Problematic Groups of Multidrug-Resistant Bacteria and Their Resistance Mechanisms

Verena Kohler, Ankita Vaishampayan, and Elisabeth Grohmann

Abstract

The occurrence of multidrug-resistant pathogenic bacteria is steadily increasing, not only in medical centers but also in food, animals and the environment, which is of primordial concern for health authorities worldwide. The World Health Organization (WHO) published a global pathogen priority list to encourage international interdisciplinary research initiatives on the occurrence, dissemination, and epidemiology of the most dangerous multiresistant pathogens with the aim to develop effective prevention strategies against the spread of these bugs and new therapeutic approaches to treat infections in agreement with the One Health concept. According to the WHO global pathogen priority list, the most critical resistant pathogens include carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* and carbapenem-resistant as well as third-generation cephalosporin-resistant *Enterobacteriaceae.* This critical group is followed by pathogens of high priority including vancomycin-resistant *Enterococcus faecium*, methicillin- and vancomycin-resistant *Staphylococcus aureus*, and clarithromycin-resistant *Helicobacter pylori*. Here, we summarize recent data on the occurrence and spread of these and other harmful resistant pathogens, on their resistance mechanisms as well as on the modes of resistance spread, as far as is known. We finish the chapter with an outlook on promising innovative strategies to treat infectious diseases caused by multiresistant pathogens – in combination with antibiotic therapy – as well as on approaches to combat the antibiotic resistance spread.

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Antibiotic resistance · Bacterial pathogen · Biofilm · Horizontal gene transfer · Multidrug resistance · WHO pathogen priority list

Abbreviations

Agr	accessory gene regulator
BLNAR	ß-lactamase-negative ampicillin resistant
CDC	Centers for Disease Control and Prevention
COPD	chronic obstructive pulmonary disease
CRAb	carbapenem-resistant *Acinetobacter baumannii*
CRE	carbapenem-resistant *Enterobacteriaceae*
CRPa	carbapenem-resistant *Pseudomonas aeruginosa*
ESBL	extended spectrum ß-lactamase
EU	European Union
FDA	Food and Drug Administration
G-	Gram-negative
HGT	horizontal gene transfer
ICU	intensive care unit
IMP	active on imipenem
IS	insertion sequence
KPC	*Klebsiella pneumoniae* carbapenemase
MBL	metallo-ß-lactamase
MDR	multidrug resistant
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *S. aureus*
NDM	New Delhi MBL
OMP	outer membrane protein
OXA	oxacillinase
PBP	penicillin-binding protein
PMQR	plasmid-mediated quinolone resistance
PNSP	penicillin-non-susceptible *Streptococcus pneumoniae*
RND	resistance-nodulation-cell division
SCC*mec*	staphylococcal chromosome cassette *mec*
VIM	Verona integron-encoded MBL
VRE	vancomycin-resistant *Enterococci*
VREfm	vancomycin-resistant *E. faecium*
VRSA	vancomycin-resistant *S. aureus*
WHO	World Health Organization
XDR	extremely multidrug resistant

1 Introduction

Antibiotic drugs are unquestionably the most successful form of chemotherapy, and since people started to use them commercially, antibiotics have increased life expectancy in recent history by up to two decades (Shallcross 2014; Martens and Demain 2017). Nevertheless, modern mankind is facing the so-called antimicrobial resistance crisis (Barriere 2015; Martens and Demain 2017), annually accounting for an estimated two million antibiotic-resistant infections worldwide. It is proposed that, by 2050, 10 million deaths worldwide will be attributed to this issue (Robinson et al. 2016). In past times, the arsenal of new antibiotic drugs was satisfactory to manage the observed resistance in bacteria, but in recent years, overconsumption combined with the inappropriate prescription of antibiotics has resulted in the elevated occurrence of multidrug-resistant (MDR) and extremely multidrug-resistant (XDR) bacteria (Davies and Davies 2010; Banin et al. 2017). Beyond the abusive and not indicated use of antibiotics, poor infection control and substandard sanitation contribute to the resistance crisis. Widespread use of antibiotics in the agricultural industry has further accelerated this problem (Srinivas et al. 2017). For livestock applications, 50–80% of antibiotic drugs are administered (Cully 2014; Chang et al. 2015b), with a large fraction used at sub-therapeutic concentrations, aiming to promote growth and prevent diseases of livestock in several countries (Ter Kuile et al. 2016). Nevertheless, the European Union (EU) has banned the use of antibiotics as growth promotors. Further, countries outside the EU (such as the USA and Australia) have restricted the application of antibiotics in agriculture (Cogliani et al. 2011; Maron et al. 2013). Major mechanisms of how bacteria exert antibiotic resistance is, in addition to biofilm formation, also by acquiring new determinants via horizontal gene transfer (HGT) and mutations leading to suppressed antibiotic susceptibility (Blair et al. 2015). Bacterial biofilms in general show increased resistance to exsiccation, clearance by the immune system and lower susceptibility to antibiotics (Høiby et al. 2011). The increase in international mobility in the twenty-first century has had further strong effects on the spread of pathogenic bacteria throughout the world (Harvey et al. 2013; Laxminarayan et al. 2013; Shallcross 2014). The observed increasing rates of global antibiotic resistance has been accompanied with a decline in the number of companies developing new antibiotic drugs. Further, the number of approvals for new agents has significantly decreased (Chaudhary 2016; Sciarretta et al. 2016). This evolves as a major threat, as within a few years after the commercial introduction of new antibiotic drug, resistant strains are reported (Davies and Davies 2010; Smith et al. 2015). Since 1998, only two antibacterial agents that were approved by the Food and Drug Administration (FDA) have had a novel mechanism of action (Spellberg et al. 2004; Luepke et al. 2017). The problem of modified agents of known drug classes is, when widely applied, antibiotic-resistant bacterial strains might evolve more rapidly (World Health Organization 2001; Jensen et al. 2010). Thus, there is an urgent need for discovering new targets and designing new compounds. Recently, alternative therapeutics, such as phage therapy or antibodies, for the treatment of infections have been discussed

(Natan and Banin 2017; Pachón-Ibáñez et al. 2017; Tracanna et al. 2017; van der Meij et al. 2017).

Taking the alarming development and the imminence of antibiotic resistance into account, the WHO was asked to create a priority list of bacteria other than multiresistant *Mycobacterium tuberculosis*, in the hope it would support and focus research on the development of new antibiotic drugs effective against these pathogens. The introduced WHO global priority pathogen list aims to take a step forward in addressing this global crisis of antimicrobial resistance (World Health Organization 2017; Willyard 2017; Tacconelli et al. 2017). Thus, a multi-criteria decision analysis method was applied to prioritize resistant bacteria. Twenty bacterial species were selected and organized into three groups based on ten criteria. These three groups divided bacteria into critical, high-, and medium-priority pathogens (Fig. 1) (Tacconelli et al. 2017).

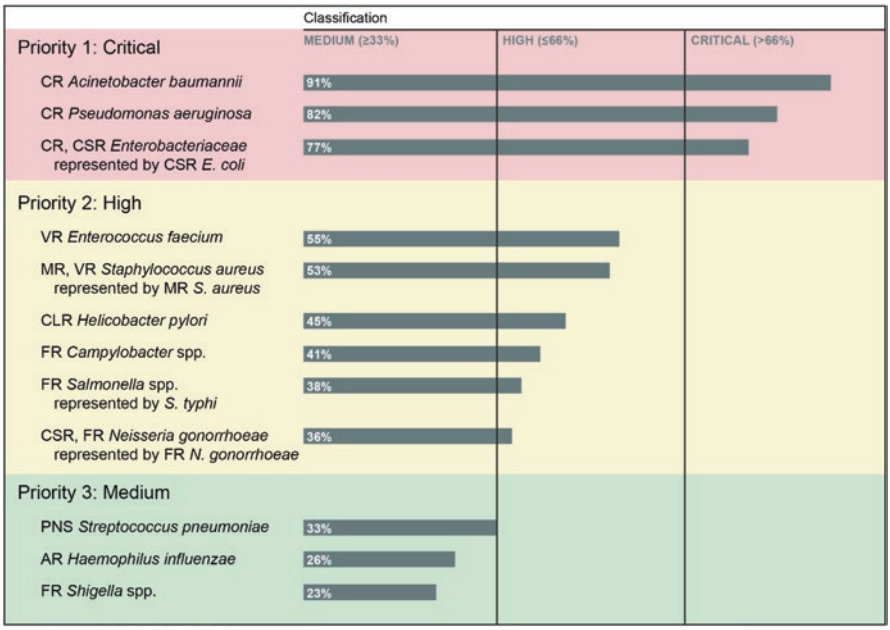

Fig. 1 Ranking of antibiotic-resistant bacteria according to the 10-criteria catalogue**.** Antibiotic-resistant bacteria were categorized according to ten criteria: treatability, mortality, healthcare burden, trend of resistance, prevalence of resistance, transmissibility, community burden, preventability in the healthcare setting, pipeline, and preventability in the community setting. 20 strains of drug-resistant bacteria were ranked and grouped according to the highest representative. Pathogens exhibiting more than 66% of the final weight were assigned to the priority 1 (critical) group, those between 33% and 66% were assigned to priority 2 (high), and bacteria less or equal 33% of final weight were ascribed to priority 3 (medium). *CR* carbapenem resistant, *CSR* 3rd-generation cephalosporin resistant, *VR* vancomycin resistant, *MR* methicillin resistant, *CLR* clarithromycin resistant, *FR* fluoroquinolone resistant, *PNS* penicillin non-susceptible, *AR* ampicillin resistant. (Figure adapted from Tacconelli et al. (2017))

In this review, we will give detailed information on bacterial species that, according to the WHO's global priority pathogen list, represent the most imminent dangers, further fueling the antibiotic resistance crisis. In addition to providing statistical information about their distribution, we will focus on the underlying mechanisms that have ultimately led to their emergence as antibiotic-resistant pathogens.

2 The Global Priority Pathogen List

2.1 Priority 1: Critical

2.1.1 Carbapenem-Resistant *Acinetobacter baumannii*

Acinetobacter are non-glucose-fermenting Gram-negative (G-) coccobacilli, primarily related with healthcare-associated infections. These bacteria harbor extensive intrinsic resistance determinants and have the capability to acquire new resistance factors (Peleg et al. 2008). *Acinetobacter baumannii*, an opportunistic pathogen, is associated with hospital-acquired infections and outbreaks worldwide, affecting particularly critically ill patients (Runnegar et al. 2010; Correa et al. 2017). The first reported *Acinetobacter* infections within an intensive care unit (ICU) date back to the 1960s (Stirland et al. 1969). Early *Acinetobacter*-mediated infections were easily treatable with ß-lactams and sulfonamides (Stirland et al. 1969; Abrutyn et al. 1978), but these treatment strategies shortly evolved to be inefficient due to the rising resistance rates (Lecocq and Linz 1975). In the 1980s, carbapenems were used as therapeutics to treat infections caused by MDR bacteria, but resistances to these antibiotics in *Acinetobacter* were reported shortly after their commercial introduction (Paton et al. 1993; López-Hernández et al. 1998; Gonzalez-Villoria and Valverde-Garduno 2016). Carbapenems are broad-spectrum ß-lactam antibiotics, widely used as last-line antibiotics, especially for the treatment of critically ill patients and infections induced by antibiotic-resistant G- bacteria (Papp-Wallace et al. 2011).

A. baumannii colonization rates in healthy humans are low (about 1%) but higher in some Asian populations. Community-acquired infections caused by carbapenem-resistant *A. baumannii* (CRAb) are uncommon and most likely occur in patients with underlying pulmonary disease, renal failure, diabetes, or excessive alcohol abuse (Falagas et al. 2007a). Nosocomial outbreaks of *A. baumannii* are generally difficult to control, as this bacterium is able to survive on abiotic surfaces for extended periods of time. The hands of the hospital staff are a common mode of transmission, but the spread can also be caused by exposure to contaminated equipment and aerosolized water droplets (Dijkshoorn et al. 2007). Elderly people, especially those in long-term care facilities, were shown to be an important reservoir of MDR *A. baumannii* (Denkinger et al. 2013).

In the 1990s, multiresistant strains were first detected in Asia, where they developed as a great public health challenge (Kuah et al. 1994; Siau et al. 1996). In South and Southeast Asian hospitals, high rates of carbapenem resistance among G- pathogens, especially in *A. baumannii* isolates, were observed (Hsu et al. 2017). In some

Asian countries, including Malaysia, Thailand, Pakistan, India, and Taiwan, *A. baumannii* belongs to the group of most abundant nosocomial pathogens (Chawla 2008). In Korea, the resistance rate of *A. baumannii* to imipenem, a representative of carbapenems, had increased to 85% by 2015, thus representing an enormous health threat (Kim et al. 2017). A combination of factors involving non-indicated prescription of antibiotic drugs and international travel, including medical tourism, contributed to the accelerated rise and spread of *A. baumannii* in South and Southeast Asia (Hsu et al. 2017). Interestingly, the increased frequency of *A. baumannii* isolated in the clinical setting showed a high correlation with the observed rise in antibiotic resistance (Carlquist et al. 1982). In the USA, it was observed that when *A. baumannii* causes healthcare-associated infections, more than 60% of the isolates showed resistance to carbapenems (Sievert et al. 2013). Even though the occurrence of *A. baumannii* changed only marginally from 2000 to 2009 in the USA, an ongoing decrease concerning the susceptibility to most classes of antibiotic drugs was observed. Further, a threatening third of all isolates manifested combined resistances to carbapenems, aminoglycosides, and fluoroquinolones (Landman et al. 2007).

While uncomplicated urinary tract infections and other minor infections have low mortality, patients with bloodstream infections from CRAb showed mortality rates of more than 40% (Wisplinghoff et al. 2004; Munoz-Price et al. 2010). Between 2010 and 2014, 60 cases of bacteremia caused by CRAb from 7 states in the USA were studied. Catheter-related bloodstream infections were the most abundant infections observed, and nearly half of the patients died within 30 days of diagnosis (Olesky et al. 2017). *Acinetobacter* infections are generally associated with several risk factors, including the use of mechanical ventilation and previous antimicrobial therapy. Prior hospitalization, longer duration of hospital stay, especially in ICUs, but also preceding the prescription of carbapenems, and the use of invasive procedures were identified as potential risk factors (Sheng et al. 2010).

The ability of *A. baumannii* to form biofilms most probably contributes to the observed prolonged survival on abiotic surfaces leading to subsequent transmission (de Breij et al. 2010). Further, biofilm formation on urinary catheters, central venous catheters, and endotracheal tubes may also prompt infection (Longo et al. 2014).

Differing but complementary mechanisms leading to reduced carbapenem susceptibility have been described for *A. baumannii* (Vila et al. 2007; Tang et al. 2014). The mechanisms of resistance include various carbapenemases (most commonly oxacillinases, OXA, and metallo-ß-lactamases, MBLs), AdeABC efflux systems, modification of penicillin-binding proteins (PBPs), and modification of outer membrane proteins (porins) (Yoon et al. 2015). A major intrinsic resistance mechanism is facilitated by the reduced number and size of certain outer membrane proteins (OMPs), leading to a compromised bacterial permeability to antibiotics than when compared to other G- organisms (Vila et al. 2007). Three OMPs have been associated with carbapenem non-susceptibility (Poirel et al. 2011). Intrinsic resistance-nodulation-cell division (RND)-type efflux pumps such as AdeABC, AdeFGH, and AdeIJK further play a role in carbapenem non-susceptibility (Yoon et al. 2015). The main way for resistance is hydrolysis of the drugs by an arsenal of intrinsic and

acquired carbapenem-hydrolyzing ß-lactamases (carbapenemases). The acquirement of carbapenemases, such as Ambler class A carbapenemases, class B MBLs, and class D oxacillinases, leads to the observed increased emergence of carbapenem resistance. Molecular classes A, C, and D comprise ß-lactamases characterized by a serine in their active site, while class B ß-lactamases are metalloenzymes containing zinc in their active center. While rare-chromosomally encoded cephalosporinases (Ambler class C enzymes) may possess a slightly extended activity on carbapenems, they most likely play a minor role in the clinics. Carbapenemases with catalytic efficiency on carbapenems are mostly grouped into Ambler classes A, B, and D (Queenan and Bush 2007). Ambler class B carbapenemases comprise a broader spectrum than the other enzyme classes. They show a strong hydrolytic activity against most ß-lactam antibiotics and are not inhibited by ß-lactam inhibitors (Palzkill 2013). Ambler class D OXA-type ß-lactamases are native chromosomal oxacillinases and are encoded by several bla$_{OXA}$ genes, the most common are *bla*$_{OXA\text{-}23\text{-like}}$, *bla*$_{OXA\text{-}24\text{-like}}$, *bla*$_{OXA\text{-}51\text{-like}}$, and *bla*$_{OXA\text{-}58\text{-like}}$ genes. These enzymes and the presence of insertion sequences (IS), like IS*Aba1*, IS*Aba3,* IS*Aba4*, and IS*Aba9,* play an important role in the development of CRAb. While native chromosomal oxacillinases are generally expressed in low abundance, IS contribute to the mobilization and expression of the OXA-type-ß-lactamases, thus conferring carbapenem resistance. The IS*Aba1* sequence is the most prevalent and was described in *A. baumannii* isolates for the first time in 2001. This IS has been found to be associated with a number of OXA-type ß-lactamases (Evans and Amyes 2014). Today OXA-23 belongs to the most prevalent subgroup of oxacillinases worldwide (Mugnier et al. 2009; Poirel et al. 2011).

Many CRAb isolates were further shown to be MDR, carrying additional resistance determinants for several other groups of antibiotics like aminoglycosides, fluoroquinolones, and tetracycline (Doi et al. 2015), thus leading to a major threat to modern healthcare and significantly fueling the global resistance crisis.

2.1.2 Carbapenem-Resistant *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is an opportunistic pathogen frequently responsible for nosocomial infections (Rossi Gonçalves et al. 2017), especially in ICUs or in patients with predisposing conditions (Pirnay et al. 2009). This bacterium can be found ubiquitously in the hospital, not only associated with patients or hospital staff but also on abiotic surfaces (Tsao et al. 2017). *P. aeruginosa* is the causative agent of pneumonia, urinary tract infections, and infections of skin and soft tissue but is especially implicated in pneumonia of critically ill and/or immunocompromised patients. The pathogen is prevalently isolated from the respiratory tracts of patients with chronic lung disease, such as cystic fibrosis (Aloush et al. 2006; Gellatly and Hancock 2013). Delayed detection and treatment lead to rapid progression to respiratory failure, sepsis, and multi-organ failure, which are all associated with high mortality rates (Kang et al. 2003). *P. aeruginosa* is also often isolated from lakes, sewage, soil, animals, plants, and plant detritus (Pirnay et al. 2009), and resistant strains are detected in swimming pools and hot tubs in the USA (Lutz and Lee 2011). Carbapenem-resistant *P. aeruginosa* (CRPa) was also detected in wastewater

treatment plant effluent and in downstream rivers in Switzerland (Czekalski et al. 2012; Slekovec et al. 2012). These strains act as a potential reservoir for determinants of carbapenem resistance (Pappa et al. 2016).

The highest rates of carbapenem resistance in *P. aeruginosa* were observed in Eastern Europe, with Hungary, Slovakia, Poland, Lithuania, Croatia, Romania, Bulgaria, and Greece presenting resistance rates of >25% (European Centre for Disease Prevention and Control 2015). An extensive spread of carbapenemase-producing clones was observed in Belarus, Kazakhstan, and Russia, thus showing a gradient of resistance in Europe that rises from Northwest to Southeast (Edelstein et al. 2013). In Brazil, 43.9% of the isolates from patients with *P. aeruginosa* bacteremia, most of them from ICU residents, were carbapenem resistant. Among these patients, 31.2% received inadequate therapy, and the mortality rate was as high as 58.6% (Rossi Gonçalves et al. 2017). In Brazil, the high prescription rate of antibiotics, particularly of ß-lactams, carbapenems, and fluoroquinolones (Rodrigues Moreira et al. 2013) was described to be instrumental in *P. aeruginosa* developing resistance to various antibiotic agents during therapy. This was shown to occur either by mutation in chromosomal genes or by HGT (Zavascki et al. 2005; Xavier et al. 2010). The carbapenem resistance of *P. aeruginosa* in Brazil is mostly due to the production of MBLs (Rossi Gonçalves et al. 2017). In some hospitals, the resistance rates can be up to 60% (Kiffer et al. 2005; Baumgart et al. 2010). In Taiwan, 15.9% of the *P. aeruginosa* isolates from infected patients were carbapenem resistant. This study stated that the risk of infection with CRPa increased by 1% with each day in hospital (Tsao et al. 2017); thus, prolonged stays in healthcare settings were identified as a major risk factor leading to *P. aeruginosa*-mediated infections. Further risk factors include the preceding use of antibiotics, invasive procedures, comorbidities, and antecedent surgery. Mechanical ventilation, enteral/nasogastric tubes and inappropriate therapy are also associated with bacteremia by CRPa (Rossi Gonçalves et al. 2017). Infections caused by resistant *P. aeruginosa* are further frequently related with age, cancer, heart disease, diabetes, and invasive procedures like hemodialysis and tracheostomy (Aloush et al. 2006; Buehrle et al. 2017). The presence of a central venous catheter as a significant risk factor is a matter of debate, as some studies suggest that catheter exchange helps to prevent *P. aeruginosa* biofilm formation and thus significantly reduced infection risk (Jamal et al. 2014), whereas others did not identify these as priority risk factors (Rossi Gonçalves et al. 2017).

The capability of *P. aeruginosa* to form biofilms (Suárez et al. 2010) has enabled the bacterium to proliferate in water distribution systems and colonize central venous catheters (Fig. 2) (Wang et al. 2012; Jamal et al. 2014). As example, all strains analyzed in the Brazil study mentioned above were identified as strong biofilm producers (Rossi Gonçalves et al. 2017). Additionally, all MBL-positive *P. aeruginosa* isolates from Brazil showed the ability to form biofilms in vivo (Perez and Bonomo 2018). The severity of infections, especially associated with invasive procedures, might be more pronounced due to biofilm formation, as the antibiotic is inhibited from penetrating the cells by the surrounding polymeric matrix composed of polysaccharides, proteins, and DNA (Costerton et al. 1999; Hoiby et al. 2010).

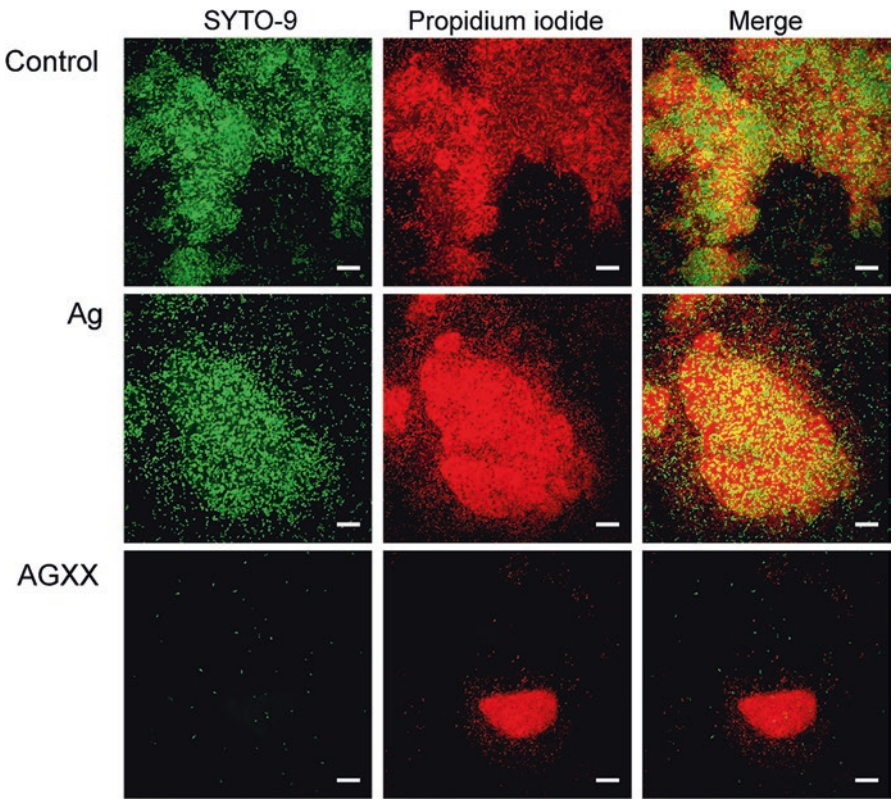

Fig. 2 Biofilm formation in *Pseudomonas aeruginosa*
Confocal images of biofilm formation by *Pseudomonas aeruginosa*. *P. aeruginosa* was grown on sterile coverslips for 24 h. The 24-h-old biofilms were exposed to silver (Ag) sheet or AGXX® sheet. The control panel refers to biofilm without any metal sheet. Biofilms were stained with SYTO9 (green) and Propidium Iodide (red) to visualize live and dead cells. Images show an average of Z-projections (500 nm spacing). Scale bars are 10 μm

The production of different enzymes, the lack of the outer membrane porin OprD, and the RND efflux pump systems MexAB-OprM and MexCD-OprJ, encoded on the genome, lead to the intrinsic resistance of *P. aeruginosa* to several classes of antibiotics. Resistance determinants, such as carbapenemase production, can also be acquired by HGT (Pirnay et al. 2009; Breidenstein et al. 2011; Poole 2011). Thus, *P. aeruginosa* has a great potential for developing a MDR phenotype (Schwartz et al. 2015).

Mutations in or lack of the porin OprD was shown to contribute to carbapenem resistance in clinical isolates of *P. aeruginosa* in Spain. OprD is a substrate-specific porin responsible for diffusion of amino acids (and also carbapenems) into the bacterial cell (Rojo-Bezares et al. 2014). A direct association between imipenem (a carbapenem) susceptibility and the levels of OprD expression was shown. Expression of OprD was not detected in imipenem-resistant isolates, whereas susceptible

bacteria showed close to normal expression levels (Dib et al. 1995). During imipenem treatment of *P. aeruginosa* infections in French hospitals, the most common mechanism of resistance was shown to be mutations in or loss of the porin OprD, with more than 85% of the isolates having lost the *oprD* gene (Fournier et al. 2013). Overproduction of chromosomally encoded AmpC ß-lactamases (also called cephalosporinase) and efflux pumps are further implicated in meropenem (a carbapenem) resistance in *P. aeruginosa* (Rodríguez-Martínez et al. 2009).

Expression/overproduction of RND efflux pumps further reduces carbapenem efficiency in *P. aeruginosa* (Choudhury et al. 2015; Pan et al. 2016). The MexAB-OprM efflux pump system plays a significant role in the intrinsic non-susceptibility of *P. aeruginosa* toward meropenem, quinolones, tetracycline, and chloramphenicol.

An important resistance mechanism of strains non-susceptible to ß-lactams is the expression of acquired carbapenemases. These isolates are usually resistant to all ß-lactams (Breidenstein et al. 2011; Poole 2011). Especially class B carbapenemases or MBLs are primarily encountered, with IMP-type (active on imipenem) enzymes predominantly encountered in Asia and VIM-type (Verona integron-encoded MBL) enzymes mostly found in Europe. Nevertheless, both enzymes are increasingly spreading globally (Walsh et al. 2005; Poole 2011). The most abundant carbapenemase is VIM; it can be plasmid-mediated and multiple copies lead to high-level meropenem resistance (San Millan et al. 2015), but it is usually integron-associated. IMP-6, another MBL, was demonstrated to be acquired from environmental bacteria by HGT (Xiong et al. 2013). Generally, MBLs occur as part of an integron structure on large genomic islands on the bacterial chromosome, but it was shown that they can also be encoded on transferable plasmids (Wright et al. 2015).

2.1.3 Carbapenem- and Third-Generation Cephalosporin-Resistant *Enterobacteriaceae*

Several representatives of G- *Enterobacteriaceae* are human pathogens, including *E. coli*, *Klebsiella* ssp., *Proteus* spp., *Enterobacter* spp., and *Serratia* spp. *Enterobacteriaceae* represent 50% of bacteremia cases, which are usually caused by redistribution of bacteria from their primary sites (Wilson et al. 2011). Infections with *Enterobacteriaceae,* most commonly arising from the gastrointestinal tract, involve high morbidity and mortality (Patel et al. 2008; Yamamoto and Pop-Vicas 2014). Even though infections caused by G+ pathogens are more common in healthcare settings, the highest mortality rate is associated with *Enterobacteriaceae* and other G- organisms (Wilson et al. 2011). *E. coli* and *Klebsiella pneumoniae* are the most abundant community – as well as hospital-acquired pathogens. These bacteria typically cause intra-abdominal infections, urinary tract infections, and primary bacteremia (Alhashem et al. 2017). Patient-to-patient transmission is comparably low, however, *K. pneumoniae* shows a higher rate of transmission than *E. coli* (Harris et al. 2007; Hilty et al. 2012).

Enterobacteriaceae are getting increasingly resistant to first- and second-line antibiotic drugs. Carbapenems are usually the treatment strategy for life-threatening infections by MDR *Enterobacteriaceae*, some of which produce extended spectrum

ß-lactamases (ESBLs). Infections with ESBL-producing G- bacteria and carbapenem-resistant *Enterobacteriaceae* (CRE) are increasing worldwide. Different geographical regions reveal carriage rates varying over time, but ESBL-producing *Enterobacteriaceae* occur globally nowadays, and carriage rates ranging from 8 to 28.8% have been reported in ICUs in Jerusalem and Korea, respectively (Friedmann et al. 2009; Kim et al. 2014). ESBL and AmpC enzymes together are responsible for the majority of the observed third-generation cephalosporin resistances in clinical isolates worldwide (Molton et al. 2013). In North American and European hospitals, those rates are around 10% for both *E. coli* and *K. pneumoniae*, while nosocomial ESBL rates as high as 80% and 60% were found in India and China, respectively (Livermore 2012). In the Indian community, *E. coli* resistance rates were as high as in the hospital environment. This might be due to the unregulated use of antibiotic drugs in agriculture and lower sanitation standards (Chaudhuri et al. 2011). In China, the rate of ESBL-positive strains among *E. coli* increased severely from 36.1% in 2002/2003 to 68.1% in 2010/2011 (Lai et al. 2014). For about three decades, a spreading of plasmid-mediated ß-lactamases in *Enterobacteriaceae* has been reported in Brazil. ESBL-producing strains, especially *K. pneumoniae* as the predominant pathogen, are widely distributed in healthcare settings (Sampaio and Gales 2016). In the USA, 18% of healthcare-associated infections in acute care hospitals and acute rehabilitation facilities can be attributed to ESBL-producing *Enterobacteriaceae* (Weiner et al. 2016).

The inadequate antibiotic prescription and inappropriate use of antibiotic drugs accelerated the spreading of CRE, leading to public concern. Selection pressure by the prescription of carbapenem antibiotics has been proposed to fuel the rapid spread of CRE (Yigit et al. 2001; Potter et al. 2016). In Europe, 17 countries reported increased dissemination or occurrence of CRE between 2010 and 2013 (Glasner et al. 2013). Infections caused by CRE especially affect severely ill patients with multiple comorbidities. ICU-resident patients revealed a notably high burden of infections with CRE and increased mortality when compared to non-ICU patients (Debby et al. 2012; Tischendorf et al. 2016; Papadimitriou-Olivgeris et al. 2017). Among ICU-resident patients in Israel, colonization with CRE was associated with at least a two-fold increase in the risk of infection by the colonizing strain (Dickstein et al. 2016). Recently, *E. coli, K. oxytoca*, and *Enterobacter cloacae* were frequently reported to harbor carbapenem resistance (Tzouvelekis et al. 2012; Gomez-Simmonds et al. 2016). Among the hospitalized patients, 3–7% are colonized by CRE in endemic areas, but these rates can vary between 0.3% and 50% depending on the healthcare setting, with the highest rates achieved in a Greek hospital (Banach et al. 2014; Bhargava et al. 2014; Papadimitriou-Olivgeris et al. 2012; Swaminathan et al. 2013; Vatopoulos 2008; Vidal-Navarro et al. 2010; Wiener-Well et al. 2010; Zhao et al. 2014). Greece has one of the highest rates of carbapenem-resistant G-bacteria globally. By 2008, carbapenem resistance had increased to 30% in hospitals and to 60% in ICUs (Walsh et al. 2005). A study in a tertiary hospital in China revealed that *K. pneumoniae* and *E. coli* were the most prevalent species. More than 70% of all nosocomial isolates exhibited high levels of resistance against ß-lactam antibiotics, while 64.9% of the strains harbored carbapenemase genes (Yang et al.

2017). CRE have also become widely distributed in the USA with 140,000 cases of nosocomial infections annually that show mortality rates between 26 and 44% (Centers for Disease Control and Prevention 2013; Falagas et al. 2014). Furthermore, *K. pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* became prevalent in Brazil in the last 10 years. KPC production is reported to be the most common resistance mechanism in carbapenem-resistant *K. pneumoniae* (Sampaio and Gales 2016).

Colonization of ICU patients with CRE is a massive risk factor for subsequent infection with *K. pneumoniae*. Almost 50% of the patients in a hospital in the USA developed an infection within 30 days after having been tested positive for colonization with the pathogens. Endoscopy and colonoscopy were shown to be risk factors for these infections (McConville et al. 2017). Further risk factors for increased susceptibility to CRE were the prescription of ß-lactam antibiotics within 30 days and receiving trimethoprim-sulfamethoxazole or glucocorticoids concomitant with an onset of bloodstream infection, as observed in a hospital environment in the USA (Bratu et al. 2005). Other risk factors were described to be comorbid conditions, prolonged hospital stay, critical illness, invasive medical devices, and mechanical ventilation (Falagas et al. 2007b; Gupta et al. 2011; Munoz-Price et al. 2013; Temkin et al. 2014). Long-term acute care hospital-resident patients experienced additional risk. For example, in Chicago 30.4% of patients in long-term facilities were colonized with KPC-producing *Enterobacteriaceae*, while only 3.3% of ICU patients from short-stay hospitals tested positive for colonization (Lin et al. 2013).

Genes encoding ß-lactamases on mobile genetic elements are one major mechanism contributing to the rapid dissemination of MDR G- bacteria worldwide. The most abundant mechanisms of ß-lactam resistance in *Enterobacteriaceae* were indeed described to be caused by the production of ESBLs, and a smaller proportion was due to altered efflux pump levels/activities or porin expression. ESBLs are mostly plasmid-encoded and can hydrolyze penicillins, broad-spectrum cephalosporins, and oxyimino-monobactams. These enzymes alone are not effective against cephamycins or carbapenems (Bradford 2001; Paterson and Bonomo 2005).

Enterobacteriaceae, harboring transmissible carbapenem resistance, have emerged as a big issue within the last two decades, and ß-lactamases present in these pathogens are a further driving force of resistance (Logan and Weinstein 2017). Major resistance mechanisms observed in CRE are the expression of high-level ESBLs or AmpC enzymes combined with mutations of porins, leading to decreased permeability to carbapenems or the acquisition of carbapenemase genes (Dai et al. 2013).

One resistance mechanism is mainly facilitated by plasmid-encoded ESBLs and AmpC cephalosporinases. AmpC activity in *Enterobacteriaceae* is mostly related with overproduction or derepression of chromosomal genes. Both enzyme types, when combined with mutations of porins, are described to confer resistance to carbapenems. Altered or completely lost porins can reduce diffusion into bacterial cells to rates that enable the action of ESBLs and AmpC enzymes (Paterson and Bonomo 2005; Bush and Fisher 2011). Further, drug efflux pumps and alterations in PBPs are associated with carbapenem non-susceptibility (Patel and Bonomo 2013).

KPC-producing *K. pneumoniae* was isolated in 1996 in the USA for the first time (Yigit et al. 2001). By 2015, KPC had spread globally and has become endemic in the Northeastern USA, Puerto Rico, China, Israel, England, Italy, Romania, Greece, Brazil, Argentina, and Colombia (Denisuik et al. 2013; Glasner et al. 2013; Rodríguez-Zulueta et al. 2013; Saito et al. 2014; Tängdén and Giske 2015; Chang et al. 2015a). KPC-producing *Enterobacteriaceae* can harbor variants of this gene; the most common are bla_{KPC-2} or bla_{KPC-3} on a Tn*3*-based transposon, Tn*4401* (Kitchel et al. 2009; Cuzon et al. 2011). The resistance level to carbapenem in KPC-producing strains can vary. This depends either on increased bla_{KPC} gene copy number, deletions upstream of the bla_{KPC} gene, and/or outer membrane porin loss (OmpK35 and/or OmpK36) (Kitchel et al. 2010; Patel and Bonomo 2013).

MBLs are categorized as class B enzymes, and VIM, NDM-1 (New Delhi MBL), and IMP are the most abundant representatives. The Indian subcontinent is the major reservoir for NDM-1-positive *Enterobacteriaceae* (Lascols et al. 2011), and low sanitation and hygiene levels lead to their wide occurrence in healthcare settings and in the community (Tängdén and Giske 2015). Most often, VIM and IMP MBLs are embedded in class I integrons on transposons or plasmids that lead to the spread. NMD-type MBLs are harbored on different plasmid incompatibility types. It has been proposed that the most abundant variant in *Enterobacteriaceae*, NDM-1, originated from *A. baumannii* (Dortet et al. 2012, 2014). More than two decades ago, the first transmissible carbapenemase gene, *IMP-1* MBL, was detected on an integron in *Serratia marcescens* in Japan. Shortly after the first description, a plasmid-mediated outbreak was observed in seven Japanese hospitals. Subsequently, dissemination of *Enterobacteriaceae* harboring the bla_{IMP-1} gene occurred throughout Japan (Ito et al. 1995). Further, Greece has been shown to be a hotspot for VIM-type *Enterobacteriaceae* and *K. pneumoniae* (Vatopoulos 2008; Logan and Weinstein 2017). In lower-income countries, NMD-1-type MBLs can spread via environmental sources in the community. In India, 4% of drinking water samples and 30% of seepage samples (water pools in streets or rivulets) contained bla_{NMD-1}-positive bacteria in 2011 (Walsh et al. 2011). Class D OXA ß-lactamases are a large group of oxacillinases and are frequently found in *Enterobacteriaceae* (Poirel et al. 2010; Carrër et al. 2010). A transferable plasmid harboring the bla_{OXA-48} gene is often associated with the spread of OXA-48-producing *Enterobacteriaceae*. The integration of the bla_{OXA-48} gene is facilitated by the acquisition of a Tn*199* transposon (Poirel et al. 2010, 2012a, 2012b; Carrër et al. 2010). OXA-48 enzymes reveal high activity on penicillins but low-level activity on carbapenems.

Intestinal carriage of *Enterobacteriaceae* harboring transmissible MDR also presents a major threat, as the intestine provides an environment where resistance determinants can be easily exchanged between bacterial strains. Strains encoding these genes often show additional acquired resistance to fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazoles, which have evolved as major threat to human healthcare.

2.2 Priority 2: High

2.2.1 Vancomycin-Resistant *Enterococcus faecium*

Enterococcus faecium is a G+ facultative anaerobic bacterium. *Enterococci* are capable of growing at hypotonic, hypertonic, acidic, and alkaline conditions. They hydrolyze bile esculin and pyrrolidonyl-B-naphthylamide, which inhibit the growth of most microorganisms (Huycke et al. 1998; Hollenbeck and Rice 2012). *Enterococci* are part of the normal gut flora and often used as indicators of fecal contamination (Boehm and Sassoubre 2014). They are found in human stool at up to 10^8 colony-forming units/g (Huycke et al. 1998; Mundy et al. 2000). *Enterococci* cause urinary tract infections, intra-abdominal and pelvic infections, surgical wound infections, bacteremia, neonatal sepsis, endocarditis, and rarely meningitis (Marothi et al. 2005). *Enterococci,* which are nosocomial pathogens, form biofilms, most likely contributing to their virulence and antibiotic resistance (Hollenbeck and Rice 2012; Hashem et al. 2017). These bacteria are responsible for about 12% of hospital-acquired infections (Hollenbeck and Rice 2012). *E. faecalis* and *E. faecium*, colonizing the gastrointestinal tract, can cause severe infections in immunocompromised patients (Miller et al. 2014). *Enterococci* are intrinsically resistant to cephalosporins, lincosamides, and nalidixic acid and are further not susceptible to low levels of aminoglycosides and clindamycin. They show acquired resistance to penicillin, vancomycin (a glycopeptide antibiotic), chloramphenicol, erythromycin, tetracycline, and fluoroquinolones and high-level resistance to aminoglycosides and clindamycin (Marothi et al. 2005).

The antibiotic resistance mechanisms of *E. faecium* include modification/inactivation of drug targets, overexpression of efflux pumps and a cell envelope adaptive response, assisting it to survive in the human host and in the nosocomial environment (Miller et al. 2014). *E. faecium* leads to biofilm-mediated infections in patients with medical devices. Atl_{Efm}, a major autolysin in *E. faecium,* contributes to stabilization of biofilms and surface localization of the virulence factor Acm, facilitating binding of Acm to collagen types I and IV. This presents Atl_{Efm} as potential target for treatment of *E. faecium* biofilm-mediated infections (Paganelli et al. 2013).

Nowadays, the majority of *E. faecium* isolates are resistant to ampicillin, vancomycin, and aminoglycosides (Arias et al. 2010). The emergence of vancomycin-resistant *Enterococci* (VRE) was first reported in 1986 in Europe, in 1993 in the USA, and in 1994 in Asia (Uttley et al. 1988; O'Driscoll and Crank 2015; Akpaka et al. 2017). Since then, the prevalence of vancomycin-resistant *E. faecium* (VREfm) has increased worldwide. VREfm causes 4% of healthcare-associated infections as per the reports from the National Healthcare Safety Network in America (Miu et al. 2016). The prevalence of VREfm has increased worldwide since 1986. A study on healthcare-associated infections in the USA reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention (CDC) found 80% of *E. faecium* isolates analyzed in 2006/2007 to be non-susceptible to vancomycin (Arias et al. 2010). In US hospitals, VREfm incidence had risen to 0.3% in 1989 and to 7.9% in 1993 (Schouten et al. 2000; Arias and Murray 2012). By 2002, 60% and in 2007 more than 80% of the *E. faecium* isolates in US hospitals revealed

vancomycin resistance (Arias and Murray 2012; Molton et al. 2013). By 2007, the prevalence of VREfm in Europe was higher than 30% in countries like Greece and Ireland, whereas Scandinavian countries reported very low rates (<1%) (Arias and Murray 2012). In Malaysia, the VREfm rate was 25.7% in 2006 (Getachew et al. 2009). In Canadian hospitals, the prevalence of VREfm increased from 1.8% in 2007 to 6.0% in 2013. Ninety percent of vancomycin-resistant isolates harbored the gene *vanA*. Interestingly, the prevalence of *vanB* vancomycin-resistant VRE in these medical centers decreased from 37.5% in 2007 to 0% in 2013 (Simner et al. 2015). A study conducted on hospitalized patients between 2009 and 2014 from seven Caribbean countries showed 90.9% of bacterial isolates to be *E. faecium*, and all of them were vancomycin resistant (Akpaka et al. 2017). In a study conducted in 30 hospitals in Argentina between 1997 and 2000, all *Enterococci* isolates were found to be non-susceptible to vancomycin. The incidence of *vanA*-positive VREfm was 98%, with minimal inhibitory concentrations (MICs) to vancomycin of 32–512 mg/l, while *vanB*-harboring strains revealed MICs to vancomycin of 16–32 mg/l (Corso et al. 2007).

Glycopeptides, like vancomycin, which interfere with the synthesis of peptidoglycan and thus inhibit bacterial growth, are commonly used in the treatment of enterococcal infections (Kristich et al. 2014). These antibiotics form complexes with C-terminal D-Ala-D-Ala peptide termini of peptidoglycan precursors on the outer surface of the cell. This prevents the cell wall biosynthetic enzymes (i.e., PBPs) from using them as substrates for transglycosylation and transpeptidation and hence leads to impairment of cell wall integrity (Kristich et al. 2014). In VRE, the C-termini of peptidoglycan precursors are exchanged to D-Ala-D-Lac or D-Ala-D-Ser, thus reducing the binding affinity of glycopeptides (such as vancomycin) to peptidoglycan by 1000-fold and sevenfold, respectively (Kristich et al. 2014; Ahmed and Baptiste 2017). This phenomenon disables glycopeptides to inhibit cell wall biosynthesis in bacteria (Kristich et al. 2014). Glycopeptide resistance is generally encoded on mobile genetic elements. However, some types of glycopeptide resistance are also chromosomally encoded (Kristich et al. 2014).

Genetic mechanisms of vancomycin resistance in *Enterococci* involve nine gene clusters conferring resistance to glycopeptides. The *van* gene cluster has components with various functions. A two-component signal transduction system consisting of VanRS (VanR is a response regulator/activator of vancomycin resistance and VanS a sensor kinase) recognizes glycopeptides and activates the expression of resistance genes in inducible *van* types. In the presence of vancomycin, the two-component system VanRS activates a promoter responsible for co-transcription of *vanA*, *vanH*, and *vanX* to regulate vancomycin resistance (Arthur and Courvalin 1993). VanH (a dehydrogenase converting cellular pyruvate to D-lactate) and VanA (a ligase forming D-Ala-D-Lac) produce modified peptidoglycan precursors, while VanX (cleaves D-Ala-D-Ala) and VanY (D,D-carboxypeptidases) remove unaltered peptidoglycan precursors (Kristich et al. 2014). Among the *van* gene clusters, *vanA* and *vanB* types of resistances are most common in hospitals and are found in enterococcal isolates from food, clinical, and veterinary samples (Hammerum 2012). *vanA* is generally carried on the transposon Tn*1546* and was first reported on

plasmid pIP816 in *E. faecium* BM4147 (Arthur and Courvalin 1993). *vanB* is harbored by Tn*5382-*/Tn*1549*-type transposons. These transposons are either plasmid- or chromosomally encoded (Kristich et al. 2014).

Infection control and antibiotic stewardship programs are important to prevent further development of antibiotic resistance and dissemination (Hollenbeck and Rice 2012). Control measures should include identification of patients colonized and infected by resistant *Enterococci*, strict adherence to hand hygiene, and active screening of high-risk patients (Faron et al. 2016).

2.2.2 Methicillin- and Vancomycin-Resistant *Staphylococcus aureus*

Staphylococcus aureus is a G+ facultative anaerobic bacterium. It is part of the normal human microflora and is frequently found on the skin, in the respiratory tract, and in the nose. It is an opportunistic pathogen, accounting for about 80% of prosthetic infections. *S. aureus* forms strong biofilms and attaches firmly to medical devices and host tissues, causing chronic, difficult-to-treat infections (Kawada-Matsuo and Komatsuzawan 2012; Vaishampayan et al. 2018). *S. aureus* harbors a two-component regulatory quorum-sensing system, the accessory gene regulator (Agr), which plays an important role in biofilm-related infections (Qin et al. 2014).

Methicillin-resistant *S. aureus* (MRSA) is a leading cause of nosocomial infections. According to the reports from the National Healthcare Safety Network in America, MRSA is responsible for 8% of healthcare-associated infections (Miu et al. 2016). As per the recent US CDC report, among the 23,000 documented infections caused by antibiotic-resistant pathogens, almost half the cases were caused by MRSA (Hagras et al. 2017). MRSA lead to skin and soft tissue infections, respiratory tract infections, food poisoning, endocarditis, osteomyelitis, pneumonia, toxic shock syndrome, suppurative diseases, and fatal sepsis. Immunocompromised patients, patients with implants or diabetes or patients undergoing surgery, elderly people, and newborns are high-risk groups for MRSA infections (Ohlsen 2009).

In a study conducted in the USA, Canada, Latin America, Europe, and the West Pacific region from 1997 to 1999, 32 to 47% of skin and soft tissue infections were found to be caused by *S. aureus* (Schito 2006). The CDC reported 80,461 infections and 11,285 deaths caused by MRSA in 2011 (CDC 2013). The prevalence of MRSA is increasing globally, especially in developing countries. The occurrence of MRSA was reported to be 75% among hospital specimens in Hong Kong from 1997 to 1999, 53.1% in Bangladesh in 2004, 80% in Chile in 2006, 26% in Malaysia from 2006 to 2008, 92.4% in Columbia in 2009, 44.1% in Ethiopia in 2010 and 2011, and 43% in Indonesia in 2014 (Pandey 2017). However, the prevalence of MRSA in livestock is lower in some Asian countries compared to European countries, like in Japan 0.9%, Malaysia 1.4%, Korea 3.2%, China 11.4%, Sri Lanka 13.8%, and Taiwan 14.4% as compared to Poland 20.6% and Germany and the Netherlands with more than 35% (Jayaweera and Kumbukgolla 2017).

Methicillin is a β-lactam antibiotic belonging to the penicillin class. Methicillin resistance can be transferred via HGT (New et al. 2016). The penicillin-binding protein, PBP2, is a key molecule conferring resistance to β-lactams. Methicillin-sensitive *S. aureus* (MSSA) harbors four PBPs (PBP 1–4), and all of them are

inactivated by β-lactam antibiotics. In contrast, MRSA strains encode an extra PBP2', with low affinity to β-lactams, thus facilitating cell wall biosynthesis even in the presence of β-lactam antibiotics. The expression of PBP2' is controlled by the MecR1-MecI regulatory system (Kawada-Matsuo and Komatsuzawan 2012). In addition, three factors responsible for methicillin resistance in the presence of Triton X-100 have been recognized, namely, *fmtA*, *fmtB*, and *fmtC/mprF*. *fmtA* has been identified as a new PBP. Inactivation of *fmtA* reduces methicillin resistance, while mutation of *fmtB* reduces methicillin and oxacillin resistance (Kawada-Matsuo and Komatsuzawan 2012). FmtC/MprF is a membrane-associated protein and its inactivation diminishes methicillin resistance by decreased modification of phosphatidylglycerol with L-lysine. FmtC/MprF determines resistance against host defensive peptides and thus plays a role in virulence and pathogenicity of *S. aureus*. Its inactivation leads to increased negative charge of the membrane surface and increased binding of antibacterial peptides to the surface (Berger-Bächi and Rohrer 2002). Mutations in *fmtC/mprF* in *S. aureus* were shown to further cause a decrease in vancomycin and daptomycin resistance (Bayer et al. 2015; Lin et al. 2018a). Another methicillin-resistant mechanism involves the mobile cassette element SCC*mec* (staphylococcal chromosome cassette *mec*) that is integrated into a *S. aureus* gene of unknown function, *orfX* (Chambers and DeLeo 2009). This cassette carries both the *mecA* and *mecC* genes that encode a novel specific penicillin-binding protein (PBP2a) and the site-specific recombinase genes *ccrAB* and/or *ccrC*. The SSC*mec* cassette was first described in 1999 (Ito et al. 1999). SCC*mec* elements are divided into type I to XI based on the *mec* and *ccr* gene complexes and further classified into different subtypes (Liu et al. 2016).

Vancomycin, a last resort antibiotic, has been widely used in the treatment of MRSA. However, excessive use of the drug has led to the development of vancomycin-resistant *S. aureus* (VRSA) (Appelbaum 2006). In 2002, the first VRSA isolate with a MIC of higher than 100 μg/ml was reported in Michigan, USA (Gardete and Tomasz 2014). Until 2008, 11 VRSA clinical isolates, which were also resistant to methicillin, had been reported, out of which 9 cases were identified in the USA, 1 in Iran, and 1 in India. Out of the nine from the USA, seven were clinical isolates from Michigan (Périchon and Courvalin 2009). The US strains harbor a plasmid-borne Tn*1546* element, most probably acquired by conjugation from glycopeptide-resistant *E. faecalis* (Périchon and Courvalin 2009). The mechanism of resistance observed in VRSA is similar to that in *Enterococci* by alteration of peptidoglycan precursors. The C-terminal D-Ala-D-Ala is substituted by D-Ala-D-Lac, diminishing the binding of vancomycin, thus no longer inhibiting the cell wall synthesis in the bacterium (Schito 2006).

2.2.3 Clarithromycin-Resistant *Helicobacter pylori*

H. pylori is a G- microaerophilic, spiral organism (Yonezawa et al. 2013). It is a human gastric pathogen that causes peptic ulcers, gastritis, gastric adenocarcinoma, mucosa-associated lymphoid tissue lymphoma, chronic immune thrombocytopenic purpura in adults, and vitamin B12 deficiency (Shmuely et al. 2016; Alba et al.

2017). The route of transmission is commonly from person to person (Shmuely et al. 2016).

H. pylori forms biofilms, even on human gastric mucosa, reducing the susceptibility of the bacterium to different antibiotics including clarithromycin (but also metronidazole, erythromycin, amoxicillin, and tetracycline) (Yonezawa et al. 2015; Attaran et al. 2017). The incidence of clarithromycin resistance, and also the expression of efflux pump systems, is higher in biofilms compared to planktonic cells. Interestingly, the MIC of clarithromycin was increased by up to four-fold in 2-day-old biofilms and up to 16-fold in 3-day-old *H. pylori* biofilms (Yonezawa et al. 2013).

Clarithromycin is a macrolide, containing a 14-membered lactone ring with L-cladinose and D-desosamine groups of sugars (Alba et al. 2017). It binds to the 50S subunit of the bacterial ribosome and blocks the translation of peptides, thereby inhibiting bacterial growth (Yonezawa et al. 2013). The precise site of action of clarithromycin is the peptidyl transferase loop of domain V of 23S rRNA.

While clarithromycin is the first drug of choice to treat *H. pylori* infections, clarithromycin resistance in *H. pylori* has been linked to treatment failures, including poor compliance, resistance to antibiotics, and reinfection (Chey and Wong 2007; Shmuely et al. 2016). The incidence of clarithromycin-resistant *H. pylori* is higher in previously treated than in untreated patients (Shmuely et al. 2016). In developing countries, the annual occurrence of clarithromycin-resistant *H. pylori* is 4–15% higher than in industrialized countries, revealing rates of 0.5% (Gold 2001; Duck et al. 2004). A consistent increase in clarithromycin resistance has been reported in most countries. In Bulgaria, the resistance increased from 10% in 1996–1999 to 19% in 2003/2004. In the USA, the resistance was 6.2% in 1993 and the rate doubled in 9 years, to 12.9% in 2002. In Belgium, the rates increased from 6% in 1990 to 56% in 2009. In Japan, the resistance was 18.9% in 2002 and reached 27.7% in 2005. In a hospital in the USA, the resistance rate of *H. pylori* infections in patients between the ages of 3 and 19 years was as high as 50% (Shmuely et al. 2016). A meta-study compiling 87 studies on 52,008 *H. pylori* isolates from 2009 to 2014 gives a good overview of the prevalence of *H. pylori*. It included 43 Asian, 10 American, 5 African, and 29 European studies. There were 5.46% to 30.8% of *H. pylori* isolates resistant to clarithromycin, with the lowest rate in African and the highest rate observed in North American isolates. Among European countries, Norway showed the lowest resistance rate (5.9%), while Portugal showed the highest (42.4%). In Asian countries, the lowest resistance rates were observed in Malaysia (2.4%), while the highest rates were found in India (58.8%) (Ghotaslou et al. 2015). Recently, an increase in clarithromycin resistance among treatment failures showed 17.5% (primary resistance) to 63.2% after one eradication treatment failure (secondary resistance) and 75.4% after two eradication treatment failures (tertiary resistance) (Megraud et al. 2013; Selgrad et al. 2013).

Point mutations of the *23S* rRNA gene, mostly an adenine-to-guanine transition at positions 2142 and 2143, are the common mechanism of clarithromycin resistance, as they reduce the affinity of the drug to the ribosome (Megraud 1998; Yonezawa et al. 2013; Alba et al. 2017). Sporadic mutations in the translation

initiation factor IF-2, the ribosomal protein L-22, as well as in the efflux pumps, are other mechanisms of resistance (Alba et al. 2017). Excessive use of clarithromycin has led to the development of resistant strains of *H. pylori,* with the predominant mutations occurring in A2143G, A2142G, and A2142C in the *23S* rRNA gene, but T2182C, G2224A, T2215C, and C2694A in the V region of the *23S* rRNA gene have also been observed (Vianna et al. 2016; Alba et al. 2017). A2143G is the most frequently encountered mutation among the resistant strains in most European and Latin American countries (Vianna et al. 2016).

The latest Maastricht Guidelines recommend clarithromycin containing treatments against *H. pylori* infections in regions with low incidence of clarithromycin resistance. In regions with high levels of clarithromycin resistance, quadruple therapy with bismuth or the sequential therapy with 5 days of proton pump inhibitors and amoxicillin followed by 5 more days of proton pump inhibitors plus metronidazole and clarithromycin is recommended as the first-line treatment (Ghotaslou et al. 2015; Malfertheiner et al. 2012; Shmuely et al. 2016). In addition to the combinational use of antibiotics to treat infections, judicious use of antibiotics with the help of culture and antibiotic susceptibility testing of *H. pylori* and empiric eradication are essential to control further spread of antibiotic resistance (Boltin et al. 2015; Shmuely et al. 2016).

2.2.4 Fluoroquinolone-Resistant *Campylobacter* spp.

Campylobacter jejuni is a G- curve-shaped, thermophilic, and microaerophilic bacterium (Fernández and Pérez-Pérez 2016). It is a zoonotic, foodborne pathogen and causes about 500 million human infections worldwide annually (Bae and Jeon 2013; Bae et al. 2014). It is responsible for about 90% of the *Campylobacter* infections in humans (Iovine 2013) and is a leading cause of gastroenteritis since the late 1970s (Luangtongkum et al. 2009; Fernández and Pérez-Pérez 2016). *C. jejuni* has the ability to form biofilms on abiotic surfaces (Reuter et al. 2010; Bae et al. 2014) and can acquire antibiotic resistance genes in biofilms by natural transformation (Bae et al. 2014). The formation of biofilms likely increases the fluoroquinolone resistance among *Campylobacter* spp. (Bae and Jeon 2013). Gastroenteritis caused by *Campylobacter* is generally regarded as self-limiting. However, treatment is recommended in cases of a severe infection or infections in the immunocompromised elderly patients or in newborns and pregnant women (Fernández and Pérez-Pérez 2016). Fluoroquinolones such as ciprofloxacin are often used to treat *Campylobacter* infections. Spread of the bacteria from animals to humans often occurs via contaminated food. Poultry animals are especially seen as crucial reservoirs involved in this dissemination (Bae and Jeon 2013; Fernández and Pérez-Pérez 2016). The emergence of fluoroquinolone resistance in *Campylobacter* from food animals has evolved as a public health issue (Tang et al. 2017).

A study conducted among travelers returning to Finland from 1995 to 2000 showed that countries with especially high rates of ciprofloxacin-resistant *C. jejuni* were Spain with 22%, followed by Thailand and India, with 14%, and 6% of the isolates, respectively. The isolates were collected during two study periods (1995–1997 and 1998–2000). The study reported an increase in the incidence of resistance

among the investigated travelers between the two study periods from 40% to 60% within the study period (Hakanen et al. 2003). In 2000, the occurrence of ciprofloxacin-resistant *Campylobacter* spp. in clinical isolates (mostly *C. jejuni*) was 50% in Chile, 59.6% in Argentina, and 78% in Peru. In Argentina, 49.1% of the *Campylobacter coli* from a pediatric hospital were reported to be resistant to ciprofloxacin as well as to norfloxacin, another fluoroquinolone (Fernández and Pérez-Pérez 2016).

In Peru, an increase in ciprofloxacin resistance among *C. jejuni* and *C. coli* from 2001 to 2010 was reported. The highest rates of ciprofloxacin-resistant *C. jejuni* at the beginning and the end of the study were observed in Lima, with 73.1% and 89.8%, respectively, similar to resistance in *C. coli* (48.1% in 2001 and 88.4% in 2010) (Fernández and Pérez-Pérez 2016). A study conducted from 2003–2006 in Mexico reported ciprofloxacin-resistant *C. jejuni* isolates in chickens (85.8%), pigs (62.5%), cattle (39.8%), and humans (58.2%) (Zaidi et al. 2012). In Southern Ecuador, 90.9% of *C. jejuni* and 100% of *C. coli* strains, isolated from chicken liver for human consumption, were reported to be ciprofloxacin resistant (Fernández and Pérez-Pérez 2016). A recent study in the USA among feedlot cattle in 2012/2013 showed 35.4% of *C. jejuni* and 74.4% of *C. coli* to be fluoroquinolone resistant, a significant increase when compared to the 1.8% *C. jejuni* and 9% *C. coli* being non-susceptible to ciprofloxacin as reported earlier (Englen et al. 2005; Tang et al. 2017).

All fluoroquinolone resistance determinants reported in *Campylobacter* are chromosomally encoded. The frequency of emergence of fluoroquinolone-resistant mutants ranges from 10^{-6} to 10^{-8} per cell and generation (Luangtongkum et al. 2009).

The mechanisms of fluoroquinolone resistance in *Campylobacter* spp. are mainly due to mutations in *gyrA* and *parC* genes, encoding DNA gyrase and topoisomerase IV, respectively. Frequently, amino acid positions Thr-86, Asp-90, and Ala-70 of *gyrA* are mutated. Thr-86 mutations confer higher levels of resistance to ciprofloxacin as compared to Asp-90 and Ala-70. High-level ciprofloxacin-resistant *C. jejuni* isolates (MIC = 125 μg/ml) possess two mutations, in *gyrA* Thr-86 and in *parC* at Arg-139 (Engberg et al. 2001). Another mechanism of fluoroquinolone resistance in *Campylobacter* is the multidrug efflux pump CmeABC, consisting of a periplasmic protein acting as a bridge (encoded by *cmeA*) (Iovine 2013), an inner membrane drug transporter (encoded by *cmeB*), and an outer membrane protein (encoded by *cmeC*). CmeABC reduces the accumulation of the drug in the bacterial cell (Luangtongkum et al. 2009).

Regular and methodical surveillance of antibiotic resistance in *Campylobacter* spp. is an essential step in controlling the further spread of antibiotic resistance (Fernández and Pérez-Pérez 2016).

2.2.5 Fluoroquinolone-Resistant *Salmonella* spp.

Salmonella are G-, motile, zoonotic pathogenes that cause diseases like gastroenteritis, typhoid, paratyphoid, and bacteremia (Rushdy et al. 2013; Pribul et al. 2017). *S. enterica* is a human-restricted pathogen causing typhoid (González et al. 2018), a disease that is typically transmitted by the fecal-oral route (Schellack et al. 2018).

The bacterium resides in the gall bladder as the primary reservoir. Further, it forms biofilms on the gall bladder, which are recalcitrant to ciprofloxacin treatment (González et al. 2018). In 2010, 26.9 million new cases of typhoid fever and 200,000 deaths were determined worldwide (Abd-elfarag 2015; Adhikari et al. 2017; Ugboko and De 2014). A community-based prospective *Salmonella* surveillance study, conducted in Asia from 2001 to 2003, showed occurrence of *S. typhi*, namely, 37% in China, 65% in India, 84% in Pakistan, 85% in Indonesia, and 100% in Vietnam. In the same study, the prevalence of *S. paratyphi* was observed to be 63% in China, 34% in India, 14% in Indonesia and in Pakistan, and 0% in Vietnam (Khan et al. 2010). In the USA, 1.2 million cases of infection are reported annually (Boore et al. 2015). In 2016, 94,530 cases of salmonellosis were reported in the EU (European Food Safety Authority 2017).

Fluoroquinolones, specifically ciprofloxacin, are the drugs of choice to treat *Salmonella* infections. However, overuse of ciprofloxacin has resulted in increased resistance. Ciprofloxacin-resistant *Salmonella* was first reported in 1990 (Menezes et al. 2010). A study in Brazil conducted from 2009 to 2013 on isolates from food of animal sources and from environmental samples screened for fluoroquinolone resistance among the isolates. The most prevalent serotype obtained was *S. typhimurium* followed by *S. enteritidis*. The occurrence of resistance was highest for enrofloxacin (48%), followed by ciprofloxacin (43%) and ofloxacin (40%), and the lowest resistance was observed for levofloxacin (30%) (Pribul et al. 2017). Despite emerging ciprofloxacin resistance, this drug is recommended as the first-line therapy in children and adults (González et al. 2018).

The fluoroquinolone resistance in *Salmonella* is predominantly due to mutations in *gyrA* and *parC* genes, as also described for *Campylobacter* (Sjölund-Karlsson et al. 2014). The second mechanism of resistance is overexpression of the efflux system AcrAB-TolC (Rushdy et al. 2013). AcrAB-TolC belongs to the resistance-nodulation-division family and has three domains, a membrane fusion protein (AcrA), a drug efflux transporter (AcrB), and an outer membrane channel protein (TolC) (Kim et al. 2016). Overexpression increases the efflux of the antibiotic that acts synergistically with the alterations in outer membrane proteins which includes absence of some/all of these proteins, namely, Omp-A, Omp-C, Omp-D, and Omp-F (Rushdy et al. 2013).

Mechanisms of fluoroquinolone resistance in *Salmonella* food isolates were identified. Either the investigated isolates had only a single mutation in *gyrA* with S83T, S83F, and D87N being the most common amino acid substitutions or a pair of novel double mutations in *gyrA* resulting in H80N and S83T substitutions and a single *parC* mutation causing a Q91H substitution were identified (Lin et al. 2015). Another mechanism used by *Salmonella* is alteration of porin expression, thus reducing the penetration of fluoroquinolones into the bacteria (Rushdy et al. 2013). In addition to the mutations in *gyrA* and *parC* genes, and chromosomally encoded efflux pumps, a plasmid-mediated resistance mechanism encoded by *qnrA* has also been observed in *Salmonella* spp. (Sjölund-Karlsson et al. 2014).

It was recently suggested that fluoroquinolone-resistant *S. typhi* strains would occur in the future, even if the use of these drugs were diminished, as these

resistance mechanisms are not linked with fitness costs (Baker et al. 2013). This poses a great challenge to the public health. Surveillance of infections and epidemiology, as well as studying the genes responsible for antibiotic resistance in *Salmonella* spp., are imperative measures to control the spread of antibiotic resistance and to effectively treat infections (Nabi 2017).

2.2.6 Cephalosporin- and Fluoroquinolone-Resistant *Neisseria gonorrhoeae*

Neisseria gonorrhoeae is a G- pathogenic diplococcus with a special feature of antigenic variability, strengthening its survival in the human host (Patel et al. 2011). It inhabits mucosal surfaces of the urethra in male and the cervix in female (Patel et al. 2011) but can also be found in the rectal and the oropharyngeal mucosa (Costa-Lourenço et al. 2017). *N. gonorrhoeae* causes symptomatic and asymptomatic infections of the genital and extragenital tract (Patel et al. 2011). It is an etiological agent of gonorrhea and the second leading cause of sexually transmitted diseases (Costa-Lourenço et al. 2017). In men, it causes urethritis. Untreated infections may lead to epididymitis, reduced fertility, and urethral stricture. In women, the symptoms include abnormal vaginal discharge, dysuria, lower abdominal discomfort, and dyspareunia (Alirol et al. 2017). The risk of gonococcal infection is lowering with increasing age, as most cases occur in individuals under the age of 24 (Costa-Lourenço et al. 2017). *Gonococci* form biofilms in vitro and likely in vivo (Unemo and Shafer 2014). Approximately 62 million cases of *N. gonorrhoeae* infections occur every year worldwide (Patel et al. 2011).

Fluoroquinolones and cephalosporins are the drugs of choice to treat *N. gonorrhoeae* infections. Cephalosporins inhibit the growth of bacteria by inhibiting the cross-links of peptidoglycan in the bacterial cell wall by binding to PBPs. The cephalosporins, ceftriaxone and cefixime, are the most effective recommended treatment options against *N. gonorrhoeae* infections. However, resistance to these drugs has emerged in the past two decades.

Ciprofloxacin-resistant *N. gonorrhoeae* isolates were reported in the 1980s from many countries (Patel et al. 2011). By the end of 1992, the resistance rates in Japan were 40% (Patel et al. 2011). In India, the use of ciprofloxacin started in the 1990s, and by the end of 2000, most isolates were resistant (Patel et al. 2011). The resistance to ceftriaxone and cefixime was first reported in Japan and then spread all over the world (Unemo and Shafer 2014). Resistance to ceftriaxone in *N. gonorrhoeae* has been reported in several American countries since 2007 (Pan American Health Organization/World Health Organization 2018). In South Africa, among men attending healthcare clinics, the incidence of ciprofloxacin resistance in *N. gonorrhoeae* increased from 7% in 2004 to 32% in 2007. In Kenya, quinolone resistance increased since it emerged in 2007 from 9.5% to 50% in 2009 (Mehta et al. 2011). In Europe, 50,001 *N. gonorrhoeae* cases were reported in 2013, and 53% of the clinical isolates were resistant to ciprofloxacin and 4.7% to cefixime (Spiteri et al. 2014). In a report published by WHO-GASP-LAC in 2013, ciprofloxacin resistance rates in clinical *N. gonorrhoeae* isolates in Latin American countries stayed below 5% until 2004, increased to >15% in 2006, and reached >40% in 2010 (Dillon et al.

2013). The spread of these resistances is thought to occur through HGT (Hess et al. 2012). In 2014, the prevalence of gonorrhea disease in the southern part of the USA was 131 cases per 100,000 individuals (CDC 2014), and the CDC estimated 820,000 new cases annually. Thirty percent of the isolates were ciprofloxacin resistant in cases of men having sex with men and 12% in case of men having sex with women (CDC 2015).

The use of fluoroquinolones as a drug of choice to treat gonococcal infections was recommended in 1993. Already in 1997, the first strains resistant to fluoroquinolone were reported in Hong Kong and the Philippines. In 2004, fluoroquinolone was no longer recommended for treatment, but cephalosporins came into use as a treatment against gonococcal infections. In 2007, cephalosporin resistance was reported in Japan and Australia. A year later, reduced susceptibility to cephalosporins was identified in the USA. In 2011, the WHO and CDC revised the treatment guidelines, and ceftriaxone was included in the combination therapy to treat gonococcal infections. However, in 2012 the first cases of ceftriaxone resistance were reported from Japan (Buono et al. 2015).

Fluoroquinolone resistance in *N. gonorrhoeae* can be chromosomally as well as plasmid-mediated (Patel et al. 2011). As already stated for *Campylobacter* spp. and *Salmonella*, in cases of high-level fluoroquinolone resistance, mutations take place at positions 91 and 95 in *gyrA* and at positions 87 and 91 in *parC* (Kubanov et al. 2016) but also in genes associated with NorM efflux pumps that export fluoroquinolones (Golparian et al. 2014). The mechanism of cephalosporin resistance is primarily due to alteration of the structure and function of key proteins, such as PBP2, encoded by *penA*, and PorB1b showing porin activity (Ross and Lewis 2012; Golparian et al. 2014). Another strategy used by *N. gonorrhoeae* to combat cephalosporins is mutations in the MtrC-MtrD-MtrE efflux pump system, a member of the resistance-nodulation-division pump family (Golparian et al. 2014).

Gonococcal resistance to cephalosporins is severe due to limited alternatives to treat gonococcal infections. Thus, it is imperative to fill the gaps in the surveillance and MDR data to understand the epidemiology of gonococcal MDR (Wi et al. 2017). Additionally, strengthening of diagnosis of *N. gonorrhoeae* infections is recommended by the Pan American Health Organization and the WHO as a control measure (Pan American Health Organization/World Health Organization 2018).

2.3 Priority 3: Medium

2.3.1 Penicillin-Non-susceptible *Streptococcus pneumoniae*

S. pneumoniae is a G+ facultative anaerobic organism. It causes pneumonia, sinusitis, otitis media, upper respiratory tract infections, and bacteremia, resulting in morbidity and mortality in infants and children (Bogaert et al. 2000; Ahmadi et al. 2015; Diawara et al. 2017). *S. pneumoniae* also triggers meningitis, which is the most dangerous disease of the central nervous system (Ahmadi et al. 2015). The bacterium forms robust biofilms to survive in the human nasopharynx (Talekar et al.

2014) and is responsible for 11% of deaths worldwide (Ahmadi et al. 2015) with the highest mortality rates reported in Africa and Asia (Diawara et al. 2017).

The prevalence of penicillin-non-susceptible *S. pneumoniae* (PNSP) is increasing rapidly. The first PNSP was reported in Australia in 1967 (Hansman and Bullen 1967; Liñares et al. 2010). A study conducted in 11 pediatric tertiary care centers in Canada from 1991 to 1998 showed the emergence of two international clones of PNSP, serotype 9V and 14 related to the Spanish-French clone, and the 23-F Spanish-US clone (Greenberg et al. 2002). In the USA, an invasive PNSP clone 35B, which caused invasive infections in patients in ten different states from 1995 to 2001, was identified by the CDC and Prevention's Active Core Surveillance (Beall et al. 2002). The prevalence of PNSP in Canada increased from 2.5% in 1991 to 11.3% in 1998 (Greenberg et al. 2002). The occurrence of PNSP in hospitals was >70% in Korea, 45% in South Africa, 44% in Spain, and 21.8% in Brazil (Greenberg et al. 2002; Levin et al. 2003).

The prevalence of PNSP in some European countries was shown to be very high, 25–50% in Spain, France, and Greece; 10–25% in Portugal, Ireland, Finland, and Turkey, and 5–10% in Italy, and relatively low with 1–5% in the UK, Germany, Sweden, Austria, and Norway (EARSS Annual Report 2006; Reinert 2009). In Poland, the prevalence of PNSP among children (age 2 to 5 years) in 2011–2012 was 44.8% (Korona-Glowniak et al. 2016). The prevalence of PNSP in Argentina increased significantly from 15.8% in 1993 to 67.3% in 2002 (Bonofiglio et al. 2011), and in Morocco it was 22% in samples collected from 2007 to 2014 (Diawara et al. 2017).

The dissemination of antibiotic resistance in pneumococci is mainly clonal (Sjostrom et al. 2007). *S. pneumoniae* expresses six types of PBPs, namely, 1a, 1b, 2a, 2b, 2x, and 3. The mechanism of penicillin resistance involves modification within or in flanking regions of the amino acid motifs which form the active catalytic center of the PBPs. This alters the PBPs, namely, PBP2x, PBP2b, and PBP1a. These modified variants display a reduced affinity to ß-lactam antibiotics, while their enzymatic function is apparently unaffected (Hakenbeck et al. 2012; Reinert 2009; Schweizer et al. 2017; Zhou et al. 2016).

Detection of PNSP is crucial to prevent and treat infections caused by penicillin-resistant *S. pneumoniae*. Surveillance of the clonal distribution of PNSP in combination with epidemiological analyses will help in understanding the risk factors associated with them. Use of conjugate vaccines might also help in reducing non-susceptibility toward the antibiotic (Ahmadi et al. 2015; Hampton et al. 2018).

2.3.2 Ampicillin-Resistant *Haemophilus influenzae*

Haemophilus influenzae is a G- facultative anaerobic coccobacillus that can cause various diseases, with symptoms ranging from mild to severe (Baba et al. 2017). The bacterium is associated with a significant number of respiratory tract infections as well as serious invasive infections, like meningitis and sepsis (Kiedrowska et al. 2017). Further, community-acquired pneumonia, acute otitis media, acute epiglottitis, and sinusitis can be caused by *H. influenzae*. The bacterium is often part of the physiological bacterial flora of the upper respiratory tract but is frequently isolated

from the respiratory tract of COPD (chronic obstructive pulmonary disease) patients, where it can lead to severe symptoms (Finney et al. 2014; Garmendia et al. 2014).

Antibiotic treatment can give rise to the occurrence of resistant *H. influenzae* strains that are frequently non-susceptible to ampicillins, including ß-lactamase-negative ampicillin-resistant (BLNAR) strains. The highest rate of ß-lactamase production in strains of *H. influenzae* was observed in South Korea and Japan, where more than half of all isolates were tested positive (Tristram et al. 2007). High prevalence of BLNAR strains has evolved into major clinical concern. Over the last few years, a significant increase in the occurrence of BLNAR strains has been observed in many European countries and throughout the world (Sanbongi et al. 2006; Jansen et al. 2006; Tristram et al. 2007). In European countries, the prevalence of nosocomial BLNAR strains was reported to range between 15% and 30% (Jansen et al. 2006; Witherden et al. 2014).

Resistance of *H. influenzae* to ß-lactams can be either enzyme- (facilitated by ß-lactamases) or non-enzyme-mediated. Traditionally, the most commonly occurring ß-lactam resistance mechanism in *H. influenzae* is ß-lactamase production, with the gene encoded on plasmids (Tristram et al. 2007). Non-enzyme-mediated resistance (BLNAR) can be facilitated by increased expression of the AcrAB efflux pump (Kaczmarek et al. 2004). Further, in BLNAR strains, alterations in PBP3, encoded by the *fts1* gene, have been attributed to elevated resistance to ß-lactam antibiotics (Kaczmarek et al. 2004; Wienholtz et al. 2017). Distinct mutations in *fts1* led to decreased affinity for penicillins as well as cephalosporins (Thornsberry and Kirven 1974; Ubukata et al. 2001; Hasegawa et al. 2003). This has been proposed to be the main molecular mechanism of non-ß-lactamase-mediated resistance among BLNAR strains (Mendelman et al. 1984; Tristram et al. 2007; Skaare et al. 2014).

2.3.3 Fluoroquinolone-Resistant *Shigella* spp.

Shigella are G- facultative anaerobic, rod-shaped bacteria and are an important cause of acute diarrheal disease worldwide. The majority of cases occur among children under the age of five in developing countries (Kotloff et al. 2013; Khaghani et al. 2014). Generally, *Shigella* infections are restricted to the gastrointestinal tract, while extraintestinal infections, such as bloodstream infections, reactive arthritis, and neurological complications, are rare (Bhattacharya et al. 1988; Muthuirulandi Sethuvel et al. 2017). Infections caused by *Shigella* spp. in humans are easily transmittable from person-to-person or by contaminated food/water (Muthuirulandi Sethuvel et al. 2017). Shigellosis is endemic among poor populations in African and Asian countries. *Shigella* epidemics have been reported from Bangladesh, Sri Lanka, Maldives, Nepal, Bhutan, Myanmar, and the Indian subcontinent (Emerging and other Communicable Diseases and Control Organization 1994). Nowadays, global occurrence of multidrug-resistant *Shigella* spp. that reveal increased non-susceptibility to third-generation cephalosporins and fluoroquinolones has emerged as a critical health issue. This trend has been predominantly observed in Asia (Wang et al. 2006; Gu et al. 2012; Taneja and Mewara 2016). Nevertheless, reports of MDR lineages or strains with increased resistance to fluoroquinolones are piling up globally (Aggarwal et al. 2016; Nüesch-Inderbinen et al. 2016).

Resistance to fluoroquinolones in *Shigella* is based on two mechanisms occurring either singly or in combination: Alterations in the targets of these antibiotics and non-permeability of the membrane and/or overexpression of drug efflux pumps that lead to decreased drug concentrations inside the cell reduce antibiotic susceptibility. Mutations in *gyrA, a* subunit of the bacterial DNA gyrase complex, and *parC*, a subunit of the bacterial topoisomerase, have been identified as important determinants for fluoroquinolone resistance (Chu et al. 1998). Chromosomal mutations in these genes were shown to participate in the dissemination of fluoroquinolone-resistant *S. sonnei* isolates (Ma et al. 2018). Plasmid-mediated quinolone resistance (PMQR) factors seem to fulfill a minor but additive role in the reduction of the susceptibility to fluoroquinolones (Vinothkumar et al. 2017). The presence of PMQR genes can promote mutations within the quinolone resistance determining region, leading to fluoroquinolone resistance, but spread to other *Enterobacteriaceae* may occur (Nüesch-Inderbinen et al. 2016). Further, *qnr* genes on mobile genetic elements are also able to confer low-level resistance to fluoroquinolones (Ruiz 2003; Hooper and Jacoby 2015). These genes encode proteins protecting the bacterial DNA gyrase and topoisomerase from quinolone/fluoroquinolone inhibition, thus leading to low-level resistance (Tran and Jacoby 2002; Tran et al. 2005a, 2005b; Redgrave et al. 2014). These plasmids often also harbor other antibiotic resistance genes that can be transferred to other species by conjugation (Martínez-Martínez et al. 1998).

3 Conclusions and Perspectives

The occurrence of multidrug-resistant bacterial pathogens presents a global threat. Especially alarming is the increasing incidence of multiresistant pathogenic bacteria outside medical centers. For example, there is a rising incidence of multiresistant opportunistic or nosocomial pathogens in the population, in food animals, and also in wild animals, e.g., vancomycin-resistant *Enterococci* and carbapenem-resistant *P. aeruginosa* have been recently detected in migratory birds (Martins et al. 2018; Yahia et al. 2018). Thus, implementation of efficient antibiotic stewardship programs is urgently needed all over the world. In addition, alternative treatment options to cure and/or prevent severe infectious diseases caused by multiresistant pathogens are imperatively required to prevent the advent of the post-antibiotic era. Alternative options include among others antibacterial vaccines, herbal products, bacteriophages, and improved biosecurity measures, as summarized by Bragg et al. (2018). Our group has been working on the development of antibacterial vaccines targeting surface-exposed proteins involved in conjugative spread of antibiotic resistance genes among pathogens. One of these vaccine candidates directed to staphylococcal and enterococcal pathogens has been successfully tested in a mouse infection model (Laverde et al. 2017).

Treatment of infections by MDR bacteria is often aggravated by the formation of thick, robust biofilms on infected tissues. Therefore, alternative treatment approaches should include biofilm inhibitors, such as natural or engineered antimicrobial

peptides (Lin et al. 2018a; b) or extracts from medicinal plants (Mehta and Das 2018). It is well-known that biofilm formation is controlled by second messenger molecules, such as cyclic di-guanosine monophosphate (c-di-GMP), and by interbacterial cell-cell communication via quorum sensing systems. Recently, some progress has been made by detecting small-molecule inhibitors of c-di-GMP signaling (Opoku-Temeng and Sintim 2017). Another promising approach to successfully attack strong biofilm forming pathogens should be based on the continuous discovery of novel quorum sensing inhibitors which are often plant-based natural compounds (Defoirdt 2018; Mehta and Das 2018).

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