only one year after its introduction (Lim et al. 2011). The timeline in Figure 1 shows the year of deployment of antibiotics and the year of observation of their resistance (Clatworthy et al. 2007).

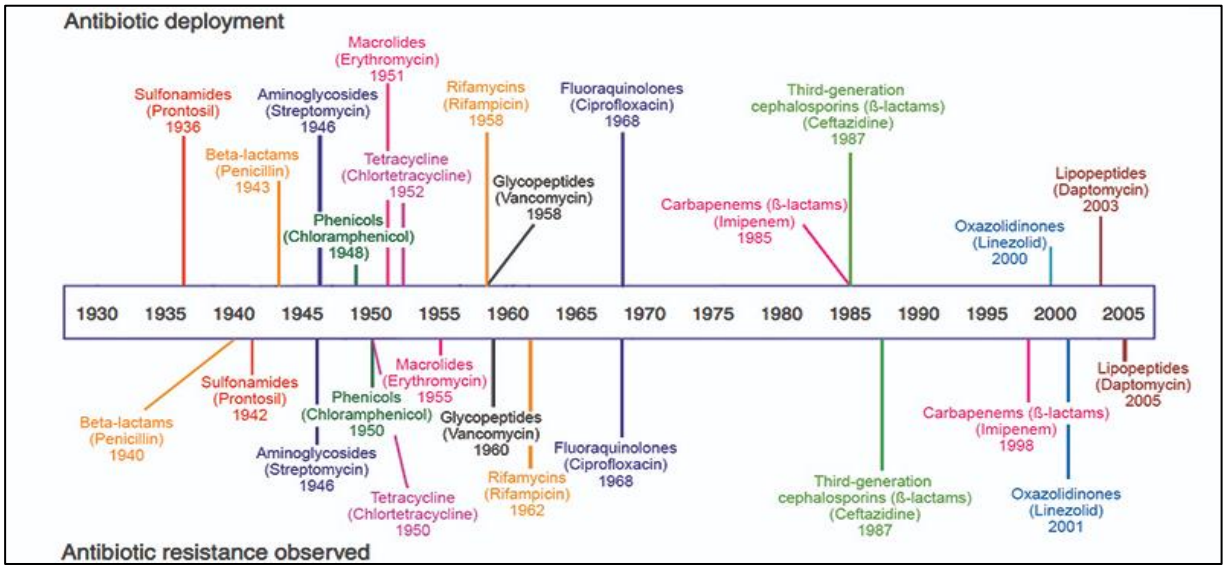

Figure 1: Timeline of antibiotic deployment and antibiotic resistance observation (Clatworthy et al. 2007)

ABR threatens the effectiveness of infectious disease treatments, leading to prolonged illness, disability, and death globally (World Health Organization 2015b). Antibiotic-resistant organisms can spread via water, which is one of the essential means of transmission between agriculture, animals, and humans (Baquero et al. 2008). India is an example where, due to the many waterways, multi-resistant bacteria are frequently present. A study showed that New Delhi metallo-beta-lactamase (NDM) type 1-producing bacteria — which is resistant to multiple antibiotics such as carbapenems, cephalosporins, and penicillins—may acquire its resistance outside of health-care facilities; it also indicated a spread of resistant bacteria from household water and sanitation facilities to human bodies (Walsh et al. 2011). Antibiotic

residues and antibiotic-resistant bacteria in animal and agriculture waste have become contributors to the prevalence of ABR (Manyi-Loh et al. 2018). They impact livestock, causing higher deaths and increasing the projected decline in global livestock production from 2.6% to 7.5% per year by 2050 (The World Bank 2016).

Bacteria can be resistant to multiple antibiotics. This is called multidrug-resistance (MDR). Multidrug-resistant bacteria were found not long after penicillin was developed. ABR poses a global threat due to the emergence, spread, and persistence of MDR bacteria (Davies and Davies 2010). Compared to single drug-resistant bacterial infections, MDR- bacterial infections lead to less available choice in antibiotic treatments and higher burdens of diseases (Chang et al. 2015). A famous example first appearing in 1966 is the "superbugs": microbes (usually bacteria, but also fungi sometimes) with higher prevalence towards resistance to various classes of antibiotics (Osmundsen 1966). MRSA was widespread in Europe by the 1970s and in the U.S. by the 1980s (Wenzel 2004). The superbugs have high levels of resistance to multiple antibiotics, and lead to high burdens of disease (Bashir et al. 2019). The U.S. Center for Disease Control (CDC) has compiled a collection of superbugs and to date it has grown to 18 bacteria and fungi unsusceptible to many existing treatments (Centers for Disease Control and Prevention 2018).

The occurrence of extended-spectrum beta-lactamase (ESBL)-producing bacterial infections has also contributed to the MDR problem (Aslam et al. 2018). From the early 1960s, the development of beta-lactamase emerged quickly (Bushnell et al. 2013). ESBLs are enzymes produced by many bacteria. They can destroy the beta-lactam component of antibiotics,

leading to resistance to single or even multiple commonly used antibiotics such as third-generation cephalosporins and carbapenems (Blair et al. 2015). ESBL-producing bacterial infections spread quickly with the development of ESBLs. More than 150 different ESBLs have been described from a single strain of *Klebsiella ozaenae* isolated in Germany (Bradford 2001). A surveillance report from England estimated that the risk of mortality caused by ESBL-producing *Escherichia coli* (*E. coli*) has been increased to approximately 17% (Day et al. 2019).

Antibiotic-resistant bacteria can be classified based on the breadth of resistance. MDR bacteria are defined as pathogens resistant to at least one generic antibiotic in three or more antibiotic classes (Magiorakos et al. 2012). Extensive drug resistance (XDR) denotes bacteria resistant to at least one generic antibiotic in all but two or fewer antibiotic classes (Magiorakos et al. 2012). Pandrug resistance (PDR) is defined as pathogens resistant to almost all antibiotics available for treatment (Centers for Disease Control and Prevention 2019).

ABR has become important to the international economy. In 2013, it was noted in the World Economic Forum Global Risks Report (World Economic Forum 2013). Five years later, this organization focused again on the topic of drug resistance, warning of the spread of resistance to the strongest existing antibiotics (World Economic Forum 2018). The World Bank (2016) warned that the potential negative influence of drug-resistant infections on economies could likely be worse than the impact of the 2008 financial crisis (The World Bank 2016). ABR could reverse the falling global mortality rates from communicable disease, threatening further

improvements in global maternal and child health, as well as complicating treatments of non-communicable diseases (Laxminarayan et al. 2016).

Addressing ABR by optimizing the global surveillance and management of antibiotics is thus critical to global health.

1.1.2 History in China

The history of ABR and AMR in China dates back many decades. China reported an increased prevalence of resistance to chloramphenicol in isolates of *Shigella dysenteriae* and *Salmonella typhi* as early as in the 1950s (Ge et al. 1960). In the 1980s, epidemics of drug-resistant typhoid bacillus infections spread nationwide. Epidemics of typhoid resistant to other first-line antibiotics were detected in China in the following decade, and the first MDR typhoid was identified in 2010 (Wang 1989; Yan et al. 2016). In 1989, Shanghai first monitored and reported the isolation of *Staphylococcus aureus* with a high resistance rate to common antibiotics: tetracycline, erythromycin, chloramphenicol, clindamycin, kanamycin, and gentamycin (Wang 1989). Since then, surveillance results have indicated that the incidence of recognized MDR organisms is further increasing (Xiao 2018).

In 1993, a surveillance report on ABR in China stated that the morbidity and mortality rates from antibiotic-resistant bacteria were higher than in other countries (Wu and Ren 1993a; Wu and Ren 1993b). According to the report from Beijing's regional ABR surveillance system, the resistance rate of *Staphylococcus aureus* to penicillin G was 95.5%, the resistance rate of

Enterobacter species (*spp.*) to ampicillin was 80%, and the resistance rate of carious bacteria to sulfonamides (including trimethoprim/sulfamethoxazole) ranged from 30% to 65% (Wu and Ren 1993a; Wu and Ren 1993b). From 1994 to 2000, the rate of resistance in China grew much higher than in other countries, averaging 22%, compared with 6% in the U.S. from 1999 to 2002 (Zhang et al. 2006). For 2009, the Global Risks Report estimated 80,000 AMR-related deaths in China (Dong 2009; World Economic Forum 2013).

1.2 Epidemiology of antibiotic resistance

1.2.1 Global epidemiology

Consumption of antibiotics varies widely globally. The World Health Organization (WHO) reports Mongolia as the country with the highest consumption of 64.4 Defined Daily Doses (DDD) per 1,000 inhabitants per day. Burundi has the lowest consumption of 4.4 DDD per 1,000 inhabitants per day (World Health Organization 2018e). According to the same WHO report, these data represent an overall absolute weight (not adjusted by population size) of antibiotic consumptions varying from 1 ton to 2,225 tons per year in 65 participated countries and areas (World Health Organization 2018e). However, not every country participates in the WHO surveillance, for example, China is not yet part of this network.

Correspondingly, ABR rates vary greatly, depending on the country, bacteria, and antibiotics (World Health Organization 2018c). A wide variety of bacteria can be isolated from blood, stool, and urine samples (World Health Organization 2018c). Susceptibility tests have shown various ABR rates among these (World Health Organization 2018c). The overall penicillin-resistance rate, for example, ranges from zero to 51%, while bacterial bloodstream infections show ABR rates ranging from zero to 82% (World Health Organization 2018d). Multidrug-resistant *tuberculosis* cases increased globally from 160,684 in 2017 to 186,772 in 2018 (World Health Organization 2019b). Across the member countries of the Organisation for Economic Co-operation and Development (OECD), the resistance of *Acinetobacter baumannii* to imipenem (a drug belonging to the class of carbapenems) increased between 2006 and 2016–with four countries remaining unchanged at very high levels (Romania at 95%, Libya at 100%, South Africa at 80%, and Vietnam at 92%) (Xie et al. 2018).

The Drug Resistance Index (DRI) allows global assessment of the relative efficacy of countries' antibiotic therapy. High-income countries have generally lower DRI rates than low- and middle-income countries (LMICs) (Klein et al. 2019). ResistanceMap is a web-based collection of data visualization tools focusing on AMR and antibiotic use trends around the world (Center for Disease Dynamics Economics & Policy 2021). Resistance data for 12 organisms in 46 countries are represented.

Cephalosporins, a widely applied antibiotic class, comprise up to 50-70% of the total antibiotic applications among humans (Das et al. 2019). Cephalosporins are for example used against *Klebsiella pneumoniae,* which can cause pneumonia and other infections. Cephalosporin-

resistant *Klebsiella pneumoniae* can easily lead to treatment failure and cause serious public health issues (Founou et al. 2018). Figure 2 shows the resistance of *Klebsiella pneumoniae* to third-generation cephalosporins in different countries (Center for Disease Dynamics Economics & Policy 2021). Egypt has the highest prevalence of resistance, with a rate of 98% (Center for Disease Dynamics Economics & Policy 2021).

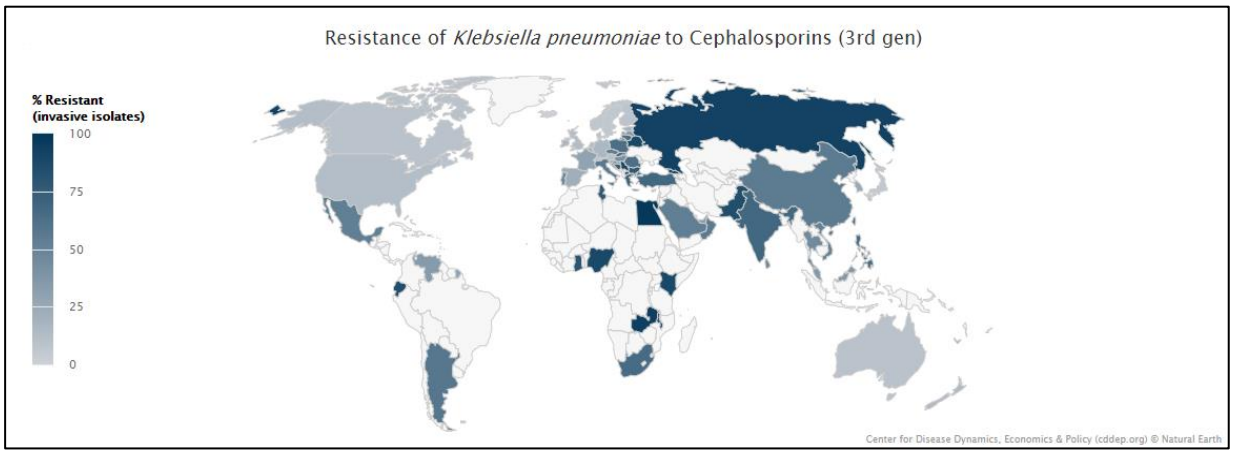

Figure 2: Resistance of *Klebsiella pneumoniae* to cephalosporins (3rd generation) (The Center for Disease Dynamics, Economics and Policy 2021)

As another example, fluoroquinolones resistance rates range from zero to 87% (Figure 3) (Center for Disease Dynamics Economics & Policy 2021; World Health Organization 2018c). Data on the resistance rates of many other bacteria to various antibiotics can be found and compared using the ABR world map (Center for Disease Dynamics Economics & Policy 2021).

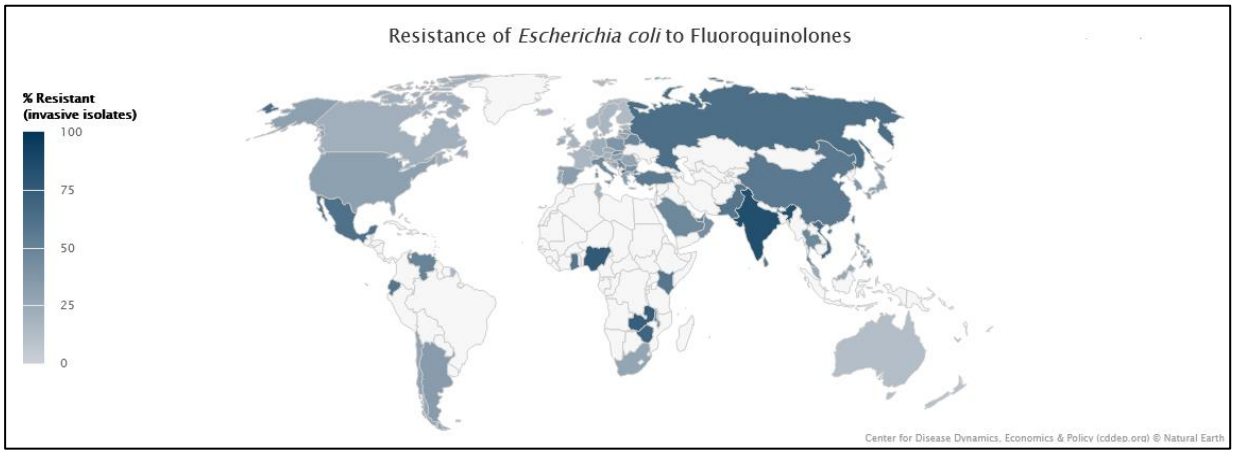

Figure 3: Resistance of *Escherichia coli* to fluoroquinolones (The Center for Disease Dynamics, Economics and Policy 2021)

In 2020, the World Economic Forum warned about the widespread fatalities and economic disruptions caused directly by ABR (World Economic Forum 2020). It was estimated in 2016 that 700,000 deaths each year globally could be attributed to AMR (O'Neill 2016). In 2018, the WHO estimated that 10 million deaths by 2050 would be due to AMR (World Health Organization 2018c).

A European Union (EU) survey reported that 33,000 people die each year from infections caused by antibiotic-resistant bacteria and that the burden of these infections is comparable to that of influenza, tuberculosis, and HIV/AIDS combined (Cassini et al. 2019). Recently, Germany, Finland, and many other European countries have reported outbreaks caused by

antibiotic-resistant bacteria, indicating the threat of fast-spreading and highly antibiotic-resistant bacteria, particularly carbapenemase-producing organisms (European Centre for Disease Prevention and Control 2019b).

The latest US national survey on ABR reported more than 2.8 million antibiotic-resistant infections each year, leading to more than 35,000 deaths (Centers for Disease Control and Prevention 2019). The threats of 18 antibiotic-resistant bacteria are graded into four categories according to their spread and risk to public health: the urgent list (the highest grade), serious list, concerning list and watch list. For example, antibiotic-resistant *Clostridium difficile* has been classified as an urgent threat, being high-consequence and causing significant morbidity and mortality (Centers for Disease Control and Prevention 2019). Nearly 5.7% of people in the country who required hospital care for *Clostridium difficile* in 2017 died (Centers for Disease Control and Prevention 2019). Given that cases of ESBL-producing *Enterobacteriaceae* have increased since 2012, and the U.S. CDC estimated 9,100 deaths in the US in 2017, ESBL-producing *Enterobacteriaceae* is on the list of serious threats (Centers for Disease Control and Prevention 2019).

Some Asian countries are epicenters of resistance due to their rapid increases in the prevalence of major resistant bacteria (Kang and Song 2013). One estimate concluded that antibiotic-resistant bacteria kill more than 38,000 people in Asia every year and that the annual related costs total 1.3 billion US dollars (Thamlikitkul et al. 2015). However, few Asian countries, have efficient surveillance systems to monitor and control trends in ABR or human, animal, and food production antimicrobial applications (Bhatia 2019). Nevertheless, enough data exists

to show the emergence of ABR across Asian countries (Koh et al. 2013). In 2012, the rate of MDR was observed at 59.3% among isolates from Asian countries (Kang and Song 2013). MRSA is a major concern in the Asian region among both community and nosocomial pathogens (Kang and Song 2013). Asian countries such as China, Indonesia, Japan, and Vietnam have reported MRSA prevalence exceeding 50% in several health-care facilities, while the AMR surveillance network in India found a rate of 41% in 2012 (Joshi et al. 2013; Kang and Song 2013).

1.2.2 Epidemiology in China

The prevalence of ABR is high in LMICs. For example, for India, China, and the Russian Federation it has been reported at above 42% (Organization for Economic Co-operation and Development 2018). Table 2 shows a summary of resistance rates of bacteria to different antibiotics in China (Center for Disease Dynamics Economics & Policy 2020).

Table 2: Antibiotic resistance in China (Center for Disease Dynamics Economics & Policy 2020)

Bacteria	**Antibiotic resistance rates among different antibiotics**

Acinetobacter baumannii	Amikacin: 56% resistant, Aminoglycosides: 73% resistant, Carbapenems: 77% resistant, Fluoroquinolones: 78% resistant
Enterobacter aerogenes/cloacae	Aminoglycosides: 14% resistant, Amoxicillin-clavulanate: 92% resistant, Carbapenems: 14% resistant, Cephalosporins (3rd generation): 48% resistant, Fluoroquinolones: 15% resistant
Enterococcus faecalis	Aminoglycosides: 31% resistant, Aminopenicillins: 4% resistant, Vancomycin: 0% resistant
Enterococcus faecium	Aminoglycosides: 48% resistant, Aminopenicillins: 91% resistant, Vancomycin: 3% resistant
Escherichia coli	Aminoglycosides: 42% resistant, Aminopenicillins: 88% resistant, Amoxicillin-clavulanate: 14% resistant, Cephalosporins (3rd generation): 64% resistant, Fluoroquinolones: 56% resistant
Klebsiella pneumoniae	Aminoglycosides: 37% resistant, Amoxicillin-clavulanate: 41% resistant, Carbapenems: 36% resistant, Cephalosporins: 55% resistant, Fluoroquinolones: 42% resistant
Pseudomonas aeruginosa	Amikacin: 6% resistant, Aminoglycosides: 10% resistant, Carbapenems: 25% resistant, Fluoroquinolones: 15% resistant
Staphylococcus aureus	Linezolid: 0% resistant, Oxacillin (MRSA): 38% resistant, Vancomycin: 0% resistant
Streptococcus pneumoniae	Macrolides: 94% resistant, Penicillin: 5% resistant

Antibiotics and resistant organisms in China are distributed widely in soils (particularly in farming fields), surface water, and livestock. For example, sulfonamide and tetracycline resistance has been detected in manure and composted, manure-amended soils (Chen et al. 2016; Cheng et al. 2016; Wu et al. 2010). ESBL-producing bacteria were identified in soil samples in the rural region of Shandong Province, China (Cheng et al. 2016; Gao et al. 2015) The concentration of antibiotics in surface waters in the country is comparable to or slightly higher than the concentrations reported in other countries (Dinh et al. 2011; Verlicchi et al. 2014; Yang et al. 2011).

The prevalence of ABR in livestock in China poses a critical threat to food security. For example, a report from Beijing and Hebei Province in 2004 found that most *E. coli* isolates from samples of farm animals were resistant to multiple classes of antimicrobials, with overall resistance rates of 98% to tetracycline, 84% to sulfamethoxazole, 79% to ampicillin, 77% streptomycin, and 76% to trimethoprim-sulfamethoxazole (Yang et al. 2004). Antibiotic-resistant isolate rates from chickens are higher than those from swine in China (Lu et al. 2010; Yang et al. 2004).

In China's healthcare system, ABR exists broadly and poses health risks among infected patients and those with hospital-associated infections (HAI). The resistance among gram-negative bacteria in China mirrors the global trend (Exner et al. 2017; Qu et al. 2019; The World Bank 2017). For example, as reported by the China Antimicrobial Surveillance Network, the resistance rate of *Acinetobacter baumannii* increased between 2005 and 2017 from 31.0% to 71.4%, with over 90% carbapenem-resistance each year (Qu et al. 2019). Also

notable is the increasing prevalence of carbapenem-resistant *Klebsiella pneumonia* enhanced with the rising from 5.5% in 2013 to 10.1% in 2018, while the rate of carbapenem-resistant *E. coli* fluctuated from 1.6% to 1.8% in the same period (China Antimicrobial Resistance Surveillance System 2019). The resistance rate of *E. coli* to florfenicol is as high as 100%, and the resistance rate to enrofloxacin is between 50-70% (Cai 2017).

ABR prevalence and increase vary in different regions of China. For example, the prevalence of quinolone-resistant *E. coli* has been found distributed variously among different regions (51.0% on average), with higher rates in the northeast and north regions (China Antimicrobial Resistance Surveillance System 2019). Henan province (in the mid-south region of China) has been reported as having the highest rate of prevalence of carbapenem-resistant *Acinetobacter baumannii, Klebsiella penumoniae,* and *E. coli,* and third-generation cephalosporin-resistant *Klebsiella pneumoniae* and *E. coli* nationwide. Qinghai province has the lowest prevalence among these antibiotic-resistant isolates (China Antimicrobial Resistance Surveillance System 2019). Henan province also reports the highest increase of carbapenem-resistant *Klebsiella pneumoniae* from 9.4% in 2013 to 32.5% in 2018 (China Antimicrobial Resistance Surveillance System 2019).

As well as single drug resistance, MDR bacteria further harm public health in China. In 2017, an estimated 73,000 Chinese people were reported to have developed multidrug-resistant *tuberculosis* (MDR-TB), representing 13% of the global incident cases of MDR-TB and the second-highest number of cases in the world (World Health Organization 2019a). Amongst intensive care unit (ICU) patients, who are critically ill and urgently need antibiotics, MDR

Acinetobacter, *Klebsiella*, and *Pseudomonas aeruginosa* are common (Peng et al. 2018; Tian et al. 2016; Wang et al. 2019a). An investigation of 3,223 patients with HAI from a general tertiary hospital in China reported that patients with MDR-HAI are distributed widely, predominantly in ICUs (Wang et al. 2019a). ABR kills 80,000 Chinese people annually and leads to an associated extra financial burden of disease of 11.7 billion U.S. dollars (Lei 2016).

1.3 Risk factors related to the spread of antibiotic resistance

ABR is a major global health challenge due to its rapid emergence and dissemination. Figure 4 shows the ABR spread and relationships among humans, animals, and the environment (Wang et al. 2018).

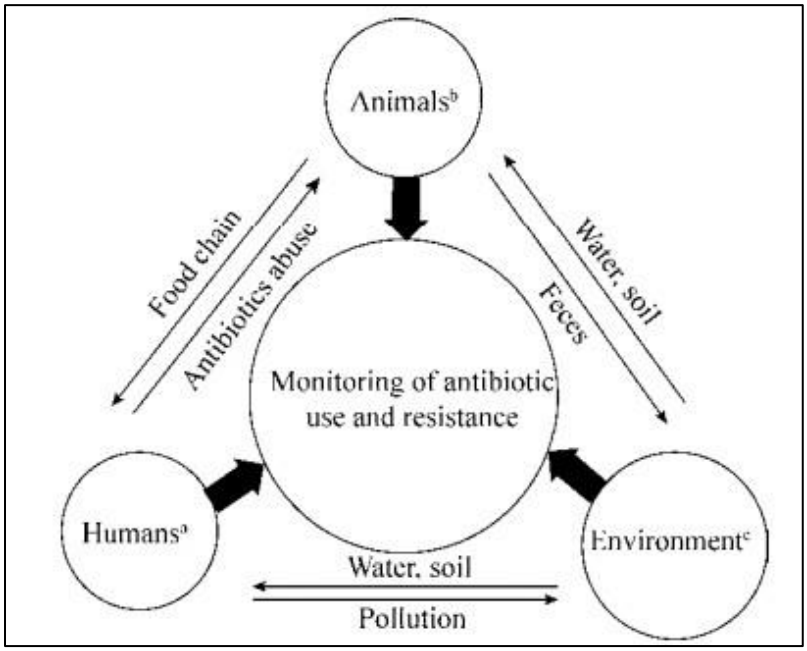

Figure 4: Antibiotic resistance in human, animals, and the environment (Wang et al. 2018)

a: ABR in humans are mainly developed from the abuse of antibiotics; b: the overuse of antibiotics in animal feeding leads to the accumulation of remain ABR in animals which can be transmitted to human ultimately via the food chain; c: ABR in the environment are mostly derived from natural resistance, human pollution and animal excretion

Various factors in the complex relationship between humans and the environment can contribute to the development of ABR. These include poor management of antibiotic application, abuse and misuse of antibiotics, poor compliance with infection therapy, low quality of available antibiotics, insufficient coordination of ABR surveillance systems, and a lack of new antibiotics and vaccines (World Health Organization 2018a).

1.3.1 General risk factors

General risk factors for ABR usually originate in the food and agricultural industries. Inappropriate antibiotic use can lead to the occurrence and spread of ABR (Rousham et al. 2018). Four main drivers exist for inappropriate antibiotic use among food animals: limited knowledge of antibiotic applications, perceived necessity to use antibiotics for increasing meat production, assessment of antibiotics with no restriction, and weak surveillance and control systems (Om and McLaws 2016).

The overuse of antibiotics in livestock likely contributes most to the prevalence of ABR. Antimicrobial consumption for livestock in LMICs will increase by an estimated 99% from 2010 to 2030 (Van Boeckel et al. 2015). China is the second-largest consumer of antibiotics worldwide and also one of the largest antibiotic producers (Qu et al. 2018b). Between 2000 and 2015, the antimicrobial consumption in China increased by 79%, higher than the 65% increase in global antimicrobial consumption (Klein et al. 2018). The total estimated antibiotic usage in China in 2013 was 162 million kilograms, approximately nine times that of the U.S. (Zhang et al. 2015). With global development, especially urbanization and population growth, the demand for animal-based foods is increasing. In particular, poultry production could be considered high-risk for ABR, especially in smaller-scale unregulated farming areas and husbandries (Rousham et al. 2018).

Resistance is more likely to develop when animals are overcrowded and poorly sanitized. These conditions occur more commonly in poultry, because of the greater application of antibiotics, than other livestock (Graham et al. 2017). A study reported high and unregulated use of antimicrobials in 98 small-scale chicken farms in Cameroon, with almost half delivering their poultry to the market with not following antimicrobial withdrawal period (Kamini et al. 2016).

The spread of ABR from food-producing animals to the environment usually takes place in two ways: through the excretion of antibiotics in urine or feces into surface waters and soils and through the use of animal manure as fertilizer in soil or ponds (Rousham et al. 2018). In rural areas of China, high consumption rates and improper application of antibiotics in livestock lead to antibiotic contamination of food and drinking water (Hao et al. 2015). Nearly half of the 210,000 tons of antibiotics produced in China are used by farms (Collignon and Voss 2015). The country is also polluted by antibiotics used on farms and pastures (Collignon and Voss 2015).

Human activities (pharmaceutical plants, hospital effluent, and untreated wastewater) have been linked to environmental contamination with antibiotic-resistant bacteria (Rousham et al. 2018). In Bangladesh, 71% of wastewater samples next to hospitals contained resistant isolates and higher concentrations of ABR genes were identified downstream from pharmaceutical producers in Western Havana (Graham et al. 2011; Islam et al. 2017). In China, ABR genes are also distributed widely in environments including clinical areas, animal waste, and sewage treatment plant effluent (Qiao et al. 2018). The overuse of high volumes of sulfonamides,

tetracyclines, and fluoroquinolones in the agricultural sector contributes to antimicrobial pollution in the surrounding environment (Collignon and Voss 2015). The spread of ABR genes has also been found in smog metagenomes in Beijing, containing multiple, carbapenem-resistant genes (Rousham et al. 2018).

Lacking comprehensive policies, regulations, and guidelines to supervise and manage antibiotics from sale to application will increase the threat to global health. In some LMICs, regulations on the sale and application of antibiotics are limited, as are policies on the quality, safety, and efficacy of antibiotic products. Policy and financial challenges for pharmaceutical companies hinder antibacterial research. Insufficient guidelines for antibiotic application contribute greatly to the overuse and misuse of antibiotics, which cause the evolution of resistance (Aslam et al. 2018). Due to gaps in adequate regulations and deficiencies in awareness of best practices, low-grade antibiotics are more accessible and the broad use of antibiotics among poultry and livestock has increased (Aslam et al. 2018).

1.3.2 Healthcare-associated risk factors

Healthcare-associated risk factors for ABR mainly include irrational prescription and application of antibiotics, poor hygiene in the clinical environment, and insufficient coordination of ABR surveillance systems. The lack of new drugs and vaccines can also

contribute to ABR prevalence, as can poor quality of available antibiotics (Chokshi et al. 2019).

Antibiotics are among the most commonly prescribed drugs in human medicine, with excessive use when not clinically indicated (Chokshi et al. 2019; Qiao et al. 2018; Zeng et al. 2017). Frequently, the application of broad-spectrum antibiotics and changes of antibiotics can cause ABR, especially for MDR strains (Qiao et al. 2018). Unnecessary antibiotic use can also contribute to the occurrence of antibiotic-resistant pathogens, which then spread to other people (Centers for Disease Control and Prevention 2019). Additionally, a lack of high-efficiency and more-affordable diagnostic tools for ABR detection could be a driver of misusing antibiotics and increasing their application. Thus, prescribing and applying antibiotics without clinical microbiological testing may cause ABR.

1.3.2.1 Primary healthcare centers and secondary hospitals

The unnecessary use of antibiotics in clinic facilities is the major driving force towards increased ABR. In many LMICs, particularly in rural areas, antibiotics are available even without a physician's prescription. This contributes greatly to increasing the unnecessary consumption of antibiotics. The reasons for the availability of antibiotics are usually incompletely developed pharmaceutical regulation and unskilled health workers (Chokshi et al. 2019). Antibiotics are readily available from local pharmacies, hospitals, drugstores, and roadside stalls without a prescription (Ardal et al. 2016; Chokshi et al. 2019).

In China's primary healthcare centers (PHCs) and secondary hospitals, the lack of fully skilled doctors and health workers certified to diagnose and prescribe treatments is an important risk factor for ABR (Wang et al. 2014). Health workers without a full understanding of antibiotics and their applications are more likely to prescribe them to their patients, which can result in excessive use (Chokshi et al. 2019). Correspondently, a study from India concluded that in primary hospitals, unqualified practitioners were likely to prescribe even more intensive antibiotic treatment, and pay less attention to the possible adverse effects (Ranjalkar and Chandy 2019).

1.3.2.2 Tertiary hospitals

Overuse and misuse of antibiotics also exist in tertiary hospitals and other specialized hospitals. In the USA, around 50% of antibiotic use in hospitals is not necessary (Centers for Disease Control and Prevention 2017). A report from Nigeria concluded that the over-prescription of antibiotics could cause and spread ABR in hospitals (Bashir et al. 2019). Some patients received prescriptions of more than one antibiotic with similar mechanisms (Hu et al. 2003). Surgical admissions and ICUs are two of the hospital departments with the highest need for antibiotics. They also urgently require systematic approaches to optimizing antibiotic therapy (Labricciosa et al. 2018).

Taking antibiotic therapy prescribed by physicians only according to clinical experience puts patients in danger of antibiotic-resistant diseases. Experts in many countries such as China

have scientifically developed national and local guidelines for the application of antibiotics and suggestions for clinical practice (Labricciosa et al. 2018). However, almost one in four surgeons still do not use or consult local guidelines when considering an antibiotic for a patient (Labricciosa et al. 2018). A general hospital of Wuhan highlighted that only 3.8% (39/1025) of patients prescribed antibiotics had a microbiological examination afterward (Hu et al. 2003).

Hospitals and long-term nursing facilities have patients at high risk for severe morbidity and mortality (Baquero et al. 2008). The clinical conditions underlying comorbidities, along with knowledge about the treatment history of infections due to antibiotic-resistant bacteria, are factors that impact the development of ABR in subsequent antibiotic treatment (Bassetti and Righi 2013). Although the volume and intensity of total antibiotic application have decreased in recent years, the consumption of carbapenem antibiotics significantly increased between 2011 and 2014. This is reflected in the national prevalence of carbapenem resistance (Qu et al. 2018b).

The clinical environment should also be considered a substantial factor in infection control practices because hygienic cleanser–resistant organisms may survive both drugs and sanitizer (Chemaly et al. 2014). Long-term hospitalization can be a risk for patients to have antibiotic-resistant laboratory results. Outbreaks and clusters caused by antibiotic-resistant bacteria could endanger everyone in the clinical environment, especially in health service facilities with poor infection control practices (Bhatia 2019).

Due to the increasing application of invasive procedures, aggressive antibiotic therapies, surgical interventions, and severe underlying comorbidities, patients in ICUs and other

emergency healthcare units are at risk of HAI or, worse, infection with antibiotic-resistant bacterial diseases. Several underlying diseases have been identified as risk factors for patients becoming infected with these (Aslam et al. 2018).

1.3.2.3 Populations at risks

ABR partly results from the inappropriate use of antibiotics. Adherence to first-choice antibiotics contributes to the reduction of ABR (Llor and Bjerrum 2014). Poor knowledge and attitudes toward compliance with antibiotic therapy are among several factors educing treatment adherence. Additionally, during long-term therapy, interruption of treatment is more likely in patients with less adherence behavior (Axelsson 2013). In 2015, the WHO surveyed 10,000 people in multiple countries and reported that close to 32% believed that they should stop taking antibiotics when they feel better, rather than completing the prescribed course of therapy (World Health Organization 2015a).

ABR may develop when antibiotics are misused by people without common knowledge of their application, especially when they self-medicate. People may take antibiotics for a viral or fungal infection in cases where they show similar symptoms to bacterial infections. In a survey conducted by the WHO in 2015, 64% of respondents believed that antibiotics could be used to treat colds and the flu (World Health Organization 2015a). People are not clear about the current status of ABR as a global issue, with 44% of respondents thinking that ABR occurs only when people take antibiotics regularly (World Health Organization 2015a). Additionally,

inappropriate consumption of antibiotics without prescription could impact ABR. Of the 1,002 Chinese respondents to the WHO survey, nearly 3% purchased antibiotics on the internet (World Health Organization 2015a).

1.4 Antibiotic resistance control measures

1.4.1 Diagnostics, new antibiotics, and vaccines

While ABR emerges rapidly, vaccines, as well as new antibiotics, can contribute to the control of infections (Tagliabue and Rappuoli 2018). However, since 1987, no development has occurred of new-mechanism drugs worldwide (Silver 2011). Some pharmaceutical companies began to show less interest in developing new drugs because they received lower commercial returns and paid higher investments on anti-infective drugs (Conly and Johnston 2005; Venkatesh et al. 2011). At the 68th World Health Assembly in 2015, the WHO endorsed a global action plan to address antimicrobial resistance, including increasing investment in new medicines, diagnostic tools, vaccines, and other interventions (World Health Organization 2015c). Additionally, the goal of this World Health Assembly was to ensure the continuous availability of effective and safe medicines for the treatment of infectious diseases (World Health Organization 2015c).

Practical prescription of antibiotics should be based on results from laboratory examinations. Evidence for antibiotic therapies is still missing in clinical practice, especially in LMICs (Bhatia 2019). Improper diagnostic methods are often utilized when treating infections, and therefore, antibiotics are prescribed when not necessary. For example, some LMICs still have limited availability and use of diagnostic tools for detecting tuberculosis, which causes increased use of broad-spectrum antibiotics and other harmful antibiotic applications that transfer resistance to future infections (Chokshi et al. 2019). Thus, a lack of proper and efficient diagnostic methods can increase global ABR.

Despite the many pharmaceutical companies producing antibiotics globally, an emergent need remains for the availability of good-quality antibiotics and new drugs to defend against ABR. In 2018, the WHO published a list of bacteria for which new antibiotics were urgently needed (World Health Organization 2018d). Many developing countries do not have the necessary quality-assurance mechanisms to ensure high-quality antibiotics supplies (Chokshi et al. 2019). Resistance prevalence rates increase between two- and six- fold through the application of expired medications compared with unexpired medications (Chokshi et al. 2019). Medicine transportation and storage conditions also increase the risk of quality loss. These latter factors can be noticed by both healthcare workers and patients (Chokshi et al. 2019).

The development of new antibacterial agents has reduced steadily across the world over the last several decades (Fair and Tor 2014). Higher economic and time costs, as well as more experimentation, have led to decreased interest from the pharmaceutical industry in developing new antibiotics. Political, regulatory hurdles have led to a similar decline (Fair and Tor 2014).

Limited, clear trial guidelines and decreased tolerance for adverse effects for new drugs have stifled new antibiotic development (Fair and Tor 2014).

Since the development of new antibiotics is not promising, a possible answer to ABR is vaccination (Tagliabue and Rappuoli 2018). Both antibiotics and vaccines are important in the control of infections. The availability of vaccines to control infectious diseases leads to a decrease in the application of antibiotics and generates less ABR (Tagliabue and Rappuoli 2018). Since 1980, 22 new vaccines have become available. More vaccines are required to prevent infections caused by newly detected antibiotic-resistant bacteria, so that the overuse and misuse of antibiotics can also be controlled and prevented.

1.4.2 Policies and surveillance systems

Many factors affect the appropriate application of antibiotics, including demand from patients, competition from alternative health services systems, and financial incentives (Howard et al. 2013). Policy interventions and surveillance systems are vital to improving the public's understanding of ABR (Behdinan et al. 2015; Hoffman and Outterson 2015). Thus, inadequate policies, regulations, and guidelines at the national and global levels increase the risk of ABR, from development to production to sale and prescription to usage and application (Hoffman et al. 2015; Rizvi and Hoffman 2015).

In 1998, the United Kingdom Department of Health and Social Care released a governmental action plan for addressing the problem of AMR (Department of Health and Social Care 1998). The European Antimicrobial Resistance Surveillance System (EARSS) was established in the same year and involved 30 of EU countries and European Economic Area countries (European Centre for Disease Prevention and Control 2019a). In 2010, EARSS was renamed the European Antimicrobial Resistance Surveillance Network" (EARS-Net) (European Centre for Disease Prevention and Control 2019a). In 2014, the U.S. released a national strategy for combating antibiotic-resistant bacteria with the goal of reducing the national and international threat of ABR while working with domestic and international partners (Centers for Disease Control and Prevention 2014). The prevalence of ABR has been controlled since the establishment of these surveillance systems and policies (Centers for Disease Control and Prevention 2019; European Centre for Disease Prevention and Control 2019a). Additionally, Germany has developed national stewardship programs and policies to address drug resistance in both the human and animal sector (Cecchini et al. 2015; Federal Government of Germany 2017; Kickbusch et al. 2017).

Respect for surveillance, sufficient financial backing, standardization, and coordination are long-term missing elements for a globally efficient surveillance system (Podolsky 2018). In 2001, the WHO released the "Global Strategy for Containment of Antimicrobial Resistance" (World Health Organization 2001). In this strategy, the terminology shifted from “antibiotic” to “antimicrobial”, emphasizing the effects of antimicrobial resistance more broadly from direct health effects to economic and national security implications (World Health Organization 2001). The WHO has involved its member states in a Global AMR Surveillance

System (GLASS), with the flow of surveillance information shown in figure 5 (World Health Organization 2015d). Clinicians at participating healthcare facilities send primary data (samples for culture) to the laboratory serving the surveillance site, while susceptibility tests of the samples are usually performed locally (or sent to a reference laboratory). When participating surveillance sites enter data into the data management software, resistance data are collected and managed at a national level, then reported to the WHO and worldwide.

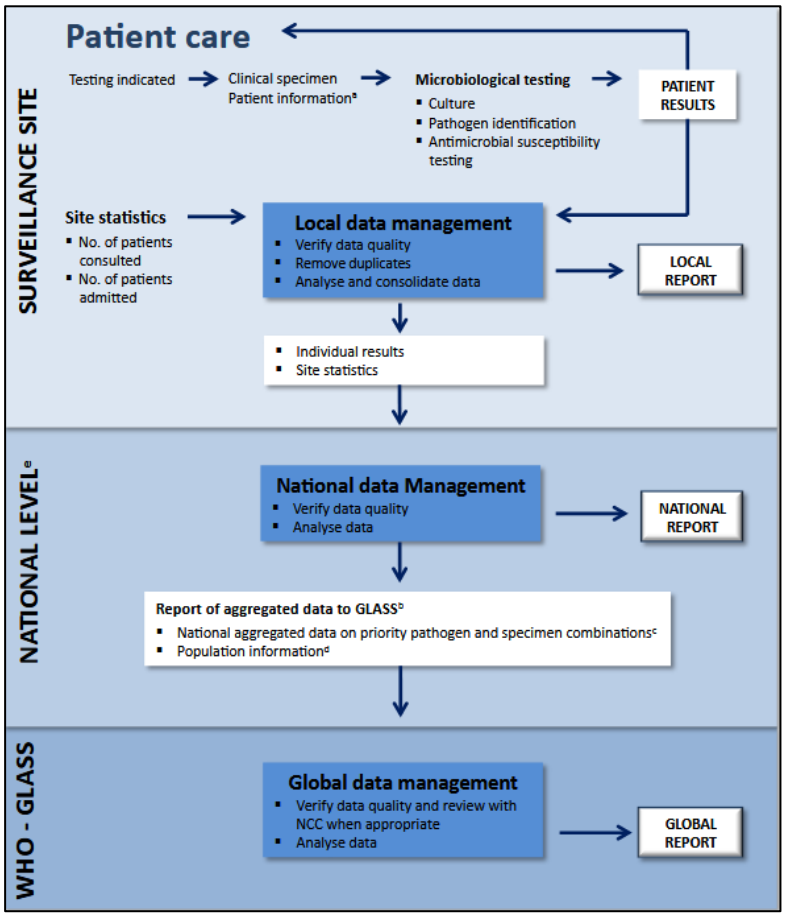

Figure 5: Schematic view of the AMR information flow (World Health Organization 2015d)

a: Clinical patient information includes the basic demographics like age, date of birth, gender, specimen type, date of specimen collection, hospital or community origin, use of antimicrobial agents; b: Structure for reporting aggregated data at country level is given by GLASS and collected from participating countries; c: Priority pathogen-specimen combinations are listed by GLASS; d: Population information includes national population, patient population over 12 months in total and the numbers of patients with isolation per specimen type and the susceptibility of these cultured pathogens; e: National level includes the national surveillance coordinating center and the national reference laboratories.

One of the aims of GLASS is to promote consistent global standards for country-level surveillance systems (World Health Organization 2015d). However, so far, less than a third of the WHO's member states are participating in the GLASS program (Podolsky 2018). Additionally, technical and data limitations of this program have been reported. Differences exist between various national surveillance systems, and these have led to substantial variability in data submission and quality (World Health Organization 2018c). The varied capabilities of different countries to structure and run their surveillance systems has impacted the surveillance data quality. These capabilities are linked to access to and use of laboratory diagnostics, personnel training, availability of detection resources, and national infrastructure (World Health Organization 2018c). Hence, the gap in the continuous flow of information gathering and real-time analysis of the surveillance data remains one of the challenges to the GLASS surveillance system (World Health Organization 2018c).

ABR is a major global challenge (Aslam et al. 2018). With widespread world travel and global economic activities, infectious disease agents such as resistant microbes, could be transmitted

across borders and pose a transnational health risk (Klein et al. 2018). Hence, ABR can only be properly addressed on a global level. In line with increasing calls for global collective action, ABR and AMR are receiving more political attention (Laxminarayan et al. 2020; Rahimi 2019). For example, Germany has been reported as a leader in global health, particularly AMR. When Germany hosted the G7 and G20 meetings in 2015 and 2017, respectively, AMR was among the top-priority agenda points. Particularly, in the 2017 meeting of G20 health ministers, AMR was one of the three main discussed topics (Cecchini et al. 2015; Federal Government of Germany 2017; Kickbusch et al. 2017). Global policies with legally binding and enforceable commitments are already proposed (Behdinan et al. 2015; Hoffman and Outterson 2015; Hoffman et al. 2015).

1.5 Problem statement

Risk factors such as misuse and overuse of antibiotics are associated with ABR worldwide. Many of these factors relate to the healthcare setting, including over-consumption and inappropriate use of antibiotics. Between increases in drug resistance among pathogens and high rates of HAIs driven by incompletely trained public health workers, China's healthcare system still faces many challenges to fighting ABR (Yezli and Li 2012).

1.5.1 Study purpose

The main aim of this study is to contribute to a better understanding of healthcare-associated risk factors for ABR in China. The specific objectives are:

1) To identify modifiable healthcare-associated risk factors for ABR in China.
2) To assess the challenges for China in the management and control of ABR in healthcare sectors.
3) To address potential solutions for these challenges.

2 METHODOLOGY

2.1 Definitions

In this thesis, a bacterial species is defined as “a distinct organism with certain characteristic features, or a group of organisms that resemble one another closely in the most important features of their organization” (Baron 1996a). Above the species level, a genus is defined as “a group of related species” (Baron 1996a). Genera is the plural form of genus. A family is a group of related genera (Baron 1996a). Bacteria could be classified on the basis of biochemical characteristics. For example, the Gram stain is a traditional test used to identify bacteria by the composition of their cell walls. Thus, bacteria are quickly classified into two broad categories according to the structure of their cell walls. Gram-positive (GP) bacteria are bacteria that give a positive result (retain the color of the crystal violet stain) to the Gram stain test (Baron 1996b). Gram-negative (GN) bacteria are bacteria do not retain the crystal violet stain from the Gram stain test (Baron 1996b).

Additionally, antibiotic susceptibility test (AST) is defined as tests that specify the susceptibility of organisms to antibiotics (Khan et al. 2019). Minimum inhibitory concentrations of various AST are categorized by various international agencies as guidelines that determine whether an antibiotic is susceptible or not (Khan et al. 2019). For example, the Clinical and Laboratory Standards Institute provides the most popular guidelines, and disk diffusion method is the gold standard of AST (Khan et al. 2019). ABR refers to the bacteria

have become resistant to the antibiotics designed to kill them (Centers for Disease Control and Prevention 2018). When ABR occurs, antibiotic-resistant bacteria will not be killed by antibiotics and will continue to grow.

2.2 Study design and setting

This study aimed to systematically review research on ABR in humans and the related healthcare-associated risk factors in mainland China. A systematic review refers to "a literature review associated with a clearly formulated research question that uses systematic explicit methods to identify, select, and critically appraise relevant research from previously published studies related to the question at hand" (The Cochrane Collaboration 2005). Relevant reports from primary research were selected and included, and data from those studies were extracted and synthesized.

2.3 Search strategy

Literature was searched through Cochrane Library (CENTRAL), PubMed, The China National Knowledge Infrastructure (CNKI), Wanfang, and VIP. By using English search terms, English publications were searched from online databases including Cochrane Library (CENTRAL)

and PubMed. Chinese publications were searched from online databases including The China National Knowledge Infrastructure (CNKI), Wanfang and VIP, by using Chinese search terms.

The search terms were defined and included controlled vocabulary (Medical Subject Headings [MeSH]). Mesh terms are identified as labels assigned to each article in Medline in order to describe what the article is about (Baumann 2016). A detailed overview of the search strategy can be found in table 3.

Table 3: Detailed overview of the search strategy

Database	**Languages**	**Search terms**	**# of Hits**
PubMed	English	**Drug resistance, antimicrobial*[2]**	215
CENTRAL		Drug Resistance, Microbial [MeSH] OR Drug Resistances, Microbial [MeSH] OR Antimicrobial Drug Resistance [MeSH] OR Drug Resistances [MeSH] OR Antibiotic Resistance, Microbial [MeSH] OR Antibiotic Resistance [MeSH] OR Resistance, Antibiotic[MeSH] **Risk factors*** (Risk Factors [MeSH] OR Factor, Risk [MeSH] OR Factors, Risk [MeSH] OR Risk Factor [MeSH] OR Population at Risk [MeSH] OR Risk, Population at	3

		[MeSH] OR Populations at Risk [MeSH] OR Risk, Populations at [MeSH]))	
CNKI	Chinese	((主题: (抗生素耐药) OR : (细菌耐药)) AND (主题: (危险因子) OR : (风险因素)))	302
VIP		((Subject: (antibiotic resistance) OR Subject:(bacteria resistant)) AND (Subject:(risk factors) OR Subject:(factors, risk)))	48
WANFANG			1411
Total	**Total**	**Total**	**1979**

2.4 Selection criteria

All published literature including Chinese and English language about ABR in China between January 1, 2003, and June 30, 2019, were systematically reviewed.

Only publications containing original data focusing on ABR among patients in hospital settings were included. Reviews, opinion papers, commentaries, communications, theses, and conference reports were excluded as well as studies that did not focus on humans. Articles about viral, parasite and fungal drug resistance were also excluded. There was no exclusion criteria regarding study methodology.

2.5 Quality assessment

The quality assessment of the selected studies was done according to the Methodological Index for Non-Randomized Studies (MINORS) (Slim et al. 2003). Accordingly, twelve methodological domains were evaluated: *aim stated clearly*, *inclusion of consecutive patients*, *prospective collection of data*, *endpoints appropriate to the aim of the study*, *unbiased assessment of the study endpoint*, *follow-up period appropriate to the aim of the study*, *loss to follow up less than 5%*, *prospective calculation of the study size*, *an adequate control group*, *contemporary groups*, *baseline equivalence of groups*, and *adequate statistical analyses*. Each domain was scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). A category "not applicable" was added in case the domain was not applicable to the respective study design. The risk of bias assessment of included literature was conducted by usage of Review Manager (Version 5.3, Copenhagen, Denmark, for Windows). It was performed by QC with a random sample of paper assessments rechecked by two colleagues (Duguang Li from General Surgery Department of Sir Run Run Shao Hospital (DL, Chinese papers) and Claudia Beiersmann from Heidelberg Institute of Global Health (CB, English papers)). Any disagreement was resolved through discussion.

2.6 Data extraction and analysis

All publications generated from the search strategy were carefully screened and read by the PhD candidate. Independently, they were also screened by DL. A random sample was rechecked by Guangyu Lu (GL, from Preventive Medicine Department of Yangzhou University). Disagreements were resolved through joint discussion. The study selection process followed the "Preferred Reoprting Items for Systematic Review and Meta Analysis" (PRISMA) guidelines and is shown in the PRISMA flow diagram (figure 6) (Liberati et al. 2009).

Articles meeting the selection criteria were included in the analysis. Search results were collected and de-duplicated in EndNote (Version X9, Philadelphia, USA, for Windows & Mac). A data extraction table was developed in Microsoft Excel (Version 2016, Washington, USA, for Windows), the results analyzed and described accordingly. 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 summarized. The figure for the result of study regions (figure 7) was drawn with the use of Scalable Vector Graphics (Version 1.1 Second Edition, Cambridge, USA, for Windows).

The study was conducted on data from the mainland of People's Republic of China, including twenty-two provinces, five autonomous administrative regions and four direct-controlled municipalities. In this study, six different statistical regions were divided from the mainland of

China: North China, Northeast China, East China, South central China, Southwest China and Northwest China. The list of 31 provincial-level divisions of the country are grouped in table 4 as follows.

Table 4: Study regions of 31 provincial-level divisions of mainland China

Statistical region	Provinces/Regions
North	Beijing, Tianjin, Hebei, Shanxi, Inner Mongolia
Northeast	Liaoning, Jilin, Heilongjiang
East	Shanghai, Jiangsu, Zhejiang, Anhui, Fujian, Jiangxi, Shandong
South Central	Henan, Hubei, Hunan, Guangdong, Guangxi, Hainan
Southwest	Chongqing, Sichuan, Guizhou, Yunnan, Tibet
Northwest	Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang

We summarized risk factors that were identified by the included papers as significant (p-values less than 0.05 among univariate or multivariate analyses) into four domains: socio-demographics (1), patient clinical information (2), admission in healthcare settings (3), and drug exposure (4). Reported socio-demographic risk factors include age, sex, education level, patient residence (local or migrant), and annual income. Risk factors subsumed in the category patient clinical information include assessments for severity of underlying disease (i.e. high scores in certain clinical assessments performed - for a detailed list of the assessments see Appendix 4), laboratory test results (e.g. hemoglobin level, Tb sputum smear-positivity, vitamin D level, drug susceptibility of bacteria), and underlying diseases (non-communicable diseases (NCDs), infectious diseases (IDs), and other underlying conditions). Admission in healthcare settings risk factors include previous and current hospital stay, the type of hospital facility (e.g. general department or ICU), length of hospital stay, surgery and other invasive procedures. Drug exposure risk factors include the risks of prior and current medications (in particular antibiotics but also other drugs), monotherapy (refers to using a single medication to treat a disease) and combination therapy (refers to using multiple medications to treat a single disease), and longer duration of treatment/drug exposure. Prior medication refers to the medication history of the investigated patients within the past three months, such as the prescription from clinical staff before having been transferred to another hospital or clinical department, or the self-medication by patients.

3 RESULTS

3.1 Study selection process

3.1.1 Search results

A total of 1,979 records were identified, including 218 records from English online databases and 1,761 records from Chinese online databases (table 3, figure 6). Two hundred and fifty-three duplications were removed. With the reason of denoted by Endnote (Version X9, Philadelphia, USA, for Windows & Mac) being theses and conference papers, 16 records were removed.

3.1.2 Excluded studies

Records that did not pass the quality check for Chinese literature were also removed during the study selection process (n=1,039), including 490 papers from the journals that are on only one of the three core academic journal lists, and 549 papers from the journals that are on none of the three lists. Hence a total of 457 records (in Chinese) passed the quality check (figure 6). A total of 671 records were left for title/abstract screening. During title/abstract screening a total of 484 records were excluded. Hence 187 articles were included in full-text screening (figure

6). During full-text screening, 11 articles were excluded for the following reasons: eight articles were excluded because they were not related to the research question, three studies were removed because they were conference files. The process of the selection of studies is shown in the PRISMA flow diagram (figure 6) (Liberati et al. 2009).

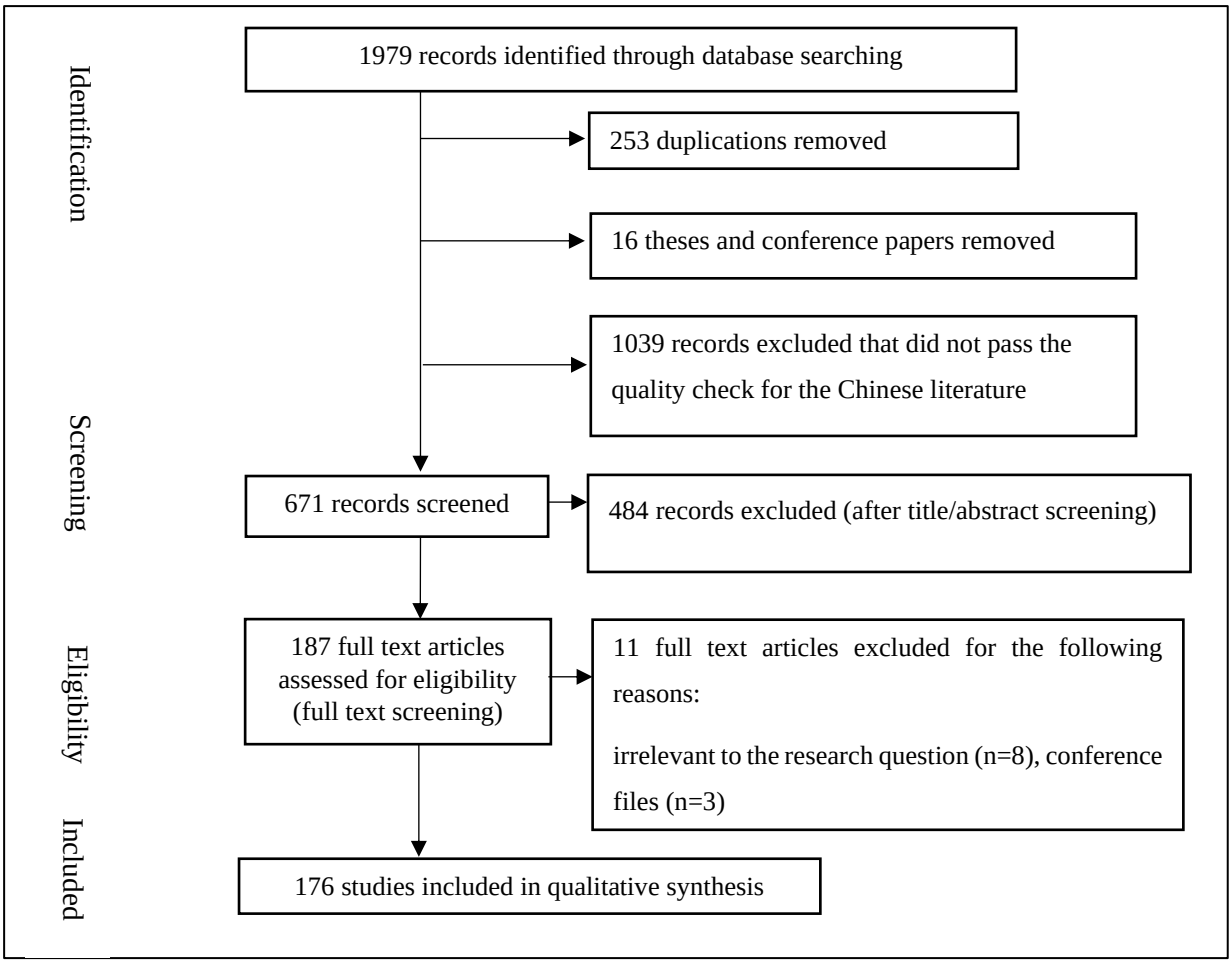

Figure 6: Process of study selection for systematic review based on PRISMA flow diagram (Liberati et al. 2009)

3.1.3 Included studies

A total of 176 studies were included in the review for data extraction and qualitative synthesis. Annex 1 presents a full list of included papers. Among these included papers, 60/176 (34.1%) papers are English publication, 106/176 (60.2%) papers are Chinese publication with English title and abstract, and 10/176 (5.7%) are only available in Chinese.

Regarding study design, 125/176 (71.0%) were case-control studies, 28/176 (15.9%) were cohort studies (21/176 (11.9%) retrospective cohort studies and 7/176 (4.0%) prospective cohort studies), 17/176 (9.7%) were cross-sectional studies. There were 1/176 (0.6%) case report and 4/176 (2.3%) case series. One study (0.6%) was a clinical trial. Table 5 provides the information about the included studies in more detail. While 122/176 (69.3%) studies used univariate analysis to analyze risk factors, multivariate analysis was used in 114/176 (64.8%) studies.

Table 5: 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%)
	Case report		1 (0.6%)
	Clinical trial*		1 (0.6%)
Healthcare setting	General hospital		140 (79.5%)
	Specialty hospital	Cancer hospital	2 (1.1%)
		Children's hospital	4 (2.3%)
		Chinese medical hospital	2 (1.1%)
		Eye, ear, nose and throat hospital	1 (0.6%)
		Geriatric hospital	1 (0.6%)
		Maternity and child health hospital	1 (0.6%)

	Metabolic disease hospital	2 (1.1%)
	Pulmonary hospital	1 (0.6%)
	Sexually transmitted infection and skin disease hospital	1 (0.6%)
	Tuberculosis (TB) hospital	20 (11.4%)
	Woman and children's hospital	1 (0.6%)
General information		
	Total participants	53,056
	Sex (Male/Female)	23,762/13,062
	Participants with ABR	17,083
	Total isolates	63,075
	Resistant isolates	26,383

*evaluation of treatment outcomes in adults with smear-positive TB and discordant rifampicin resistance results

3.2 Study regions

Studies took place in all 31 provinces of the mainland China. Apart from the 168 studies included in figure 7, five studies (5/176, 2.8%) targeted the occurrence of ABR in the whole of mainland China, two studies (2/176, 1.1%) were conducted in the East as well as Southwest Region, and one study (1/176, 0.6%) focused on a total of six provinces covering north, northeast, east, south-central and southwest regions of China.

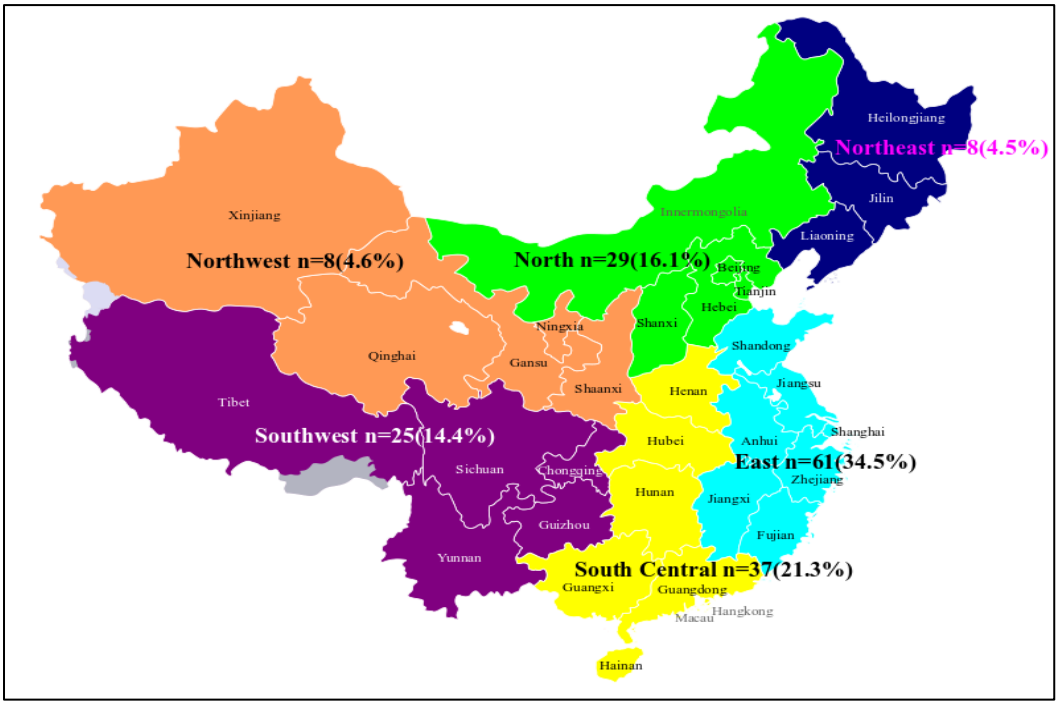

Figure 7: Geographical distribution of included studies (adapted from Wikimedia Commons contributors) (Wikimedia Commons contributors 2013)

3.3 Characteristics of antibiotic-resistant bacteria

Of the 176 included papers, 159 (159/176, 90.3%) reported to have been studying either drug resistant (DR) bacteria (n=64, 36.4%), MDR bacteria (n=87, 49.4%), XDR bacteria (n=3, 1.7%), or PDR (n=5, 2.8%). Of the remaining 17 papers, 14/176 (8.0%) papers reported both DR and MDR pathogens, 2/176 (0.7%) papers reported both MDR and XDR bacteria, and 1/176 (0.6%) paper reported both MDR and PDR.

An overview of the bacteria species as reported in the papers is given in table 6. Regarding bacteria type, 107/176 (60.8%) papers explored one type of bacteria species only. 69/176 (39.2%) papers report more than one bacteria species. Additionally, 43/176 (24.4%) studies mentioned investigating extended-spectrum beta-lactamases producing organisms.

Table 6: Investigated antibiotic-resistant species as reported by papers

Genus	Species	No. of papers
Klebsiella		**77 (43.8%)**
	Klebsiella pneumoniae	68 (38.6%)
	Other *Klebsiella species*	9 (5.4%)
Staphylococcus		**73 (41.5%)**

Genus	Species	No. of papers
	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.**	14 (8.0%)
	Enterobacter aerogenes	7 (15.91%)
	Other *Enterobacter species*	1 (0.6%)
Enterococcus		**36 (20.5%)**
	*Enterococcus**	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%)**

Genus	Species	No. of papers
Streptococcus		**9 (5.1%)**
	*Streptococcus**	5 (2.8)
	Streptococcus pneumoniae	4 (2.3)
Others		**32 (18.2%)**

*no more detail given by the paper

Some papers offered information about studied bacteria only at a broader level, reporting the studied bacteria genus only without the exact species (e.g. *Streptococcus*) or reporting the studied bacteria as *spp.* (Latin: species plurals), which denotes the investigation of more than one bacteria species, however not defined in more detail by the paper – as for example *Enterobacter* species(*spp.).* More gram-negative antibiotic-resistant bacteria were reported by papers than gram-positive antibiotic-resistant bacteria.

3.4 Characteristics of affected antibiotics

Regarding to the identified antibiotics with resistance, 129/176 (73.3%) papers reported results of antibiotic susceptibility tests of the investigated organisms, while 47/176 (26.7%) papers did not report such data. Antibiotic susceptibility was determined by different test methods and interpreted according to the guidelines systematically.

Among these 129 papers, a total of 87 antibiotics were identified as antibiotics with resistance. An overview of tested antibiotics as reported in the papers is given in Table 7. According to existing knowledge (Wanger et al. 2017), these reported antibiotics were classified into 11 classes including beta-lactams, quinolones/fluoroquinolones, aminoglycosides, penicillin combinations, monobactams, sulfonamides, antituberculosis, tetracyclines, macrolides, nitrofurans, and lincosamides. Table 7 describes the main characteristics of the identified resistant-antibiotics from the data of those 129 papers. Classes of resistant-antibiotics identified by less than 5.0% of the 129 papers such as for example glycopeptides and others are listed in annex 2.

With regard to classes of antibiotics as reported with resistance, the beta-lactams class was reported most frequently. Within this class, five families including carbapenems and four generations of cephalosporins were reported. Seven papers reported resistance of carbapenems without specifying the generic names of the antibiotics.

Regarding the genera of antibiotics as reported with resistance, ceftazidime and ciprofloxacin were reported in most of the included papers (64/129, 49.6% for each one). Amikacin and gentamicin were identified as resistant by a slightly lower number of papers (59/129, 45.7% for each one).

Table 7: Identified antibiotics with resistance as reported by papers*

Class	Family	Agent	No. of papers
Aminoglycosides		Amikacin	59 (45.7%)
		Gentamicin	59 (45.7%)
		Tobramycin	27 (20.9%)
		Streptomycin	11 (8.5%)
Antituberculosis		Rifampicin	23 (18.8%)
		Isoniazid	16 (12.4%)
		Ethambutol	10 (7.8%)
Beta-lactams	Carbapenems	Imipenem	57 (44.2%)
		Meropenem	35 (27.1)
		Ertapenem	9 (7.0%)
		Not reported specifically	7 (5.4%)
	Cephalosporins (1^{st} generation)	Cefazolin	24 (18.6%)
		Cephalothin	7 (5.4%)
	Cephalosporins (2^{nd} generation)	Cefoxitin	16 (12.4%)

		Cefuroxime	13 (10.1%)
	Cephalosporins (3rd generation)	Ceftazidime	64 (49.6%)
		Ceftriaxone	40 (31.0%)
		Cefoperazone/Sulbactam	29 (22.5%)
		Cefotaxime	28 (21.7%)
		Cefoperazone	13 (10.1%)
	Cephalosporins (4th generation)	Cefepime	48 (37.2%)
Lincosamides		Clindamycin	12 (9.3%)
Macrolides		Erythromycin	14 (10.9%)
Monobactams		Aztreonam	37 (28.7%)
Nitrofurans		Nitrofurantoin	13 (10.1%)
Penicillin combinations		Piperacillin/Tazobactam	52 (40.3%)
		Ampicillin/Sulbactam	27 (20.9%)
		Amoxicillin/Clavulanate	12 (9.3%)
Quinolones/Fluoroquinolones		Ciprofloxacin	64 (49.6%)
		Levofloxacin	50 (38.8%)

	Ofloxacin	8 (6.2%)
Sulfonamides	Trimethoprim-Sulfamethoxazole	33 (25.6%)
	Sulfamethoxazole	22 (17.1%)
Tetracyclines	Tetracycline	16 (12.5%)

*Antibiotics are reported as mentioned in the papers (No.=number of papers). Because some papers reported multiple susceptibility results for multiple antibiotics, the individual rows will add up to more than 100%.

3.5 Risk factors

Applying the risk categories used by Chatterjee et al (REF), we identified 62/176 (35.2%) papers with significant risk factors from univariate analyses, 60/176 (34.1%) papers with significant risk factors using multivariate analyses, and 54/176 (30.7%) papers reporting both univariate and multivariate results.

3.5.1 Risk factors reported by univariate analyses

Risk factors were summarized into four categories: socio-demographics (1), patient clinical information (2), admission in healthcare settings (3), and drug exposure (4). An overview of the risk factors reported by the 122 studies analyzed through univariate analysis is given in figure 8. Only risk factors showing a significant effect ($p < 0.05$) were included. The percentages shown in the figure provide the proportions of papers having reported significant effects of respective risk factor categories, and frequently more than one significant effect occurred in the individual studies (i.e. adding up to more than 100%).

Reported **socio-demographic risk factors** (1) were mentioned in 31.1% of the papers, with age (either very young/newborns or older age) being the prominent risk factor (27.9%), follow by sex (male or female), patient residence (local or migrant), education level (high school or college), and annual income.

Risk factors concerned with **patient clinical information** (2) was reported as risk factor by 67.2% of papers, with underlying diseases having been the most cited risk factor (63.9%), then with the assessment for severity of underlying disease by 20.5% of papers, such as Acute Physiology and Chronic Health Evaluation II score (APCHE II), Encephalopathy grade, modified Medical Research Council (mMRC) dyspnea scores, High-resolution Computed Tomography (HRCT) score, New York Heart Association (NYHA) classification, Pitt Bacteremia score, Wagner classification, and sequential organ failure assessment (SOFA) scores, and with abnormal laboratory test results by 20.5% of papers (including regular tests - such as e.g. on hemoglobin, sputum smear-positivity, serum albumin - and drug susceptibility).

Factors concerned with **admission to healthcare settings** (3) was found to be a risk factor in 81.1% of papers, reporting previous and current hospital stay (64.8%), general department and ICU hospital stay, length of stay, invasive procedures (65.6%), and surgery (9.8%).

Reported **drug exposure** (4) was found to be of equal importance as the risk factor of admission in healthcare settings, including information on prior and current medications, concerning therapies antibiotics and other drugs.

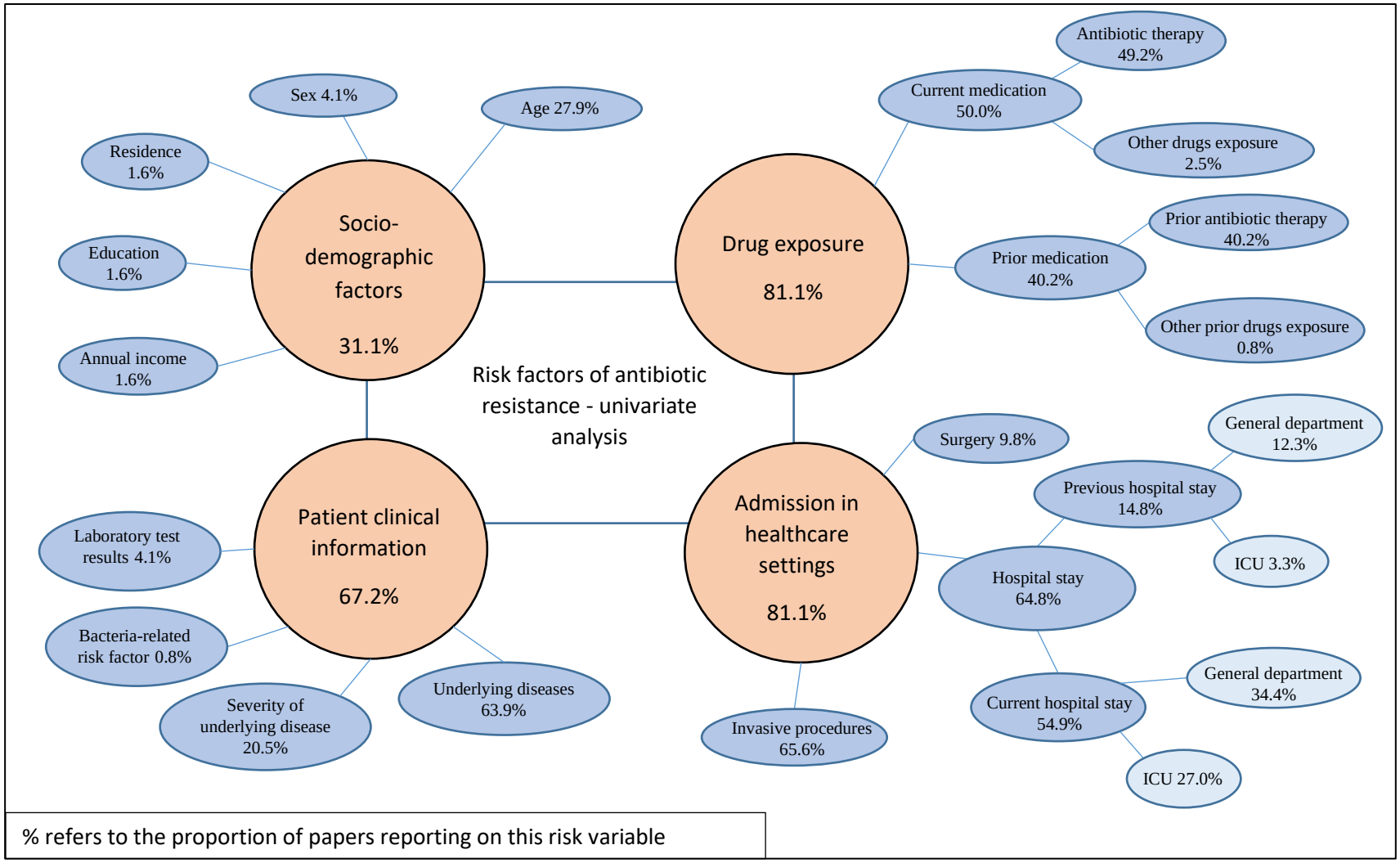

Figure 8: Significant healthcare sector associated risk factors from univariate analyses (n=122)

3.5.2 Risk factors reported by multivariate analyses

Risk factors from papers reporting on multivariate analyses (n=114) were summarized into the same four broad risk categories. To analyze the strength of the reported evidence, ORs showing significant effects were summarized into ten different ranges, adopted from Chatterjee et al. (Chatterjee et al. 2018) (see tables 8 and 9). The ORs were mainly reported to be between 1 and 5. In the four risk categories, the following factors were identified as important independent risk factors for ABR.

Regarding **socio-demographics**, 5/114 (4.4%) papers reported older age as significant risk factor to ABR. Three papers (3/114, 2.6%) referred to annual income as one of the contributing factors to ABR, with one paper (1/3, 33.3%) not specifying the income and two papers (2/3, 66.7%) identifying lower/higher income (less than 10,000/more than 20,000 Chinese Yuan per year) as a risk factor. Regarding residence, migration/a floating population and living in an urban area were cited as risk factors for ABR.

Regarding **patient clinical information**, higher scores in the physical assessments denoting less health (e.g. functional status score in APACHE II over 20 points or Encephalopathy grade higher than II) contribute to the infection of ABR. Regarding laboratory test results, ORs range mainly between 1 and 8. Here, 5/114 (4.4%) papers reported abnormal results of regular tests (e.g. on blood glucose, hemoglobin, sputum smear, and serum albumin) contribute as a risk

factor. Seven papers (7/114, 6.1%) recognized characteristics of infected pathogens could contribute as risk factors to ABR. Some bacteria tested produce extended-spectrum beta-lactamase which is a hint that the pathogen had developed and spread multidrug resistance. Annex 3 describes such information and refers to the severity of underlying diseases and abnormal laboratory test results in more detail. Regarding underlying diseases, infections (including osteomyelitis, pneumonia, tuberculosis and other infections), non-communicable diseases (including chronic respiratory diseases, diabetes, cardiovascular diseases, malignancies), and other specific underlying diseases (for example, injuries) were identified as risk factors contributing to ABR.

Regarding **admission in healthcare settings**, factors like hospital stay, invasive procedures, and surgery/operations were reported by the papers as significant risk factors. Papers reported on current and previous hospital stays, distinguishing general departments and ICUs. Most ORs in current hospital stay range between 1 and 7, while in previous hospital stay range mostly from 1 to 9. Some papers reported the specific length of stay and here OR range mainly from 1 to 7. A longer stay is reported to be a significant risk factor, starting from a stay longer than seven days, fourteen days, up to 30 days. Regarding the current hospital stay, the length of stay in general department was identified as a major risk factor by 15/114 (13.2%) papers. Among these 15 papers, 1/15 (6.7%) paper specified the length of hospital stay as at least 7 days, 5/15 (33.3%) papers specified the length as more than 14 days, 2/15 (13.3%) papers specified the length as more than 19 days, 3/15 (20.0%) papers specified the length as more than 28 days, and 4/15 (26.7%) papers did not specify the length of hospital stay. Additional, seven papers recognized surgery as a risk factor, with most ORs range from 2 to 7.

Invasive procedures describe five groups as where they were carried out in the human body system (respiratory tract, urinary tract, circulatory system, digestive tract and other tract/system). Invasive procedures on the respiratory tract are most often found to be a risk factor, including procedures like sputum aspiration and oxygen inhalation. Circulatory system invasive procedure includes continuous renal replacement therapy (CRTT), peripherally inserted central catheter (PICC) and arteriovenous catheterization. The OR ranges here mainly distribute between 2 and 9. Additionally, 11 papers (27.5%) report the length of procedure as a risk factor (duration longer than two days, OR range between 1 and 7).

Papers reporting on **drug exposure** reported on current and prior medication, with an exposure to antibiotics and other drugs. OR ranges mainly between 1 and 10. Papers reported also on whether the drugs were combined or uncombined, as well as the duration of treatment. Antibiotics exposure were recognized as risk factor both in the current medication and prior medication. Even more papers reported prior antibiotics exposure as a risk factor. OR of the current medication ranges mainly from 1 to 7, while of the prior medication ranges mainly from 1 to 10. Regarding the duration of antibiotic therapy in the sub-category of current medication, 1/12 (8.3%) paper specified the length of therapy as more than 3 days, another one paper (1/12, 8.3%) specified the length as more than 5 days, 2/12 (16.7%) papers specified the length as more than 10 days, 1/12 (8.3%) paper specified the length as more than 14 days, and 3/12 (25.0%) papers did not specify the length of antibiotic therapy in the current medication. Among the 5 papers reported duration of antibiotic therapy in the sub-category of prior medication, 1/5 (20.0%) paper specified the duration as more than 3 days, while 4/5 (80.0%) papers did not

specify the days of prior antibiotic therapy. Furthermore, the papers reporting other drug exposure did not list the drug specifically.

Table 8: OR ranges reported by risk factor domain 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
Socio-demographic factors										
Age (n=5)	5 (62.5%)	3 (37.5%)	1 (12.5%)	1 (12.5%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5%)	0 (0)
Sex (n=5) Male (n=3)	2 (66.7%)	1 (33.3%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Female (n=2)	1 (50.5%)	1 (50.0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Education (n=1)	1 (100.0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Residence (n=3)	1 (33.3%)	1 (33.3%)	0 (0)	1 (33.3%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Annual income (n=3)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient clinical information										
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)

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
Laboratory test results (n=5)		2 (40.0%)	2 (40.0%)	0 (0)	0 (0)	0 (0)	1 (20.0%)	0 (0)	0 (0)	0 (0)	0 (0)
Underlying diseases (n=38)	NCDs****** (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											
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%)
Current hospital stay (n=31)		12 (38.7%)	4 (12.9%)	3 (9.7%)	5 (16.1%)	4 (12.8%)	3 (9.7%)	0 (0)	0 (0)	1 (3.2%)	4 (12.9%)
General department (n=17)		8 (47.1%)	2 (11.8%)	1 (5.9%)	3 (17.6%)	2 (11.8%)	2 (11.8%)	0 (0)	0 (0)	1 (5.9%)	1 (5.9%)

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
Length of stay (n=15)		8 (53.3%)	0 (0)	1 (6.7%)	2 (13.3%)	1 (6.7%)	2 (13.3%)	0 (0)	0 (0)	1 (6.7%)	0 (0)
ICU (n=15)		4 (26.7%)	2 (13.3%)	2 (13.3%)	2 (13.3)	2 (13.3%)	1 (6.7%)	0 (0)	0 (0)	0 (0)	3 (20.0%)
Length of stay (n=7)		3 (37.5%)	1 (12.5%)	0 (0)	2 (25.0%)	1 (12.5%)	1 (12.5%)	0 (0)	0 (0)	0 (0)	0 (0)
Previous hospital stay (n=14)		3 (21.4%)	5 (35.7%)	6 (42.9%)	0 (0)	0 (0)	0 (0)	1 (7.1%)	1 (7.1%)	0 (0)	1 (7.1%)
General department (n=14)		3 (21.4%)	4 (28.6%)	6 (42.9%)	0 (0)	0 (0)	0 (0)	1 (7.1%)	1 (7.1%)	0 (0)	1 (7.1%)
Length of stay (n=2)		2 (100.0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ICU (n=1)		0 (0)	1 (100.0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Invasive procedures (n=48)	Respiratory system (n=25)	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%)
	Circulatory system (n=5)	1 (20.0%)	0 (0)	2 (40.0%)	1 (20.0%)	0 (0)	0 (0)	0 (0)	1 (20.0%)	2 (40.0%)	2 (40.0%)

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
	Urinary system (n=8)	0 (0)	2 (25.0%)	0 (0)	0 (0)	0 (0)	1 (12.5%)	2 (25.0%)	0 (0)	0 (0)	0 (0)
	Digestive system (n=3)	0 (0)	0 (0)	1 (33.3%)	0 (0)	0 (0)	2 (67.7%)	0 (0)	0 (0)	0 (0)	0 (0)
	Not clear (n=8)	0 (0)	1 (12.5%)	2 (25.0%)	2 (25.0%)	2 (25.0%)	0 (0)	1 (12.5%)	0 (0)	0 (0)	0 (0)
	Length of procedure (n=11)	2 (18.2%)	0 (0)	5 (45.5%)	0 (0)	0 (0)	2 (18.2%)	0 (0)	1 (9.1%)	0 (0)	1 (9.1%)
Surgery (n=3)		0 (0)	1 (33.3%)	0 (0)	0 (0)	0 (0)	2 (66.7%)	0 (0)	0 (0)	0 (0)	1 (33.3%)
Drug exposure											
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%)
Antibiotics exposure (n=32)	Monotherapy (n=20)	5 (25.0%)	3 (15.0%)	5 (25.0%)	4 (20.0%)	0 (0)	2 (10.0%)	0 (0)	1 (5.0%)	0 (0)	5 (25.0%)
	Longer duration (n=12)	3 (25.0%)	3 (25.0%)	3 (25.0%)	1 (8.3%)	0 (0)	`1 (8.3%)	0 (0)	0 (0)	0 (0)	3 (25.0%)

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
	Combination therapy (n=7)	3 (42.9%)	2 (28.6%)	0 (0)	1 (14.3%)	0 (0)	1 (14.3%)	0 (0)	0 (0)	0 (0)	1 (14.3%)
Other drugs exposure (n=2)		0 (0)	1 (50.0%)	1 (50.0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Prior medication* (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%)
Antibiotics exposure*** (n=57)	Monotherapy (n=51)	8 (15.7%)	9 (17.7%)	7 (13.7%)	8 (15.7%)	8 (15.7%)	8 (15.7%)	2 (3.9%)	5 (9.8%)	3 (5.9%)	14 (27.5%)
	Longer duration (n=5)	2 (40.0%)	1 (20.0%)	0 (0)	2 (40.0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Combination therapy (n=10)	1 (10.0%)	2 (20.0%)	1 (10.0%)	4 (40.0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20.0%)

*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 will add up to more than 100%.

**Abbreviations: Non-communicable disease (NCD), Infectious Diseases, (ID).

***Prior medication refers to the medication history of the investigated patients within the past three months, such as the prescription from clinical workers before they transferred from another hospital or clinical department, or the self-medication by patients.

****Papers only referred to antibiotic exposure (not to any other type of medication).

Table 9 describes the OR distribution for drug classes used during antibiotic monotherapies in current and prior medication, identified in the multivariate analyses as risk factors. Unfortunately, none of the included papers specifies any detail for combination therapies. The ORs of mono-antibiotics exposure at current medication are mainly between 1 and 5, while the ones at prior medication are mainly between 1 and 9. The drug classes carbapenems and cephalosporins were reported as risk factors in a considerable number of papers both regarding current medication and prior medication.

Other antibiotic exposures in the current antibiotic monotherapies include for example beta-lactamase inhibitor, fluoroquinolones, piperacillin, tazobactam, and imipenem with a distribution of ORs mainly ranging between 1 and 4. Other antibiotic exposures in the prior antibiotic monotherapies include imipenem, glycopeptides, fluoroquinolones, aminoglycoside, macrolides, and tigecycline with ORs mainly between 2 and 6.

Table 9: 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*										
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*										
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%)

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
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%)

*20/51 papers reported monotherapy in the current/prior medication as a significant risk factor in multivariate analyses (see table 8) respectively; among these, different and multiple drugs could have been in use – hence the numbers of the papers citing the specific drug adds up to more than 20/51.

3.6 Quality assessment

The quality assessment regarding risk of bias which was done according to MINORS (Slim et al., 2003) and performed with the software RevMan5 (see methods section) showed that studies were overall graded with low risk regarding most of the domains (see figure 9). High risk of bias was only found in 8 (4.5%) of the studies with regards to the domain of adequate statistical analyses and in 11 (6.3%) of studies with regards to the domain of the prospective calculation of the study size. The domains follow-up period appropriates 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".

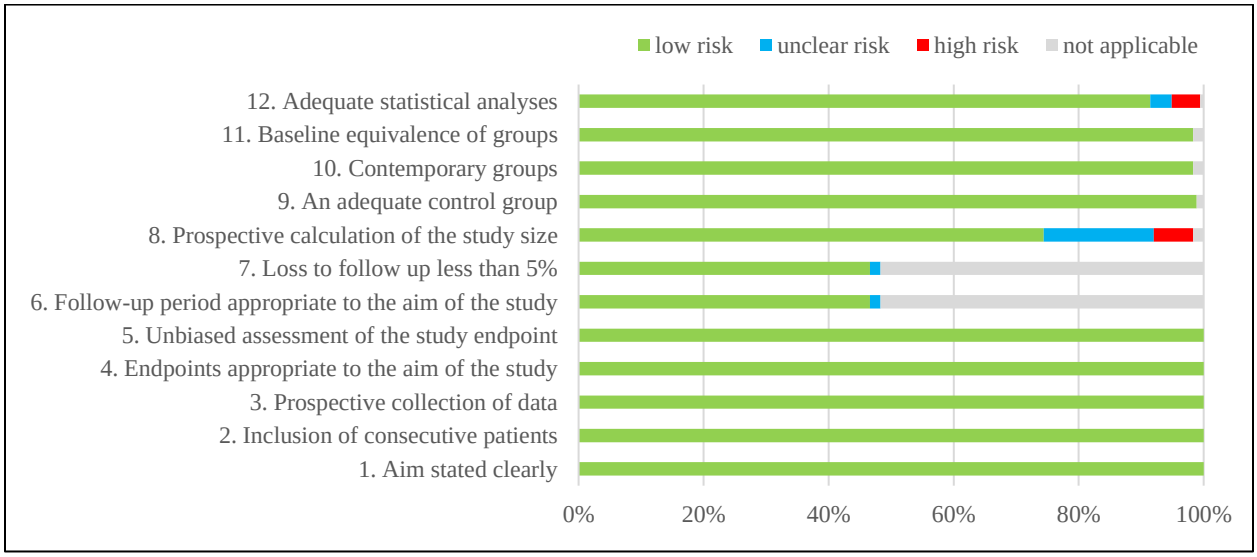

Figure 9: Study quality - Risk of bias assessment

4 DISCUSSION

4.1 Findings from the systematic review

This thesis addresses the driving factors associated with the emergence of antibiotic resistance that occurs in China's healthcare sector. It summarizes the information included in over 16 years of studies (in English and Chinese). The relevant contributing factors identified by the included papers encompass characteristics of admission to healthcare settings (e.g., current or previous hospital stay, underlying diseases, invasive procedures), patient clinical information (e.g., abnormal laboratory test results), socio-demographic factors (age), and drug exposure (e.g., current or prior medications).

4.1.1 Spatial distribution of antibiotic resistance in China

Of the 176 included papers, the majority focused on the eastern region (Jiangsu Province, Zhejiang Province, Anhui Province, Fujian Province, Jiangxi Province, Shandong Province, and Shanghai Municipality; 34.5% of the studies), the southcentral region (Henan Province, Hubei Province, Hunan Province, Guangdong Province, Guangxi Province, and Hainan Province; 21.3%)), and the northern region of China (Hebei Province, Shanxi Province, Inner Mongolia Province, Beijing Municipality, and Tianjin Municipality; 16.1%). Together, these areas were the

focus of 71.9% of the included studies. All other regions in China were represented by only 28.1% of the reported studies.

These three regions have the highest populations within China, as well as strong economic development, prominent agricultural economies, and high healthcare service densities (China Statistics Press 2020). Correspondingly, these regions also have higher prevalence of antimicrobial resistance according to the recent observations and national reports (China Antimicrobial Resistance Surveillance System 2019; Fang et al. 2018; Xiao et al. 2011). The prevalence of recognized bacterial ABR is higher in the eastern regions of China, followed by the northern and southcentral regions (Hu et al. 2018). This is in line with the tendency for the inappropriate consumption and overuse of antimicrobials in these regions (Hu et al. 2018; Xiao et al. 2011).

These findings correspond to those of other countries, such as India, where a high prevalence of AMR is reported in highly populated and productive regions (Qu et al. 2019; Yam et al. 2019). A European review argued that antibiotics were used with higher frequency in districts that have higher median family incomes and employment rates than other districts (Machowska and Stålsby Lundborg 2018).

4.1.2 Antibiotic-resistant bacteria

In general, antibiotic-resistant gram-negative bacteria have higher resistance profiles than antibiotic-resistant gram-positive bacteria. *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Acinetobacter baumannii*, and *Staphylococcus aureus* were the top five antibiotic-resistant pathogens identified in the included papers. *Staphylococcus aureus* is a GP organism, while the other four are GN bacteria. These identified organisms are comparable with those in China's national surveillance report (China Antimicrobial Resistance Surveillance System 2021). Moreover, in many other regions of the world, the crisis of ABR arising in GN bacteria is also growing, as well as the number of MDR organisms (Centers for Disease Control and Prevention 2019; European Centre for Disease Prevention and Control (ECDC) 2019; Fang et al. 2018; Hu et al. 2018; Lohr et al. 2018).

4.1.3 Affected antibiotics

Many studies (26.7%) did not report susceptibility test results. However, before an antibiotic is prescribed and used, the bacteria should be tested to ascertain whether they are susceptible to it. To help guide appropriate antimicrobial prescribing, international guidelines (e.g., WHO and EU) and many national guidelines (such as from Canada, the US, and Germany) recommend the use of AST for clinicians when they prescribe antibiotics to patients (Barlam et al. 2016; de With et al. 2016; Langford et al. 2020; Pulcini et al. 2017; World Health Organization 2016). Among

these recommendations, the practice of *selective reporting* of AST results has been considered as applicable both in hospital and community settings (Barlam et al. 2016). This includes: a) not reporting AST results to discourage prescriptions; b) reporting primarily narrow-spectrum antibiotics rather than broad-spectrum antibiotics, with the aim of assisting physicians to select the most appropriate antibiotic; and c) reporting AST results that exclude target antibiotics to discourage their prescription (Langford et al. 2020; Tebano et al. 2020). Studies have shown that these AST reporting procedures are promising antibiotic stewardship tools for reducing inappropriate antibiotic prescriptions among clinicians (Langford et al. 2020; Tebano et al. 2020). However, the implementation of *selective reporting* has several barriers. An EU study found considerable heterogeneity in the practice of *selective reporting* implementation, such as a lack of guidelines, poor system support, and a lack of professional capability (Pulcini et al. 2017). To bridge those gaps, professional societies, further explorations, and facilitating the exchange of good practices can play essential roles in improving the performance of *selective reporting* (Tebano et al. 2020). In China, the current national strategy to reduce AMR is mainly concerned with AST for inpatients in secondary and tertiary hospitals and includes *selective reporting* as an optional and additional supplementary tool for antibiotic therapy protocols, AST is not currently reported for outpatients (He et al. 2019). To further develop the national strategy on reducing ABR, the *selective reporting* of AST for both inpatients and outpatients could be conducted as part of clinical antibiotic prescription procedures.

Bacteria resistant to ciprofloxacin and ceftazidime were identified as the most frequently occurring antibiotic-resistant bacteria in the healthcare settings, with equally high frequencies found in the included papers, followed by bacteria resistant to gentamicin and amikacin, with

equal frequency. These antibiotics were developed and introduced into medical use in the second half of the 20th century and are widely used today (Wanger et al. 2017; Wenzel 2004). These four agents are broad-spectrum antibiotics that act against a wide range of disease-causing bacteria (Aminov 2017; Tamma et al. 2012). However, it has been observed, both in China and throughout the world, that bacteria can develop resistance to broad-spectrum antibiotics after continual exposure to them (Fair and Tor 2014; Qu et al. 2019). International organizations and researchers have warned that the increased prevalence of resistance to these broad-spectrum antibiotics could limit global economic development and decrease life spans (Cassini et al. 2019; Qu et al. 2019; Thamlikitkul et al. 2015).

Some pharmacies in China sell antibiotics to customers without prescriptions and without educating them about the negative consequence of misuse (Chang et al. 2019). In China's primary and secondary healthcare facilities, doctors prescribe broad-spectrum antibiotics more frequently than narrow-spectrum antibiotics (Wang et al. 2014; Yin et al. 2017). A lack of opportunities for continued professional medical education for primary healthcare staff may explain their tendency to overuse broad-spectrum antibiotics (Wang et al. 2014). Rural areas particularly lack available skilled and certified healthcare staff (Aastha Chokshi 2019). *Selective reporting* could be an optional tool to improve the clinical capacity of community healthcare settings, particularly in rural areas, and reduce inappropriate antibiotic prescriptions. Previous inappropriate antibiotic prescriptions and easy access to antibiotics have increased the risks of ABR. Further discussion about the risks of prior antibiotic therapies can be found in section *4.1.4.4 Drug exposure*. Additionally, because the characteristics of epidemic diseases have changed, the application of some broad-spectrum antibiotics (such as carbapenems and third-

generation cephalosporins) for the treatment of those infectious diseases (such as infections caused by hypervirulent *Klebsiella pneumoniae*) has increased. This change has been seen in China and other countries, such as the EU and the US. A consequence of exposure to these antibiotics is the increased prevalence of antibiotic-resistant bacteria (Centers for Disease Control and Prevention 2019; China Antimicrobial Resistance Surveillance System 2021; Machowska and Stålsby Lundborg 2018).

4.1.4 Healthcare-associated risk factors

Factors that contribute to the emergence of ABR vary by country and region owing to differences in economic, agricultural developments and the population level (Chokshi et al. 2019). There are many factors of the Chinese healthcare system that contribute to the emergence of ABR (Chokshi et al. 2019). These healthcare-related risk factors are found not only in China but also globally (Chang et al. 2019; Chokshi et al. 2019). Four categories of risk factors that contribute to ABR in hospitals are defined in this thesis: socio-demographics factors, patient clinical information, admission to healthcare settings, and drug exposure. Within these four categories, between 2003 to 2019, the five most frequently identified risk factors contributing to ABR in China were current and prior medication (subcategories of drug exposure), invasive procedures and hospital stay (subcategories of admission to healthcare settings), and underlying diseases (a subcategory of patient clinical information).

4.1.4.1 Sociodemographic factors

Regarding patient sociodemographic characteristics, older age, education attainment, a migration background, and bad health status were found to be risk factors that contribute to the development of ABR in China's healthcare settings. Several studies have reported that age and sex are risk factors related to the emergence of ABR (Erb et al. 2018; Sinha et al. 2017); however, others did not find such an association (Lee et al. 2016; Wolfe et al. 2014). In this thesis, the patients of the included papers had various underlying diseases. Furthermore, the age ranges that were reported as a significant risk factor were not the same across all papers.

An inadequate understanding of antibiotics and inappropriate restrictive attitudes toward antibiotic use may contribute to poor adherence to antibiotic treatment, ultimately leading to the occurrence of ABR (Kai Wang 2014; Sun et al. 2017; Yang et al. 2015). For social situation and financial reasons, migrant patients may tend to have poor adherence to antibiotic therapies when they are prescribed by clinicians (Xiujun Yang 2015). There is also evidence that non-prescription consumption through community pharmacies still exists in some LMICs, including China (Kai Wang 2014). The misuse of antibiotics among migrants and people with lower annual income contributes to the inappropriate use of antibiotics, which then leads to the risk of ABR development. Additionally, migrants with low annual incomes tend to have poor nutritional levels, and thus they may have a weaker health status. Accordingly, these populations are at higher risk of infection when exposed to clinical environments that harbor antibiotic-resistant

bacteria (Sun et al. 2017; Yang et al. 2015). Indeed, studies in China and Sri Lanka have shown that migrants with poor nutritional levels are at a higher risk of antibiotic-resistant infection when exposed to clinical environments (Jayatissa and Wickramage 2016; Sun et al. 2017).

4.1.4.2 Patient clinical information

Regarding patient clinical information, underlying diseases were the most frequently reported risk factors in the included papers, followed by the severity of the underlying disease and abnormal laboratory test results.

It is known that patients with a weaker health status have a higher likelihood of developing antibiotic-resistant bacterial infections when exposed to certain environments such as healthcare settings. Underlying diseases such as NCDs and certain infections identified as associated with ABR in China were also found to be risk factors in other countries (CDC 2019; European Centre for Disease Prevention and Control (ECDC) 2019; Nouvenne et al. 2014; Pachori et al. 2019). During the course of disease, the health status of a patient is weakened, which may, in turn, increase their risk of being infected with antibiotic-resistant bacteria during their time in a healthcare setting. In the subcategory of underlying diseases, infections were identified as the second major concern for the emergence of ABR. HAI is a major concern related to the spread of antibiotic-resistant bacteria (Chemaly et al. 2014; Laxminarayan et al. 2016). Some studies demonstrated that inappropriate antibiotic therapies may also lead to ABR (Chatterjee et al. 2018; Fang et al. 2018; Shallcross and Davies 2014) (see section 4.1.4.4 for details).

4.1.4.3 Admission to healthcare settings

Many of the included papers identified admission to healthcare settings as a healthcare system-associated risk factor for the emergence of ABR. This corresponds to findings from several countries and regions (European Centre for Disease Prevention and Control (ECDC) 2019; Sonmezer et al. 2016; Toubes et al. 2003). The occurrence of ABR infection is a major concern in ICUs. Exposure to antibiotic-resistant bacteria can occur in these environments because patients who are being treated with antibiotic therapies can act as carriers of infection (Sonmezer et al. 2016). Exposure to healthcare is a risk factor for being infected with antibiotic-resistant pathogens due to cross-transmission or selective pressure on the microbiome during antibiotic therapy (Chemaly et al. 2014). Considering the evidence that resistant pathogens can be spread due to poor environmental hygiene (Dalhoff 2012), proper risk control measures taken by medical staff (including nurses and other clinical professionals) are necessary to limit antibiotic-resistant bacteria-associated HAIs (Fournier et al. 2012; Jarlier et al. 2010). This thesis identified that prolonged ICU stays are a risk factor for the emergence of ABR; in particular, prolonged stays of at least 7 days. This finding corresponds to those of a study from Southeast Asia, which found that ICUs are a main route for the emergence of ABR and the transmission of these pathogens, and prolonged ICU stays can increase the risk of antibiotic-resistant infection transmission (Chereau et al. 2017).

Resistant bacteria can be transferred because of poor hygiene, poor sanitation, and poor infection control in hospital settings (Aslam et al. 2018). Compared to other body systems, invasive/surgical procedures involving the respiratory system were reported more frequently as a significant risk factor (see Table 8). One of the most common invasive procedures is ventilation, which can result in ventilator-associated antibiotic-resistant infection. Similar results are found in investigations and reports from other countries, such as the US and Canada (CDC 2019; Ellis et al. 2015; Sonmezer et al. 2016). In a study in Belgium, Vincent identified the use of catheters as a major risk factor for antibiotic-resistant infection during surgical or invasive procedures (Vincent 2003). Sterilized medical instruments and clean healthcare environments help to prevent the spread of resistant pathogens (Ramasethu 2017).

As discussed in section 4.1.4.2, patients in adverse conditions are predisposed to carry or be infected by resistant microbes (Guillamet and Kollef 2017; Prestinaci et al. 2015). Elderly and immunocompromised patients in hospitals may be more vulnerable to opportunistic infections (Bassetti and Righi 2013). Furthermore, insufficient numbers of healthcare workers, particularly nurses and midwives, also hinders the ability to control ABR in healthcare facilities. Like many countries, China has an insufficient number of nursing personnel. In 2019, the ratio of doctors to nurses in China was 1.13, which is less than the average ratio of 1.2 in Asia (China Statistics Press 2020). Except in ICUs, patients are often accompanied by their family members to the hospital. An intervention in the form of health education for patients and their accompanying family members could have preventive effects for the development of ABR (Centers for Disease Control and Prevention 2018; Tong et al. 2018; World Health Organization 2018a).

4.1.4.4 Drug exposure

Because the emergence of ABR is associated with high frequencies of antibiotic use, drug exposure plays an important role in the prevalence of antibiotic-resistant bacteria (CDC 2019; Chatterjee et al. 2018; Fang et al. 2018; Shallcross and Davies 2014; World Health Organization 2018b). The inappropriate consumption, prescription, and application of antibiotics, as well as interrupted antibiotic treatment, all contribute to the rise of ABR (Bell et al. 2014; Charani and Holmes 2019; Qu et al. 2018a; Tong et al. 2018). Among the included papers, concerning drug exposure, prior antibiotic therapy (monotherapy) was the most reported risk factor for the emergence of ABR. In addition to prescriptions from healthcare professionals, patients can be exposed to antibiotic via self-medication (Kamata et al. 2018). The results of this thesis showed that monotherapy was the most frequent risk factor in this subcategory, followed by combination therapy and prolonged medication.

It is currently understood that the inappropriate use of antibiotics is a major concern for the emergence of ABR (Aslam et al. 2018; Zaman et al. 2017). In China, inappropriate antibiotic use has been reported in communities, primary healthcare facilities, and secondary hospitals (Qu et al. 2019; Zhao et al. 2021). The inappropriate application of antibiotics, such as prematurely discontinuing antibiotic therapy, is commonly reported (Aslam et al. 2018; Machowska and Stalsby Lundborg 2018). The current work found that prior antibiotic use among patients puts them at higher risk of developing an antibiotic-resistant infection. A lack of understanding and

casual attitudes towards the necessity for completing a course of antibiotic therapy, as well as, the prevalence of inappropriate antibiotic consumption and application among patients, contribute to the emergence of ABR (Kamata et al. 2018; Waaseth et al. 2019).

Easy access to antibiotics facilitates their inappropriate use, ultimately leading to the development of ABR. The phenomenon of easy access to antibiotics exists worldwide. Over-prescription by doctors and the easy attainment of non-prescribed antibiotics at community pharmacies have been observed in China (Chang et al. 2019; Sun et al. 2009) and other countries (Machowska and Stålsby Lundborg 2018). In China, for example, 51.4% of the antibiotic prescriptions in secondary- and tertiary- level hospitals were inappropriate, and an additional 4.8% could not be linked to any diagnosis (Zhao et al. 2021). In a survey from Portugal, 7.5% of the respondents stated that it is easy to obtain antibiotics without a prescription (Ramalhinho et al. 2014). A survey reported that even 4% of Europeans obtained their most recent course of antibiotics without a prescription (TNS Opinion Social 2016). A study from Japan found antibiotic overuse by self-medicating patients (Kamata et al. 2018). Furthermore, antibiotic prescription surveillance data from general practices in the United Kingdom during the COVID-19 epidemic showed a significantly increased number of prescriptions, which was 6.71% higher than expected (Armitage and Nellums 2020). As a vital strategy to curb the emergence of ABR, along with more stringent over-the-counter policies, clinicians should prescribe antibiotics only when appropriate. These measures will help to address the overuse of antibiotics, which may lower the risk of ABR emergence.

Increasing resistance to some widely used antibiotics has been observed worldwide (Bassetti and Righi 2013; CDC 2019; European Centre for Disease Prevention and Control 2019a; Qu et al. 2019). As an aspect of current/prior medication, the application of carbapenems and cephalosporins as a monotherapy was recognized as a factor leading to ABR; prior antibiotic therapy with glycopeptides (applied as monotherapies) was also identified. In China, carbapenems and cephalosporins are commonly used, and their resistance prevalence is high (Hu et al. 2018; Qu et al. 2018b; Wu et al. 2011). Between 2014 and 2018, the third- and second-generation cephalosporins, macrolides, and fluoroquinolones became the top four most-prescribed antibiotics to outpatients in China (Zhao et al. 2021). This threatens the effectiveness of these essential life-saving antibiotics (Hu et al. 2018; Qu et al. 2018b; Wu et al. 2011). In United Kingdom general practice, amoxicillin (a broad-spectrum antibiotic) was reported as the most often inappropriately prescribed antibiotic for otitis externa and upper respiratory tract infection, with high proportions of use for these conditions (62.3% and 34.5%, respectively) (Nowakowska et al. 2019). This overuse may result in the failure of antibiotic therapies and may further increase the risk of resistance development (Xiao 2018). The National Institute for Health and Care Excellence in the United Kingdom developed detailed guidelines for the management of common infections and to address AMR, including suggested doses and lengths of antibiotic therapy for adults and children (The National Institute for Health and Care Excellence 2017). The guidelines help clinicians to make prescriptions by referencing a clear and convenient list that describes potential treatment suggestions for each infectious disease (Nowakowska et al. 2019). The appropriateness of a given antibiotic can be reviewed according to the guidelines (Nowakowska et al. 2019). Such a guideline could be a potential tool in China's national effort to reduce the risk of ABR emergence when clinicians give prescriptions. Although China has

released several similar national guidelines to control and reduce inappropriate antibiotic prescriptions, a guideline in such a comprehensive form would be useful. The United Kingdom guideline contains suggested doses by age group, length of antibiotic therapy, the main aspects of the different antibiotics, and the treatment protocols in one document (The National Institute for Health and Care Excellence 2017). Such a guideline should be considered to improve the prudent prescription of antibiotics across the country.

4.2 Lessons and challenges to the healthcare system in China

4.2.1 Rational application of antibiotics

Recognized measures to prevent ABR include periodic reviews of antibiotic susceptibility patterns among commonly used antibiotics; proper disease diagnosis; and the provision of ABR-related health education for the general population and healthcare workers (Chem et al. 2018; Dominey-Howes et al. 2015; Qin et al. 2014; Shallcross and Davies 2014). China has developed multifaceted approaches to improve the stewardship of antibiotic use. These approaches include pharmacist-on-duty regulations, resistance-related training for healthcare staff in all healthcare settings, and educating the general public about the appropriate use of antibiotics (Chang et al. 2019; Grundmann 2014; He et al. 2019).

Regulations and guidelines can promote the rational application of antibiotics. Since 2009, policies and guidelines have been implemented in the healthcare system to improve the prudent use of medicines (National Health & Family Plan Commission of China 2009; National Health & Family Plan Commission of China 2012; National Health & Family Plan Commission of China 2016). Regarding PHCs, in 2014 the National Health and Family Planning Commission of China issued the first policy on the rational use of antibiotics in PHCs (He et al. 2019; Qu et al. 2019). The national consumption of antibiotics and the prevalence of certain antibiotic-resistant bacteria have decreased in recent years (National Health Commission of the People's Republic of China 2019).

Furthermore, to ensure the sustainable improvement of the rational use of antibiotics, China has issued a guidance document to promote appropriate antibiotic prescribing practices among doctors and veterinarians working in multiple sectors throughout the country (Chen et al. 2019). ABR is identified as a One Health challenge; it not only relates to clinical issues but also to many other fields such as food-animal production systems and environmental contamination (Rousham et al. 2018). This is because antibiotic-resistant bacteria transmission is not limited to humans; it also between humans and animals and in the natural environment (Brown et al. 2017). The One Health approach aims to decrease such transmission through a comprehensive and multifaceted strategy, both globally and nationally, via integrated and cooperative programs, policies, regulations, and research in multiple sectors to decrease antibiotic exposure in healthcare, agriculture, and the environment (Zinsstag et al. 2020). For example, the US developed a five-year national plan to strengthen the national One Health approach to decrease the rapid emergence of ABR (Centers for Disease Control and Prevention 2015). This national plan

includes developing rapid and innovative diagnostic tests for the identification and characterization of resistant bacteria, conducting research on new antibiotics and vaccines to combat ABR, promoting rational antibiotic prescriptions in human and animal medicine, and eliminating antibiotic use for growth promotion in animals agriculture (Centers for Disease Control and Prevention 2015). In 2019, the US government stated that the One Health approach has been critical to reducing the threat of ABR in the country (Centers for Disease Control and Prevention 2019). Adopted from the Global Action Plan on Antimicrobial Resistance, Germany developed a national One Health approach as part of their national strategy to combat AMR (Federal Ministry of Health 2019a). Germany's approach emphasized the importance of international multisector cooperation between human and veterinary medicine and with agriculture (Federal Ministry of Health 2019a). To promote the wider development of ABR control and international cooperation, this idea was discussed among Germany and other countries (including China) during the G20 summit in 2017 (Federal Ministry of Health 2019a). To ensure the sustainable improvement of rational antibiotic use, China issued a national One Health approach as a guidance document to promote appropriate antibiotic prescription practices among doctors and veterinarians throughout the country (Chen et al. 2019). This strategy may become a critical factor for the success of national ABR control in the near future.

4.2.2 ABR control in healthcare facilities

The findings of this thesis indicate that, poor hygiene management, prolonged hospital admissions, and prolonged antibiotic use can cause the transmission of drug-resistant bacteria. These findings are in accordance with previous studies on the spread of ABR (Aslam et al. 2018; World Health Organization 2018b). In 2005, to contain AMR spread and enhance the visibility of antimicrobial stewardship in hospitals, the WHO launched a global "Clean Care is Safer Care" campaign to improve hand hygiene. This campaign has achieved a 50% reduction in HAI through improved hand hygiene and saved approximately 70–80 million lives in the subsequent 10 years (Harbarth et al. 2015). In addition to a policy on hand hygiene promotion in healthcare facilities, the EU produced key messages regarding HAI prevention measures in hospitals, such as aseptic techniques and clinical interventions; decontamination of instruments, equipment, and the ward environment; ensuring available guidelines, protocols, and checklists for HAI prevention and control; and education on ABR-related HAI prevention and control for all relevant healthcare professionals (European Centre for Disease Prevention and Control 2020). All of these measures contribute to the effort to prevent and control the transmission of resistant pathogens within healthcare facilities (Centers for Disease Control and Prevention 2019; Ramasethu 2017).

China saw the need for an administrative ABR control working group that is responsible for the hygienic management of healthcare facilities and the surveillance of antibiotic-resistant bacteria and infections among at-risk patient populations. In 2012, China developed a regulation on the administration of antibiotic prescriptions (National Health & Family Plan Commission of China

2012). The regulation includes the establishment of an administrative working group among hospitals to evaluate the effects of antibiotic use (National Health & Family Plan Commission of China 2012). The evaluation process also includes follow-ups for patients who received antibiotic therapy (National Health & Family Plan Commission of China 2012). In recent years, alongside China's national program to prevent ABR, workgroups that aim to prudent antibiotic prescriptions and prevent the spread of ABR have made progress to improve the management and control of clinical antibiotic prescriptions and rational antibiotic use (National Health Commission of the People's Republic of China 2019; Wang et al. 2019b). However, some challenges remain. Particularly in pediatric departments, national antibiotic administration strategies do not provide sufficient guidance regarding the control of ABR. This is, partly due to the lack of general surveillance data of clinical antibiotic application, improper standards for preventing antibiotic-resistant infections in children, the inadequate development of the science surrounding pediatric infectious disease, and the inappropriate application of antibiotics (National Health Commission of the People's Republic of China 2019). In addition, follow-ups for patients in PHCs need further improvement (National Health Commission of the People's Republic of China 2019).

Widespread MDR is also becoming a major concern related to ABR (Rousham et al. 2018). The development and spread of MDR bacterial disease may lead to increased clinical complications and economic losses, in addition to more deaths (Aslam et al. 2018; Bassetti and Righi 2013). Furthermore, the potential impact of the COVID-19 pandemic on MDR bacteria HAIs has

recently been highlighted (Donà et al. 2020; Karakonstantis et al. 2020). These impacts include increased rates of admission, shortages of clinical staff and personal protective equipment, and overcrowded healthcare facilities (Phua et al. 2020; Zhou et al. 2020). Moreover, severe COVID-19 patients with comorbidities may acquire an MDR infection due to their prolonged hospitalization with mechanical ventilation and their intense use of broad-spectrum antibiotics (Donà et al. 2020; Phua et al. 2020; Zhou et al. 2020). Hence, further exploration on the prevention and control of ABR in the context of the COVID-19 pandemic is needed.

4.2.3 Early warning systems for ABR control

National and locally developed guidelines and early warning systems related to antibiotic use are considered valuable tools for controlling ABR, and these systems can operate at different levels of the healthcare system (Labricciosa et al. 2018). A well-informed, early warning system should provide up-to-date and accurate information to govern the appropriateness of antibiotic therapy guidelines, antibiotic formulations, antibiotic stewardship plans, public interventions, infection control policies, and antibiotic development (Tacconelli et al. 2018). Networks for surveilling the prevalence and trends of bacterial resistance have been continually developed either in China, the US, Europe, and elsewhere (Centers for Disease Control and Prevention 2013; China Antimicrobial Resistance Surveillance System 2019; European Centre for Disease Prevention and Control 2019a; Hu et al. 2018; World Health Organization 2015d; World Health

Organization 2018c). These surveillance systems generate information regarding the prevalence and trends of antibiotic resistance as they develop.

Although ABR surveillance strategies have been implemented globally through successful surveillance networks such as GLASS from the WHO and EARSS from the EU, the databases of these surveillance networks are usually based on the small numbers of laboratories and participating hospitals that have registered to contribute information (European Centre for Disease Prevention and Control 2019a; Ombelet et al. 2018; World Health Organization 2018c). Additionally, laboratory- and hospital-based surveillance is prone to selection bias, which leads to bias when estimating the prevalence of ABR (Ombelet et al. 2018). Population-based surveillance could be considered as future unbiased surveillance approach, although the necessary resources and infrastructure are not yet in place (Ginting et al. 2019; Oldenkamp et al. 2021).

Technology to rapidly detect antibiotic-resistant bacteria is another key aspect of ABR prevalence surveillance and related early warning systems (Oldenkamp et al. 2021). During the G7 Summit in 2015, Germany proposed and led an initiative to increase the research and development of diagnostic tools for ABR (Federal Ministry of Health 2019a). A timely diagnosis is important both for the prudent use of antibiotics and to prevent the spread of resistant bacteria (Federal Ministry of Health 2019b). In 2018, to improve the reimbursement for ABR-related diagnostic procedures, new methods for resistance testing were included in the doctor's fee schedules in Germany (Federal Ministry of Health 2019b). This change provided a practical connection to the latest scientific developments in ABR diagnostic technology. These

reimbursements also helped Germany to develop a national ABR early warning system, and because resistance can be recognized at an early stage, the chain of infection can be interrupted earlier (Federal Ministry of Health 2019b).

It is recommended that China develops an early warning system for ABR that can link incidence and prevalence data with relevant epidemiological, clinical, or outcome data (National Health Commission of the People's Republic of China 2019). Additionally, the diversity of an early warning system for ABR control needs to be large (National Health Commission of the People's Republic of China 2019). For example, tailored monitoring guidelines and ABR risk evaluations among specific populations (such as children, elderly people, and pregnant women) require further and regular development (National Health Commission of the People's Republic of China 2019).

In 2016, the Lancet published an article about the globalization of AMR (Das and Horton 2016). With the development of international communication and a greater awareness of the public health ramifications of ABR, calls for a global convention on ABR policies and legally binding and enforceable commitments have grown (Hoffman et al. 2015; Laxminarayan et al. 2020). The development of a well-formed surveillance network within and between countries can provide evidence for such regulations and further promote the prevention and control of ABR (Chang et al. 2019; Grundmann 2014; He et al. 2019). The Fleming Fund, established by the United Kingdom Government in 2015, provides support to many LMICs on the establishment of national action plans and surveillance systems for ABR (Kinh et al. 2017). As discussed in sections 1.4.2 and 4.2.1, international forums such as the G20 have made historic commitments

to address ABR (Federal Government of Germany 2017). During Germany's G20 presidency, the global networks involved in combating AMR came together to advocate for global antibiotic research (Federal Government of Germany 2017; Kickbusch et al. 2017). Furthermore, the COVID-19 pandemic has clearly showed that diseases can easily cross borders and has motivated countries and international organizations to strengthen global collaboration and governance architecture for the prevention and control of communicable diseases (including antibiotic-resistant infections) (Strathdee et al. 2020). This has increased global participation and action to address ABR (Strathdee et al. 2020).

4.3 Strengths and limitations

The fundamental strength of this study is that it considered not only English but also Chinese literature. Only papers of the highest quality were included. For example, among the Chinese articles, only those from journals on at least two of the three Chinese core academic journal lists were included. This study also covered a sufficiently long period of 16 years. However, there are some limitations. First, during the quality check for Chinese articles, several were from journals on only one of the three Chinese core academic journal lists; hence, they were excluded. Because of this, information on certain parameters of interest might have been lost. Second, the articles did not uniformly report on the parameters, for example the age ranges of patients, the duration of hospital stay, and the duration of medication. In addition, because the included papers contained patients with different underlying diseases, the reporting may have been different as

well and might have led to missing values and, hence, some biases in data extraction and description. Furthermore, because of the COVID-19 pandemic, planned and complementary field investigations on ABR in China could not be conducted.

4.4 Conclusions

Antibiotic resistance constitutes an ongoing major public health challenge in China. Apart from the risk factors from agriculture, food-animal production systems and environmental contamination, contributing factors associated with the healthcare settings are also major contributors to the high prevalence of ABR in this large-population country. This study addressed contributors to ABR in healthcare settings by studies from 31 provinces of mainland China.

The study found that gram-negative ABR bacteria (such as *Klebsiella spp.*, *Pseudomonas spp.*, and *Acinetobacter spp.*) occurred most frequently in healthcare facilities. The development of MDR, such as ESBLs bacteria, is also a major concern for antibiotic resistance. In China, resistance to antibiotic classes such as beta-lactams and aminoglycosides and antibiotic agents (such as carbapenems and cephalosporins) were reported as been resistant most frequently by healthcare settings in China.

Four categories of contributors to the emergence of ABR in healthcare settings were recognized by this study, including sociodemographic factors, patient clinical status related factors, admission to healthcare settings, and drug exposure. Regarding sociodemographic factors, migrant background is identified as a concern of development of ABR emergence, and this concern is recognized globally. High age, as well as male and female sex are not stated as contributors for the emergence of ABR in countries like the US and Korea, these two factors are reported as contributors to China's emergence of ABR. In China, patients characterized with the above mentioned three factors were reported to have inappropriate attitudes toward antibiotic application, which contribute to poor adherence to antibiotic therapy and ultimately lead to the occurrence of ABR. Patients with weaker health status, particularly suffering from NCDs were highlighted as having a higher risk of developing hospital-associated antibiotic-resistant bacterial infections. Hence clinical information of patients is important information for healthcare workers about the risk of patients being infected with ABR-related diseases and then take corresponding interventions to prevent ABR emergence in hospitals. In the category of admission to hospitals, contributors to the emergence of ABR include ICU admission (particularly prolonged admissions), invasive/surgical procedures (particularly such procedures involving the respiratory system). Well performed sanitation and sterilization of healthcare environment and medical instruments helps to control ABR emergence in hospitals. In addition to the proper risk control measures for ABR emergence, an insufficient number of medical staff in China is a barrier to ABR prevention in healthcare settings. Regarding the drug exposure category, prior antibiotic monotherapy is identified as a major contributor to the ABR emergence in hospitals. Several studies stated inappropriate antibiotic consumption, prescription, and application of antibiotics, all contributing to the rising emergence of ABR. To reduce over-prescriptions of antibiotics by

doctors and stimulate prudent antibiotic use in healthcare settings, *selective reporting* of AST results could be an optional tool.

The risk factors identified in this study require recognition by the national health authorities. The emergence of ABR is a big challenge to the One Health Approach. In addition, during the COVID-19 pandemic, multidrug-resistant bacterial infections threat lives of patients. Further improvement of China's regulations, policies, and guidelines to promote appropriate antibiotic consumption and prescribing practices in healthcare settings are urgently needed. For example, working groups in hospitals that are responsible for hygienic management of healthcare facilities, ensuring available guidelines and protocols for HAI prevention, education on ABR-related HAI control for relevant healthcare workers, and establishment of links between hospital- and population-based ABR surveillance systems are necessary to control ABR emergence. Moreover, rapid antibiotic-resistant bacteria detection technology is an important support for better performance of population-based ABR surveillance system. Since ABR has became a crisis for global health, global participation and action to address ABR are critical for prevention and control of ABR emergence.

5 SUMMARY

Antimicrobial resistance and in particular antibiotic resistance (ABR) contribute to the failure of infectious disease treatments, as well to the increased global morbidity and mortality. Since the 1950s, the prevalence of ABR in China constitutes an ongoing major public health challenge to this country. Nowadays, the occurrence of ABR in healthcare settings in China poses serious health risks among infected patients. The identification of risk factors to ABR in China is important for the development of effective interventions against ABR.

A systematic review was conducted to identify modifiable risk factors within healthcare settings in the mainland China. The search was conducted using two English online databases (including the Cochrane Library and PubMed) and three Chinese online databases (including the China National Knolwedge Infrastructure, WanFang, and VIP). Articles that present original data published in either English and Chinese between January 2003 and June 2019 were included for this study.

Out of a total of 1,979 results of the literature search, 176 facility-based references were included in the final analysis (66% in Chinese and 34% in English). These included articles that range across 31 provinces in mainland China and report information from over 50,000 patients. The results of this systematic review identified four major categories of ABR risk factors associated with the healthcare sector: socio-demographic factors, patient clinical information, admission to healthcare settings, and drug exposure. This study highlights the following independent risk factors for ABR: old age, migrant status, low annual income and urban residence (first category);

weaker health status and certain laboratory results (second category); prolonged hospitalization and performance of invasive procedures (third category); and current or prior antibiotic monotherapy, in particular with broad-spectrum antibiotics (such as carbapenems and cephalosporins) (fourth category).

Despite China has developed a multifaceted national stewardship plan to address ABR, the healthcare settings-associated risk factors require recognition by the national health authorities. China needs a more comprehensive and detailed guideline of appropriate antibiotic prescriptions for clinicians, as well as measures such as hygienic management in healthcare settings, development of new antibiotics, vaccines for antibiotic-resistant infection prevention, and rapid antibiotic-resistant bacteria detecting technology. Moreover, workgroups for prevention and control of ABR emergence need to be further improved in all healthcare settings.

5 ZUSAMMENFASSUNG

Antimikrobielle Resistenzen, insbesondere Antibiotikaresistenzen (ABR), tragen maßgeblich zum Scheitern der Behandlung von Infektionskrankheiten bei. Die Folgen sind eine global erhöhte Morbidität und Mortalität. Seit den 1950er Jahren stellt die Verbreitung von ABR in China eine anhaltend große Herausforderung für die öffentlichen Gesundheitssysteme des Landes dar. Auch heutzutage birgt ABR ernsthafte Gesundheitsrisiken für infizierten Patienten. Um eine wirksame Intervention zu gewährleisten, ist es wichtig entsprechende Risikofaktoren für ABR in China zu identifizieren.

Um veränderbare Risikofaktoren im chinesischen Gesundheitswesen zu identifizieren, wurde eine systematische Studie nötig. Die hierfür benötigte Suche wurde unter Verwendung von zwei englischen Online-Datenbanken (einschließlich der Cochrane Library und PubMed) und drei chinesischen Online-Datenbanken (einschließlich der China National Knolwedge Infrastructure, WanFang und VIP) durchgeführt. Originaldaten aus zwischen Januar 2003 und Juni 2019 (in englischer und chinesischer Sprache) veröffentlichten Artikeln, wurden in diese Studie aufgenommen.

Von insgesamt 1.979 Ergebnissen der Literaturrecherche wurden 176 einrichtungsspezifische Referenzen in die endgültige Analyse einbezogen (66% auf Chinesisch und 34% auf Englisch). Dazu gehörten Artikel, die sich über 31 Provinzen des chinesischen Festlandes erstrecken und Informationen von über 50.000 Patienten enthalten. Die Ergebnisse dieser systematischen Überprüfung identifizierten vier Hauptkategorien von ABR-Risikofaktoren im Zusammenhang

mit dem Gesundheitssektor: soziodemografische Faktoren, klinische Patienteninformationen, Zulassung zum Gesundheitswesen und Arzneimittelexposition. Diese Studie hebt die folgenden unabhängigen Risikofaktoren für ABR hervor: Alter, Migrantenstatus, niedriges Jahreseinkommen und städtischer Wohnsitz (erste Kategorie); schwächerer Gesundheitszustand und bestimmte Laborergebnisse (zweite Kategorie); längerer Krankenhausaufenthalt und Durchführung invasiver Eingriffe (dritte Kategorie); und aktuelle oder frühere Antibiotika-Monotherapie, insbesondere mit Breitbandantibiotika (wie Carbapeneme und Cephalosporine) (vierte Kategorie).

Die nationalen Gesundheitsbehörden Chinas haben einen vielfältigen nationalen Stewardship-Plan zur Bekämpfung der ABR entwickelt, der aber noch erweitert werden sollte um den spezifischen Risikofaktoren des Gesundheitswesens entgegen zu wirken. China benötigt eine umfassendere und detailliertere Richtlinie für geeignete Antibiotika-Verschreibungen durch Ärzte. Ergänzt werden sollte dies durch ein verbessertes Hygienemanagement im Gesundheitswesen und die Entwicklung neuer Antibiotika. Impfstoffe zur Verhütung antibiotikaresistenter Infektionen und eine schnelle Technologie zur Erkennung antibiotikaresistenter Bakterien würden weitergehende Sicherheit ermöglichen. Darüber hinaus müssen Arbeitsgruppen die Prävention und Kontrolle der Entstehung von ABR in allen Bereichen des Gesundheitswesens weiter verbessern.

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7 PERSONAL PUBLICATIONS

7.1 Publications related to the doctoral research

- **Chen Q**, Li D, Beiersmann C, Neuhann F, Moazen B, Lu G, Müller O. Risk factors for antibiotic resistance development in healthcare settings in China: a systematic review. (Under review with *Epidemiology and Infection*; manuscript ID: *HYG-OM-11727-Mar-21*)

7.2 Further publications during the doctoral study period

- **Chen Q**, Li Y, Liu Y, Zhang Y, Huang Y, Zhu L, Lu G. Antibiotic residues in milk in China: A systematic review. (Under review with *Food Research International*; manuscript ID: *FOODRES-D-21-00109*)

7.3 Other publications

- **Chen Q**, Wang X, Qi Y, Liu X, Jiang L, Hou W, Zhou L, Lu X. The Impact of Directly Observed Therapy (DOT) on Preventive Treatment for Latent Tuberculosis Infection (LTBI) among Universities' Students in Dalian City of China. *Biomedical and Environmental Sciences.* 2015, 28(8): 611-615. Doi: 10.3967/bes2015.085.
- **Chen Q**, Lu X, Yang Y, Qi Y, Wang X, Zhou L. Analysis of risk factors for school tuberculosis outbreaks in Dalian. *International Journal of Epidemiology and Infectious Disease.* 2015, 42(3): 174-178. Doi: 10.3969/j.issn.2095-3755.2015.01.007.
- Jia X, Shen Z, Liu R, Han Y, Yang Y, **Chen Q**, Duan N. The Association of Fine Particulate Matter to Allergic Rhinitis: A Systematic Review and Meta-Analysis Based on Cohort and Cross-sectional Studies. (Submitted to *European Journal of Public Health*; manuscript ID: *EJPH-2021-04-OM-0467*)

8 ANNEX

8.1 List of included papers

Literatures written in English:

1. CAO, B., WANG, H., SUN, H., ZHU, Y. & CHEN, M. (2004). **Risk factors and clinical outcomes of nosocomial multi-drug resistant *Pseudomonas aeruginosa* infections**. *J Hosp Infect,* 57**,** 112-8.
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* titles were translated if not available in English.

8.2 Identified antibiotics with resistance as reported by papers

Class	Agent	Type	No. of papers *
β-lactams	Carbapenems	Imipenem	57 (44.2%)
		Meropenem	35 (27.1%)
		Ertapenem	9 (7.0%)
		Imipenem/Cilastatin	6 (4.7%)
		not reported specifically	7 (5.4%)
	Cephalosporins (1st generation)	Cefazolin	24 (18.6%)
		Cephalothin	7 (5.4%)
		Ceftezole	1 (0.8%)
	Cephalosporins (2nd generation)	Cefoxitin	16 (12.4%)
		Cefuroxime	13 (10.1%)
		Cefotetan	5 (3.9%)
		Cefaclor	2 (1.6%)
		Cefmetazole	1 (0.8%)

		Cefprozil	1 (0.8%)
	Cephalosporins (3rd generation)	Ceftazidime	64 (49.6%)
		Ceftriaxone	40 (31.0%)
		Cefoperazone/Sulbactam	29 (22.5%)
		Cefotaxime	28 (21.7%)
		Cefoperazone	13 (10.1%)
		Cefixime	3 (2.3%)
		Ceftizoxime	3 (2.3%)
		Moxalactam	2 (1.6%)
		Cefpodoxime	1 (0.8%)
	Cephalosporins (4th generation)	Cefepime	48 (37.2%)
	Cephalosporins (other)	Cephalosporins (3rd/4th-generation)	1 (0.8%)
		Cephalosporins	1 (0.8%)
	Penicillins	Piperacillin	33 (25.6%)
		Ampicillin	29 (22.5%)
		Penicillin G	14 (10.9%)

		Oxacillin	11 (8.5%)
		Amoxicillin	10 (7.8%)
		Methicillin	2 (1.6%)
		Ticarcillin	2 (1.6%)
		Mezlocillin	1 (0.8%)
Quinolones/Fluoroquinolones		Ciprofloxacin	64 (49.6%)
		Levofloxacin	50 (38.8%)
		Ofloxacin	8 (6.2%)
		Moxifloxacin	6 (4.7%)
		Norfloxacin	4 (3.1%)
		Gatifloxacin	2 (1.6%)
		Pazufloxacin	1 (0.8%)
		not reported specifically	1 (0.8%)
Aminoglycosides		Amikacin	59 (45.7%)
		Gentamicin	59 (45.7%)
		Tobramycin	27 (20.9%)

		Streptomycin	11 (8.5%)
		Kanamycin	6 (4.7%)
		Sisomicin	1 (0.8%)
Penicillin combinations		Piperacillin/tazobactam	52 (40.3%)
		Ampicillin/sulbactam	27 (20.9%)
		Amoxicillin/clavulanate	12 (9.3%)
		Ticarcillin/clavulanate	4 (3.1%)
Macrolides		Erythromycin	14 (10.9%)
		Azithromycin	6 (4.7%)
		Clarithromycin	4 (3.1%)
Sulfonamides		Trimethoprim-Sulfamethoxazole	33 (25.6%)
		Sulfamethoxazole	22 (17.1%)
		not reported specifically	1 (0.8%)
Anti-tuberculosis		Rifampicin	23 (17.8%)
		Isoniazid	16 (12.4%)
		Ethambutol	10 (7.8%)

		Para-aminosalicylic acid	4 (3.1%)
		Capreomycin	3 (2.3%)
		Protionamide	3 (2.3%)
		Pyrazinamide	3 (2.3%)
		Cycloserine	1 (0.8%)
		not reported specifically	3 (2.3%)
Tetracyclines		Tetracycline	16 (12.4%)
		Minocycline	4 (3.1%)
Monobactams		Aztreonam	37 (28.7%)
Nitrofurans		Nitrofurantoin	13 (10.1%)
Lincosamides		Clindamycin	12 (9.3%)
Glycopeptides		Vancomycin	6 (4.7%)
		Teicoplanin	5 (3.9%)
Polypeptides		Polymyxin B	3 (2.3%)
		Colistin	2 (1.6%)
Oxazolidinones		Linezolid	3 (2.3%)

		Chloramphenicol	6 (4.7%)
		Fosfomycin	6 (4.7%)
Others		Metronidazole	3 (2.3%)
		Quinupristin/Dalfopristin	2 (1.6%)
		Tigecycline	6 (4.7%)

*Antibiotics are reported as mentioned in the papers (No.=number of papers). Because some papers reported multiple susceptibility results for multiple antibiotics, the individual rows will add up to more than 100%.

8.3 Information on clinical assessments found to be a significant risk factor in patients

Risk factors	**Reported terms**	**Reference number (see Additional file 3; list of included papers)**	**Study method**	**OR**	**P value**	**Results of case group***	**Results of control group***

Abnormal laboratory test results	Blood glucose (mmol/L)	31	case control	2.6	0.00**	9 ± 7	6 ± 3
	Hemoglobin (g/L)	31	case control	1.7	0.00**	104 ± 26	114 ± 26
	Serum albumin (g/L)	115	case control	2.1	0.03	25.28 ± 5.37	30.56 ± 6.55
	Positive TB sputum smear	35	cross-sectional	6.4	0.00**	56/58 (96.6%)	44/54 (81.5%)
		54	case control	1.4	0.02	304/386 (78.8%)	1663/2582 (64.4%)
Bacteria-related risk factors	*M. Tb* developed resistance to additional antibiotic***	49	case control	6.3	0.01	4/64 (6.3%)	32/541 (5.9%)
				4.5	0.02	7/64 (10.9%)	70/541 (12.9%)
		54	case control	1.6	0.00**	90/302 (40.7%)	444/1488 (29.8%)
				1.5	0.00**	120/302 (39.7%)	357/1488 (24.0%)
				5.1	0.00**	180/132 (18.9%)	529/1488 (35.6%)
				4.3	0.00**	57/302 (18.9%)	57/1488 (3.8%)
				3.9	0.00**	148/302 (49.0%)	586/1488 (39.4%)
	Produce ESBL	30	case control	4.9	0.00**	47/70 (67.1%)	68/234 (29.1%)
		100	case control	18.8	0.00**	47/56 (83.9%)	15/69 (21.7%)

		124	case control	7.2	0.00**	65/96 (67.7%)	40/192 (20.8%)
		126	case control	22.9	0.00**	64/71 (90.1%)	25/71 (35.2%)
	Virulence genes *esp*	110	case control	6.7	0.03	18/18 (88.9%)	39/72 (54.2%)
Physical functional scoring systems****	APACHE II score	21	retrospective cohort study	1.8	0.03	21.9 ± 6.8	18.0 ± 4.9
	APACHE II score (over 20 points)	168	case control	4.1	0.00**	48/84 (57.1%)	39/153 (32.7%)
		67	case control	4.6	0.04	18/30 (60.0%)	10/30 (33.3%)
		137	case control	8.1	0.00**	91/155 (58.7%)	15/46 (32.6%)
	Encephalopathy Grades (II-IV level)	37	prospective cohort study	3.7	0.01	60/70 (85.7%)	48/82 (58.5%)
		36	case control	2.3	0.01	52/57 (91.2%)	137/418 (32.8%)
	mMRC dyspnea scores	5	retrospective cohort study	1.9	0.00**	2.8 ± 1.2	1.5 ± 1.2
	Modified Reiff High-resolution Computed Tomography (HRCT) score	5	retrospective cohort study	1.2	0.00**	12.8 ± 5.0	9.4 ± 3.4

	NYHA Classification (III or IV level)	76	case control	2.5	0.00**	141/150 (94.0%)	94/128 (73.4%)
	SOFA score (>5 points)	94	case control	1.9	0.03	3.89 ± 1.91	2.19 ± 1.63
	Wagner Classification (3-5 level)	97	case control	2.9	0.01	51/76 (67.1%)	15/76 (67.1%)
	Pitt Bacteremia score (>3 points)	57	case control	1.5	0.00**	5.05 ± 2.46	2.42 ± 2.40
	Pitt Bacteremia score (>4 points)	32	case control	7.7	0.00**	31/66 (47.0%)	8/132 (6.1%)

* Results reported as mean ± standard deviations or number of patients/Total number of patients and their proportions (%)

** The p-values reported by the papers approach 0.00.

*** *M. Tb* refers to *Mycobacterium tuberculosis*.

**** Physical functional scoring systems refers to clinical assessments: Acute Physiology and Chronic Health Evaluation II score (APACHE II) (Haniffa et al. 2018); Hepatic encephalopathy Grade (Weissenborn 2019); modified score of Medical Research Council (mMRC) Dyspnea Scale (Vestbo et al. 2013); modified Reiff score of High-resolution Computed Tomography (HRCT) (Reiff et al. 1995); New York Heart

Association (NYHA) Classification (Criteria Committee of the New York Heart Association 1994); Pitt Bacteremia score (Rhee et al. 2009); Wagner classification (Wagner 1981); Sepsis-related Organ Failure Assessment (SOFA) scores (Vincent et al. 1996).

9 CURRICULUM VITAE

Personal information

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Sex: Female

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Education

October 2016-till date	*PhD candidate* In Heidelberg Institute of Global Health, Medical Faculty, Heidelberg University, Germany
September 2013-July 2016	*Master Degree on Management* in School of Public Health, Dalian Medical University, China
September 2008-July 2013	*Bachelor Degree on Medicine* in School of Public Health, Dalian Medical University, China

Awards received

- 2016-2020 *PhD Scholarship*, China Scholarship Council (CSC)

- 2015 “The national scholarship” (Top 3% students), awarded by the Ministry of Education of People’s Republic of China

Conference participations

- The 35th Jahrestagung der Gesellschaft für Tropenpädiatrie & Internationale Kindergesundheit (GTP). 2017, Heidelberg, Germany
- COVID-19 International Experience Sharing & Exchange, International Public Health Management Training (online). 2020

Clinical practices

August 2014-March 2016	Internship for control and prevention of Tuberculosis, Tuberculosis Hospital of Dalian, China
March 2013-July 2013	Internship for Hospital Management in the 406th Hospital of the Chinese People’s Liberation Army, China
March 2011-July 2011	Internship as clinical practice in the 3rd Hospital of Anshan (Orthopedic Hospital), China

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EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zu dem Thema

   ……

   Handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.
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