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Review

Antimicrobial resistance: Prevalence, economic burden, mechanisms of resistance and strategies to overcome

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ABSTRACT

Antibiotic resistance is a major health concern globally and has been estimated to cause 10 million deaths worldwide by year 2050 if the current trend of inappropriate and excessive use of antibiotics continues. Although, the discovery of antibiotics has saved countless of lives for the past 80 years, increasing levels of bacterial resistance to antibiotics would jeopardize the progress in clinical and agricultural sectors and may cause life-threatening situations even for previously treatable bacterial infections. Antibiotic resistance would increase the levels of poverty of low-middle income countries mostly due to extended hospital stays, higher cost of treatment and untimely deaths that directly affect the total productivity rate. Recent incidences of antibiotic resistance have been gradually increasing globally and this may potentiate horizontal transmission of the resistant gene and have been linked with cross-resistance to other antibiotic families as well. This review summarizes the global burden of antibiotic resistance from the economic viewpoint, highlights the recent incidences of antibiotic resistance mainly related to *Escherichia coli, Acinetobacter baumannii, Klebsiella pneumoniae, Salmonella* spp. and *Staphylococcus aureus*, describes the common mechanistic actions of antibiotic resistance and potential strategies to overcome antibiotic resistance.

1. Introduction

Antibiotic resistance is defined as the ability of microorganisms to counteract the action of antimicrobial agents and this phenomenon occurs when an antibiotic loses its efficiency to inhibit the bacterial growth (Beceiro et al., 2013; Nadeem et al., 2020). This occurrence is a silent health threat during the coronavirus disease 2019 (COVID-19) pandemic as antibiotics are being increasingly prescribed to treat secondary infections in the clinical sector. World Health Organization (WHO) has voiced concern that this pandemic could seriously undo all efforts that have been carried out to reduce antibiotic resistance globally over the years (Getahun et al., 2020). Increased hospital stays, overworked personnel, shortage of staff and obstacles in implementing infection control exercises during this COVID-19 pandemic have burdened the healthcare system and prevented the tracking of hospital-acquired antibiotic resistant bacterial infections (Afshinnekoo et al., 2021; Livermore, 2021).

Increased use of antibiotics in various health and agricultural sectors as depicted in Fig. 1. has caused the emergence of antibiotic resistant microorganisms worldwide and this trend occurs in a wide range of microorganisms with an elevated prevalence which threatens human health. This issue has become one of the major public health threats of current times and WHO has estimated that 10 million deaths can occur by year 2050 due to the increase in antimicrobial resistance (de Kraker et al., 2016; Pulingam et al., 2020; WHO, 2014). The outbreak of bacterial infection by resistant microorganisms can be severe, including prolonged illnesses due to delayed antibiotic therapy, susceptibility to infection for patients undergoing surgery, increased rate of mortality and costs. Antibiotic resistance usually occurs at a higher rate mostly in the health care sector and generally affects the immune-compromised,

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elderly and even young patients who regularly require medical care. The spread of antibiotic resistant bacteria amongst patients in the healthcare facility often occurs through inter- or intra-hospital patient transfer and may spread to the community if not contained or stopped (Farr et al., 2001; Suleyman et al., 2018).

Antibiotics have been one of the most important discoveries that transformed the quality of human health through prevention of life-threatening bacterial infections. However, antibiotic resistance weakens progress in the clinical sector, life expectancy and safe food production as well. This phenomenon is made worse by the diminishing antibiotic pipeline where the progress and commercialization of new antibiotics have declined since the 1990s (Lewis, 2012; Singer et al., 2020). While it is expected for new antibiotics to offer a better protection mechanism against pathogens, its effects would only be brief if overuse and misuse of antibiotics continues (Lee et al., 2013). It is known that resistance to an antibiotic appears soon after it's been approved for clinical use. Two of the contributing factors for this phenomenon are (1) use of antibiotic inhibits susceptible bacteria and allows resistant bacteria to survive and (2) activates dormant resistance gene in bacteria due to antibiotic pressure. The thriving bacterial isolates under antibiotic pressure would spread the resistance gene to other hosts and this may even continue to spread to other communities as well (Levy and Marshall, 2004). Therefore, restrictive use of antibiotics in the health and agricultural sector is of great importance and caution should be exercised to prevent the outbreak of multidrug resistant bacterial infections.

Resistance to antibiotics often appears due to its prolonged use and generally supports the growth of resistant bacterial isolates and inhibits the growth of susceptible bacteria. Most of the time, continuous antibiotic pressure causes resistance to not only the antibiotic in use but towards other antibiotics from the same class as well. The origin for this multiple antibiotic resistant gene has been previously associated to a single plasmid or transposon (Garneau-Tsodikova and Labby, 2016). It was previously considered that maintenance of resistance genes requires additional energy and therefore, may not be stable at laboratory conditions. However, this concept has been contradicted by findings that proved the survival and proliferation of these resistant bacterial isolates in the general culture media (Davies and Davies, 2010; Melnyk et al., 2015).

Antibiotic resistance mechanisms by bacteria are mostly categorized into three common pathways including alteration of the antibiotic target site, modification or destruction of the antibiotic molecule and finally inhibition of antibiotic binding to the target site through elimination method. Moreover, resistance genes are generally acquired by bacteria through transformation (uptake of resistant gene from the environment), transduction (transfer of resistant gene from bacteriophage) and bacterial conjugation (transfer of resistant gene between resistant bacterial strains) (Blair et al., 2015; Wright, 2010). As the emergence of antibiotic resistant bacteria is gradually on the rise, alternatives to antibiotics should be considered and some of the proposed options include antibiotic structure modifications, combinational antibiotic therapy, antibiotic-adjuvant combinations, use of aminoglycosides and derivatives and alternatives such as biopharmaceuticals. Therefore, this review summarizes the effect of current rise in antibiotic resistance through an economic viewpoint and reports recent global incidences of antibiotic resistance. Additionally, general mechanisms of resistance and alternatives to antibiotics have been described to educate the community on the importance of antibiotics.

2. Economic point of review

The loss of capital caused by antimicrobial resistance is globally estimated to be approximately \$300 billion to \$1 trillion by 2050 (Burki, 2018). The cumulative loss of economic output by 2050 for countries in the Organisation for Economic Co-operation and Development (OECD) will amount to approximately \$20 - 35 trillion (O'neill, 2014). In the United States (US) only, the total economic burden has been estimated to be as high as \$20 billion for the health care sector and approximately \$35 billion for productivity loss due to this antimicrobial resistance crisis (Ventola, 2015). Moreover, according to a research from World Bank, antimicrobial resistance would increase the levels of poverty and would have greater impacts on the poorest countries mostly (Bank, 2017).

Generally, high cost for health care due to antimicrobial resistance is

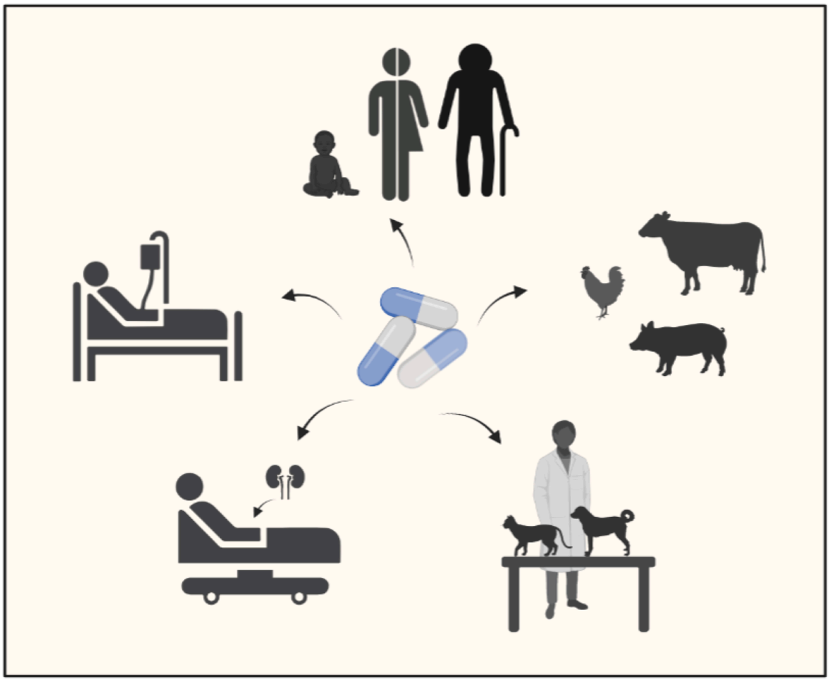

Fig. 1. Common uses of antibiotics in several sectors including normal bacterial infection treatment of the general population, hospital settings, domestic animal clinics and the animal husbandry field.

mainly used for required additional nursing and medical care and this phenomenon is more pronounced in low-income countries. This is mainly due to the high incidence of infectious cases and higher dependence on the labour incomes in these countries (Bank, 2017). Moreover, effective treatment for antimicrobial resistance for several low- and middle-income countries is usually out of reach due to poor enactment, lack of enforcement of regulations, low awareness on the responsible use of antibiotics and inadequate distribution of treatment guidelines (Bloom et al., 2017).

Studies have shown that annual Growth Domestic Product (GDP) may decrease by 1% globally but approximately 5–7% for developing countries by 2050. Additionally, this would indefinitely increase the gap between developing and developed countries, therefore, increasing the inequity level (Anderson et al., 2019; Bank, 2017). It has been estimated that people from low-income countries will be affected the most due to the dependence of these countries on labour-based income. Hence, antimicrobial resistance greatly influences the labour force due to loss of productivity due to increased hospitalization rate and premature death, which negatively impacts the total workforce, the population size and the quality of human capital (Naylor et al., 2018). The global trade sector will be severely affected if the trend in antimicrobial resistance continues to persist. World Bank has estimated a significant decrease in global exports by 2050 for labour-intensive divisions and this effect is more pronounced than global recession due to its long-term effects on the economy (Lekagul et al., 2019).

Antimicrobial resistance will also affect the output of livestock as this issue would indefinitely disrupt the levels of mortality and morbidity rate of the animals (Hao et al., 2014). Increased resistance to commonly used antibiotics in the agricultural sector would reduce the efficacy of treatment on the livestock, thus increasing the infection rate and the spread of the infection as well. Ultimately, reduction in the production and trade of livestock would cause a spike in the prices of protein sources including meat, egg and milk supplies (Bank, 2017). Lack of protein source can be worrisome as the demand for animal-based protein is increasing worldwide to satisfy the demand of rising world population (Van Boeckel et al., 2015). World Bank has estimated that antimicrobial resistance crisis will have a drastic impact on the yield of livestock especially in the low- and middle-income countries (Lekagul et al., 2019). Moreover, persistent increase in the antimicrobial resistance would result in 11% loss in the production of livestock by 2050 and this would further exacerbate the economic situation due to financial loss in animal production (Bank, 2017).

3. Incidences of cases

In 2014, antibiotic resistance caused approximately 700,000 of deaths and it was estimated that the world population by 2050 will be between 11 million and 444 million lower than it would otherwise be in the absence of this global health concern (O'neill, 2014). Fig. 2 shows the number of deaths attributable to antibiotic resistance by year 2050 for different regions in the world and failing to deal with this phenomenon will increase the number of deaths in each country. There is a substantial disparity globally in the pattern of antibiotic resistance where different countries often experience different types of obstacles. The variation in the antibiotic resistance of each country is related to the variations in the use of antibiotics, where improper and excessive use will contribute to the development of antibiotic resistance. Countries that may suffer from antimicrobial resistance include India, Nigeria, Indonesia and Russia, as these countries have already reported to have a high number of Malaria, HIV or TB rates, hence likely to suffer as resistance to current treatments increases (O'neill, 2014).

The resistant bacteria that have been increasingly involved in most of the bacterial infections are *Enterococcus* spp, *S. aureus, K. pneumoniae, A. baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp. Table 1 describes the extent of resistance of *E. coli, K. pneumoniae, Salmonella* spp., *Acinetobacter* spp., and *S. aureus* to antibiotics, extracted from the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) report 2021 for selected countries (WHO, 2021). This table summarizes antibiotic resistant incidents that occurred in WHO regions which includes Eastern Mediterranean, European, South-East, Western Pacific, Africa and America region. It was found that *E. coli* and *K. pneumoniae* are the most common isolates that pose resistance to a wide range of antibiotics including cefepime, ceftriaxone, ceftazidime, meropenem and ciprofloxacin. These isolates were recovered from community, hospital and of unknown origin (WHO, 2021).

Recent GLASS report 2021 highlights the incidence of *E. coli* strains (isolated from bloodstream infections) resistant to 3rd generation cephalosporins (WHO, 2021). Most of the participating countries have

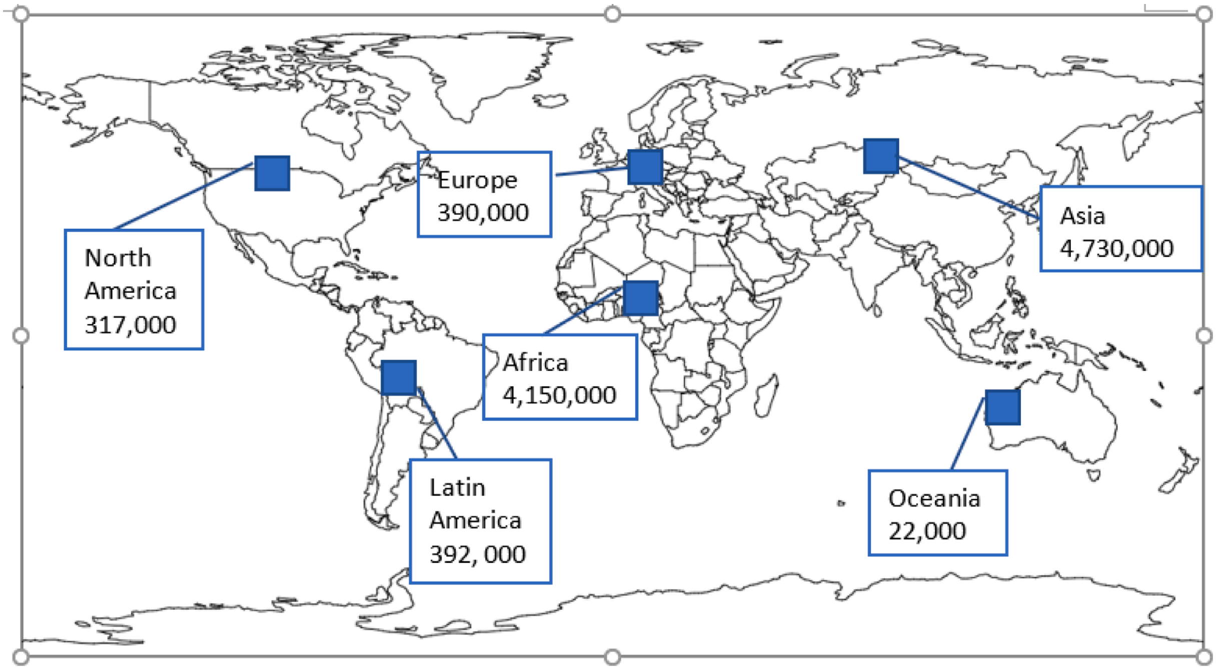

Fig. 2. The estimated number of deaths caused by antibiotic resistance by year 2050 for different regions of the world. Adapted with permission from (O'neill, 2014).

Table 1
Resistance to key antibiotics by *E. coli, K. pneumoniae, Salmonella* spp., *Acinetobacter* spp. *and S. aureus*. The data are derived from WHO GLASS report 2021(WHO, 2021).

Country Eastern Mediterranean region	Isolate[a]	No. of infected person	AMR rates[b]	Antibiotics
Bahrain	*E. coli*	1101	0–80%	Cefepime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Co-trimoxazole, Imipenem, Meropenem, Ampicillin, Cefotaxime, Colistin, Ertapenem, Levofloxacin
	Acinetobacter spp.	204	0–80%	Amikacin, Colistin, Gentamicin, Imipenem, Meropenem, Tigecycline
	K. pneumoniae	289	0–100%	Cefepime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Co-trimoxazole, Colistin, Ertapenem, Imipenem, Meropenem, Cefotaxime, Ceftazidime, Levofloxacin
	Salmonella spp.	250	0–40%	Ceftazidime, Ceftriaxone, Ciprofloxacin, Imipenem, Meropenem
	N. gonorrhoeae	277	0–84%	Azithromycin, Cefixime, Ceftriaxone, Ciprofloxacin
	S. aureus	71	30 - 50%	Oxacillin
	S. pneumoniae	51	0–20%	Ceftriaxone, Penicillin G
	Shigella spp.	3459	0–30%	Ceftriaxone, Ciprofloxacin
Lebanon	*Acinetobacter* spp.	1108	0–80%	Amikacin, Gentamicin, Imipenem, Minocycline
	E. coli	6	0–90%	Cefepime, Ceftriaxone, Ceftazidime, Co-trimoxazole, Ampicillin, Ciprofloxacin Imipenem, Ertapenem, Levofloxacin, Meropenem, Cefotaxime, Ertapenem, Colistin
	K. pneumoniae	510	6–70%	Cefepime, Cefotaxime, Ceftriaxone, Ceftazidime, Co-trimoxazole, Ciprofloxacin Imipenem, Ertapenem, Colistin, Ertapenem, Levofloxacin, Meropenem
	S. aureus	47	9–50%	Cefoxitin
	S. pneumoniae	3	NR	NR
	Salmonella spp.	74	0–50%	Cefotaxime, Ceftriaxone, Ceftazidime, Ciprofloxacin, Ertapenem, Imipenem, Levofloxacin
	N. gonorrhoeae	69	NR	NR
	Shigella spp.	86	NR	NR
Egypt	*Acinetobacter* spp.	46	6–80%	Amikacin, Colistin, Gentamicin, Imipenem, Meropenem,
	E. coli	622	4–100%	Cefepime, Ceftazidime, Cefotaxime, Ceftriaxone, Levofloxacin, Meropenem, Imipenem, Ampicillin, Ciprofloxacin, Ertapenem
	K. pneumoniae	149	38–100%	Cefepime, Ceftazidime, Cefotaxime, Ceftriaxone, Levofloxacin, Meropenem, Imipenem, Ciprofloxacin,

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Table 1 (*continued*)

Country Eastern Mediterranean region	Isolate[a]	No. of infected person	AMR rates[b]	Antibiotics
				Co-trimoxazole, Doripenem, Ertapenem
	S. aureus	46	66–88%	Oxacillin
	S. pneumoniae	46	NR	NR
	Salmonella spp.	435	NR	NR
	N. gonorrhoeae	46	NR	NR
	Shigella spp.	40	NR	NR
Tunisia	*E. coli*	36	0–85%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, colistin, Ampicillin, Ciprofloxacin, Imipenem, Ertapenem, Meropenem, Colistin, Ertapenem, Levofloxacin
	K. pneumoniae	1276	0–70%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Colistin, Ciprofloxacin, Imipenem, Ertapenem, Meropenem, Levofloxacin
	S. aureus	282	0–20%	Cefoxitin
	S. pneumoniae	149	NR	NR
	Salmonella spp.	981	0–50%	Ceftazidime, Cefotaxime, Ciprofloxacin, Imipenem, Ertapenem, Levofloxacin
	N. gonorrhoeae	152	NR	NR
	Shigella spp.	4485	NR	NR
European region				
Bosnia& Herzegovina	*Acinetobacter* spp.	237	0–100%	Meropenem, Colistin, Imipenem, Gentamicin, Amikacin
	E. coli	219	0–75%	Imipenem, Meropenem, Ceftriaxone, Ceftazidime, Cefotaxime, Ertapenem, Levofloxacin, Ciprofloxacin, Ampicillin
	K. pneumoniae	273	0–80%	Imipenem, Ertapenem, Ceftriaxone, Ceftazidime, Cefotaxime, Levofloxacin, Ciprofloxacin, Meropenem
	S. aureus	291	0–15%	Cefoxitin, Oxacillin
	S. pneumoniae	44	0–50%	Cefotaxime, Ceftriaxone, Oxacillin, Penicillin G
	Salmonella spp.	88	NR	NR
	N. gonorrhoeae	44	NR	NR
	Shigella spp.	44	NR	NR
Finland	*Acinetobacter* spp.	15,983	0–7%	Meropenem
	E. coli	1544	0–100%	Ceftriaxone, Ceftazidime, Ampicillin, Levofloxacin, Ciprofloxacin, Meropenem, Imipenem, Cefotaxime, Ertapenem, Co-trimoxazole
	K. pneumoniae	6853	0–90%	Ceftriaxone, Ceftazidime, Co-trimoxazole Levofloxacin, Ciprofloxacin, Meropenem, Imipenem, Cefotaxime, Ertapenem
	S. aureus	957	0–3%	Oxacillin
	S. pneumoniae	927	0–2%	Penicillin G
	Salmonella spp.	159,676	0–20%	Ceftriaxone, Ciprofloxacin, Meropenem, Ceftazidime, Levofloxacin
	N. gonorrhoeae	15,983	0–3%	Ceftriaxone
	Shigella spp.	124	NR	NR
Georgia	*Acinetobacter* spp.	8	0–85%	Colistin, Gentamicin, Imipenem, Meropenem

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Table 1 (*continued*)

Country Eastern Mediterranean region	Isolate[a]	No. of infected person	AMR rates[b]	Antibiotics
	E. coli	16	0–82%	Ampicillin, Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Ertapenem, Imipenem, Levofloxacin, Meropenem
	K. pneumoniae	136	0–83%	Cefepime, Ceftriaxone, Ceftazidime, Colistin, Ciprofloxacin, Meropenem, Imipenem, Ertapenem, Cefotaxime, Co-trimoxazole, Ertapenem, Levofloxacin
	S. aureus	136	9–45%	Cefoxitin, Oxacillin
	S. pneumoniae	8	NR	NR
	Salmonella spp.	91	NR	NR
	N. gonorrhoeae	8	NR	NR
	Shigella spp.	78	NR	NR
Germany	*Acinetobacter* spp.	357,718	0–12%	Meropenem, Imipenem, Gentamicin, Amikacin
	E. coli	61,112	0–50%	Ceftriaxone, Ceftazidime, Cefotaxime, Ampicillin, Levofloxacin, Ciprofloxacin, Meropenem, Imipenem, Ertapenem, Co-trimoxazole
	K. pneumoniae	23,837	0–13%	Ceftriaxone, Ceftazidime, Cefotaxime, Levofloxacin, Ciprofloxacin, Meropenem Imipenem, Ertapenem, Cefepime
	S. aureus	154	5–7%	Cefoxitin, Oxacillin
	S. pneumoniae	1534	0–2%	Cefotaxime, Ceftriaxone, Penicillin G
	Salmonella spp.	11,015	0–34%	Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Ertapenem, Imipenem, Meropenem, Levofloxacin
	N. gonorrhoeae	59,131	No data	No data
	Shigella spp.	4719	4–50%	Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Levofloxacin
	Acinetobacter spp.	198	0–91%	Colistin, Imipenem, Gentamicin, Amikacin, Meropenem
Latvia	*E. coli*	483	0–62%	Ceftazidime, Cefotaxime, Ampicillin, Ciprofloxacin, Ceftriaxone Meropenem, Imipenem, Ertapenem, Levofloxacin
	K. pneumoniae	123	0–48%	Ceftazidime, Cefotaxime, Ciprofloxacin, Meropenem Imipenem, Ertapenem, Ceftriaxone, Levofloxacin
	S. aureus	77	6–23%	Cefoxitin, Oxacillin
	S. pneumoniae	77	0–26%	Cefotaxime, Ceftriaxone, Oxacillin, Penicillin G
	Salmonella spp.	519	NR	NR
	N. gonorrhoeae	77	NR	NR
	Shigella spp.	77	NR	NR
Norway	*Acinetobacter* spp.	108	0–23%	Meropenem, Gentamicin
	E. coli	4904	0–42%	Ceftriaxone, Ceftazidime, Cefotaxime, Co-trimoxazole, Ampicillin, Ciprofloxacin

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Table 1 (*continued*)

Country Eastern Mediterranean region	Isolate[a]	No. of infected person	AMR rates[b]	Antibiotics
				Meropenem, Imipenem, Ertapenem, Cefepime
	K. pneumoniae	748	0–12%	Ceftazidime, Cefotaxime, Co-trimoxazole, Ciprofloxacin, Meropenem, Cefepime, Ceftriaxone, Ertapenem, Imipenem
	S. aureus	1501	1–2%	Cefoxitin, Oxacillin
	S. pneumoniae	325	0–24%	Cefotaxime, Ceftriaxone, Oxacillin, Penicillin G
	Salmonella spp.	1610	0–38%	Ceftazidime, Cefotaxime, Ciprofloxacin, Meropenem
	N. gonorrhoeae	330	0–60%	Azithromycin, Cefixime, Ceftriaxone
	Shigella spp.	23	1–28%	Cefotaxime, Ceftazidime, Ciprofloxacin
Sweden	*Acinetobacter* spp.	1795	2–16%	Amikacin, Meropenem, Gentamicin, Imipenem
	E. coli	21,827	0–31%	Cefotaxime, Ceftazidime, Co-trimoxazole, Ampicillin, Ciprofloxacin, Meropenem, Imipenem
	K. pneumoniae	21,999	0–12%	Ceftazidime, Cefotaxime, Ciprofloxacin, Meropenem, Imipenem
	S. aureus	5948	1–4%	Cefoxitin, Oxacillin
	S. pneumoniae	1555	0–10%	Cefotaxime, Oxacillin, Penicillin G
	Salmonella spp.	10,490	0–44%	Ceftazidime, Cefotaxime, Ciprofloxacin, Meropenem, Imipenem
	N. gonorrhoeae	253	NR	NR
	Shigella spp.	207,579	2–24%	Azithromycin, Cefotaxime, Ceftazidime, Ciprofloxacin
Switzerland	*Acinetobacter* spp.	726	0–19%	Meropenem, Imipenem, Gentamicin, Amikacin
	E. coli	120,988	0–50%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Ampicillin, Ciprofloxacin, Meropenem, Imipenem, Ertapenem Ceftriaxone, Colistin, Levofloxacin
	K. pneumoniae	284	0–13%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Ceftriaxone, Colistin, Levofloxacin, Ciprofloxacin, Meropenem, Imipenem, Ertapenem
	S. aureus	6048	3–5%	Cefoxitin, Oxacillin
	S. pneumoniae	63	0–17%	Cefotaxime, Ceftriaxone, Co-trimoxazole, Oxacillin, Penicillin G
	Salmonella spp.	21,085	0–31%	Ceftriaxone, Ceftazidime, Cefotaxime, Levofloxacin, Ciprofloxacin, Meropenem, Ertapenem
	N. gonorrhoeae	1237	0–73%	Azithromycin, Cefixime, Ceftriaxone, Ciprofloxacin, Spectinomycin
	Shigella spp.	510	2–42%	Azithromycin, Levofloxacin, Ceftazidime, Ciprofloxacin, Ceftriaxone

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Table 1 (*continued*)

Country Eastern Mediterranean region	Isolate[a]	No. of infected person	AMR rates[b]	Antibiotics
	Acinetobacter spp.	73	0–25%	Meropenem, Imipenem, Gentamicin, Amikacin
	S. aureus	1630	0–25%	Cefoxitin
South-east Asia region				
Thailand	*Acinetobacter* spp.	6907	1–63%	Meropenem, Imipenem, Gentamicin, Amikacin, Colistin, Doripenem, Tigecycline
	E. coli	1007	0–86%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Ampicillin, Ciprofloxacin, Meropenem, Imipenem, Ertapenem, Ceftriaxone, Levofloxacin, Colistin, Doripenem
	K. pneumoniae	3225	0–63%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Ceftriaxone, Imipenem Ertapenem, Ceftriaxone, Levofloxacin, Ciprofloxacin, Colistin, Doripenem, Meropenem
	S. aureus	12	5–15%	Cefoxitin, Oxacillin
	S. pneumoniae	79	1–57	Cefotaxime, Ceftriaxone, Co-trimoxazole, Oxacillin, Penicillin G
	Salmonella spp.	2633	0–28%	Ceftazidime, Cefotaxime, Ceftriaxone, Meropenem, Imipenem, Ertapenem, Ciprofloxacin, Doripenem
	N. gonorrhoeae	702	0–77%	Ceftriaxone, Ciprofloxacin
	Shigella spp.	845	No data	No data
Indonesia	*Acinetobacter* spp.	504	2–97%	Amikacin, Doripenem, Gentamicin, Imipenem, Meropenem, Tigecycline
	E. coli	110	1–91%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Ampicillin, Ciprofloxacin, Meropenem, Imipenem, Ertapenem, Ceftriaxone, Levofloxacin, Colistin, Doripenem
	K. pneumoniae	966	1–83%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Ciprofloxacin, Meropenem, Imipenem, Ertapenem, Ceftriaxone, Levofloxacin, Colistin, Doripenem
	S. aureus	358	32–45%	Cefoxitin, Oxacillin
	S. pneumoniae	962	0–50%	Ceftriaxone, Co-trimoxazole, Penicillin G
	Salmonella spp.	1342	0–31%	Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Ertapenem, Meropenem
	N. gonorrhoeae	2421	NR	NR
	Shigella spp.	3	NR	NR
Bangladesh	*Acinetobacter* spp.	98	NR	NR
	E. coli	412	7–100%	Cefepime, Ceftazidime, Ampicillin, Ciprofloxacin, Meropenem, Imipenem, Ceftriaxone, Levofloxacin

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Table 1 (*continued*)

Country Eastern Mediterranean region	Isolate[a]	No. of infected person	AMR rates[b]	Antibiotics
	K. pneumoniae	106	6–96%	Ceftazidime, Ceftriaxone, Ciprofloxacin, Imipenem
	S. aureus	8	NR	NR
	S. pneumoniae	94	NR	NR
	Salmonella spp.	20	0–90%	Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Ertapenem, Meropenem
	N. gonorrhoeae	33	NR	NR
	Shigella spp.	1	NR	NR
Western Pacific region				
Japan	*Acinetobacter* spp.	375,822	0–1%	Amikacin, Imipenem, Meropenem, Minocycline
	E. coli	105,099	0–45%	Ampicillin, Cefepime, Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Imipenem, Levofloxacin, Meropenem
	K. pneumoniae	306	0–10%	Cefepime, Ceftazidime, Cefotaxime, Ceftriaxone, Imipenem Ceftriaxone, Levofloxacin, Ciprofloxacin, Meropenem
	S. aureus	3241	36–37%	Oxacillin
	S. pneumoniae	608	0–1%	Cefotaxime, Ceftriaxone, Penicillin G
	Salmonella spp.	103,744	0–5%	Cefotaxime, Ceftazidime, Ciprofloxacin, Imipenem, Meropenem
	N. gonorrhoeae	1621	0–67%	Azithromycin, Cefixime, Ceftriaxone, Ciprofloxacin, Spectinomycin
	Shigella spp.	1023	1–23%	Cefotaxime, Ciprofloxacin
Republic of Korea	*E. coli*	7953	0–72%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Ampicillin, Ciprofloxacin, Meropenem, Imipenem, Ertapenem, Colistin
	K. pneumonia	2011	0–45%%	Cefepime, Ceftazidime, Cefotaxime, Co-trimoxazole, Ciprofloxacin, Meropenem, Imipenem, Ertapenem, Colistin
	S. aureus	36	45–52%	Cefoxitin
	S. pneumoniae	1939	0–88%	Cefotaxime, Ceftriaxone, Oxacillin, Penicillin G
	Salmonella spp.	140	0–17%	Ceftazidime, Cefotaxime, Ciprofloxacin, Imipenem
	N. gonorrhoeae	225	NR	NR
	Shigella spp.	47	NR	NR
Cambodia	*Acinetobacter* spp.	374	0–40%	Amikacin, Colistin, Gentamicin, Imipenem, Meropenem
	E. coli	650	1–89%	Ampicillin, Cefepime, Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Co-trimoxazole, ertapenem, Imipenem, Meropenem
	K. pneumoniae	748	NR	NR
	S. aureus	374	NR	NR
	S. pneumoniae	374	NR	NR
	Salmonella spp.	748	NR	NR
	N. gonorrhoeae	374	NR	NR

(*continued on next page*)

Table 1 (*continued*)

Country Eastern Mediterranean region	Isolate[a]	No. of infected person	AMR rates[b]	Antibiotics
	Shigella spp.	374	NR	NR
Philippines	*Acinetobacter* spp.	3	NR	NR
	K. pneumoniae	1616	0–60%	Cefepime, Ceftriaxone, Ceftazidime, Cefotaxime, Co-trimoxazole, Colistin, Levofloxacin, Ciprofloxacin, Imipenem Ertapenem, Doripenem, Meropenem
	S. aureus	2614	0–50%	Cefoxitin, Oxacillin
	S. pneumoniae	1420	0–20%	Ceftriaxone, Co-trimoxazole, Oxacillin, Penicillin G,
	Salmonella spp.	1433	0–30%	Ceftriaxone, Cefotaxime, Levofloxacin, Imipenem, Ciprofloxacin, Ceftazidime, Ertapenem, Meropenem
	N. gonorrhoeae	44	0–90%	Azithromycin, Cefixime, Ceftriaxone, Ciprofloxacin, Spectinomycin
	Shigella spp.	6518	0–60%	Azithromycin, Cefotaxime, Ceftriaxone, Ciprofloxacin
Africa region				
Madagascar	*E. coli*	2011	0–94%	Cefepime, Ceftazidime, Ceftriaxone, Levofloxacin, Meropenem, Imipenem, Ampicillin, Ciprofloxacin, Ertapenem, Co-trimoxazole, Colistin, Doripenem
	K. pneumoniae	39	0–80%	Cefepime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Co-trimoxazole, Imipenem, Colistin
	S. aureus	5	18–53%	Cefoxitin
	S. pneumoniae	37	NR	NR
	Salmonella spp.	10	NR	NR
	N. gonorrhoeae	446	1–100%	Azithromycin, Ceftriaxone, Ciprofloxacin
	Shigella spp.	55	0–30%	Ceftazidime, Ceftriaxone, Ciprofloxacin
Ethiopia	*Acinetobacter* spp.	4	7–95%	Amikacin, Gentamicin, Meropenem
	E. coli	134	0–100%	Ampicillin, Co-trimoxazole, Meropenem, Cefepime, Cefotaxime, Ceftazidime, Ceftriaxone, Imipenem
	K. pneumoniae	141	17–100%	Cefepime, Cefotaxime, Ceftazidime, Ceftriaxone, Co-trimoxazole, Meropenem
	S. aureus	10	NR	NR
	S. pneumoniae	332	NR	NR
	Salmonella spp.	120	NR	NR
	N. gonorrhoeae	88	NR	NR
	Shigella spp.	117	NR	NR
South Africa	*Acinetobacter* spp.	5983	0–81%	Amikacin, Gentamicin, Imipenem, Meropenem, Minocycline, Tigecycline
	E. coli	6965	0–86%	Cefepime, Ceftazidime, Ceftriaxone, Meropenem, Imipenem, Ampicillin, Ciprofloxacin, Ertapenem, Co-

(*continued on next page*)

Table 1 (*continued*)

Country Eastern Mediterranean region	Isolate[a]	No. of infected person	AMR rates[b]	Antibiotics
				trimoxazole, Doripenem, Cefotaxime
	K. pneumoniae	1228	13–73%	Cefepime, Ceftazidime, Ceftriaxone, Co-trimoxazole, Ciprofloxacin, Imipenem, Meropenem Ertapenem
	S. aureus	744	20–22%	Oxacillin
	S. pneumoniae	650	2–41%	Ceftriaxone, Co-trimoxazole, Penicillin G
	Salmonella spp.	3138	0–13%	Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Ertapenem, Imipenem,
	N. gonorrhoeae	227	0–2%	Azithromycin, Cefixime, Ceftriaxone, Spectinomycin
	Shigella spp.	4306	0–2%	Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin
America region				
Brazil	*Acinetobacter* spp.	860	0–83%	Amikacin, Gentamicin, Imipenem, Meropenem, Tigecycline
	E. coli	862	0–90%	Ampicillin, Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Co-trimoxazole, Imipenem, Meropenem, Ertapenem, Levofloxacin
	K. pneumoniae	376	19–80%	Ceftazidime, Ceftriaxone, Ciprofloxacin, Co-trimoxazole, Ertapenem, Imipenem, Meropenem, Levofloxacin, Cefotaxime
	S. aureus	166	16–26%	Oxacillin
	S. pneumoniae	3435	NR	NR
	Salmonella spp.	60	NR	NR
	N. gonorrhoeae	6	0–72%	Cefixime, Ceftriaxone, Ciprofloxacin, Gentamicin, Spectinomycin
	Shigella spp.	199	NR	NR

[a] Isolates obtained from community/ hospital/ unknown origin,.

[b] percentage of resistance depends on the types of antibiotics, NR- Not reported.

reported high incidences of antimicrobial resistance in the bloodstream, gastroenteric and urinary infections where resistance to co-trimoxazole, first-line drug, and carbapenem (imipenem and meropenem), drug of last resort, were reported in high numbers. *E. coli* is one of the most common pathogens isolated from bloodstream infections and it has been reported that a median proportion of this pathogen was found to express resistance to ceftazidime. The MIC value was found to be lower for this category of *E. coli* than isolates expressing resistance towards cefotaxime and ceftriaxone. Additionally, this resistance by *E. coli* to 3rd generation cephalosporins was recorded at a higher level of 58.3% in low-middle income countries compared to 17.5% in high-income countries. However, the difference in the percentage should be further analysed as there were large differences in the number of tested patients between these countries (WHO, 2021).

4. Mechanisms of antibiotic resistance

There is no doubt that the antibiotic arsenal has saved the human population from various pathogenic bacterial infections, however, resistance to antibiotics is not a new phenomenon as the occurrence of penicillin resistance has been reported soon after its discovery in the mid-90′s (Charles and Thelma, 1942; Lowy, 2003). Over the years, the prevalence of resistance has increased drastically especially in the developing countries and the emergence of multi-drug resistant (MDR) and extensively drug-resistant (XDR) and the recent discovery of pan-drug-resistant (PDR) has further fuelled this crisis. MDR was defined as acquired resistance to at least one agent from three or more antimicrobial categories, XDR was defined as acquired resistance to at least one agent from all but two or fewer antimicrobial categories while PDR was defined as acquired resistance to all antimicrobial categories (Basak et al., 2016; Magiorakos et al., 2012).

In order to comprehend the factors that contribute to the mechanism of resistance, it is crucial to understand the mechanism of action of the antibiotics. Generally, there are five major modes of action; interference of enzymes required for (1) peptidoglycan biosynthesis, (2) nucleic acid synthesis, (3) protein synthesis and (4) metabolism and lastly the (5) disorganisation of the cytoplasmic membrane (Kohanski et al., 2010). An antibiotic may act by either one or more of these mechanisms. The mechanism of action for major classes of antibiotics is summarized in Fig. 3 and a detailed review of these mechanisms has been reviewed in Kohanski et al. (2010).

Pathogens achieve resistance to antibiotics through the mode the agent has affected them. The emergence of resistance generally depends on the species, the nature of the drug and its target site. When the

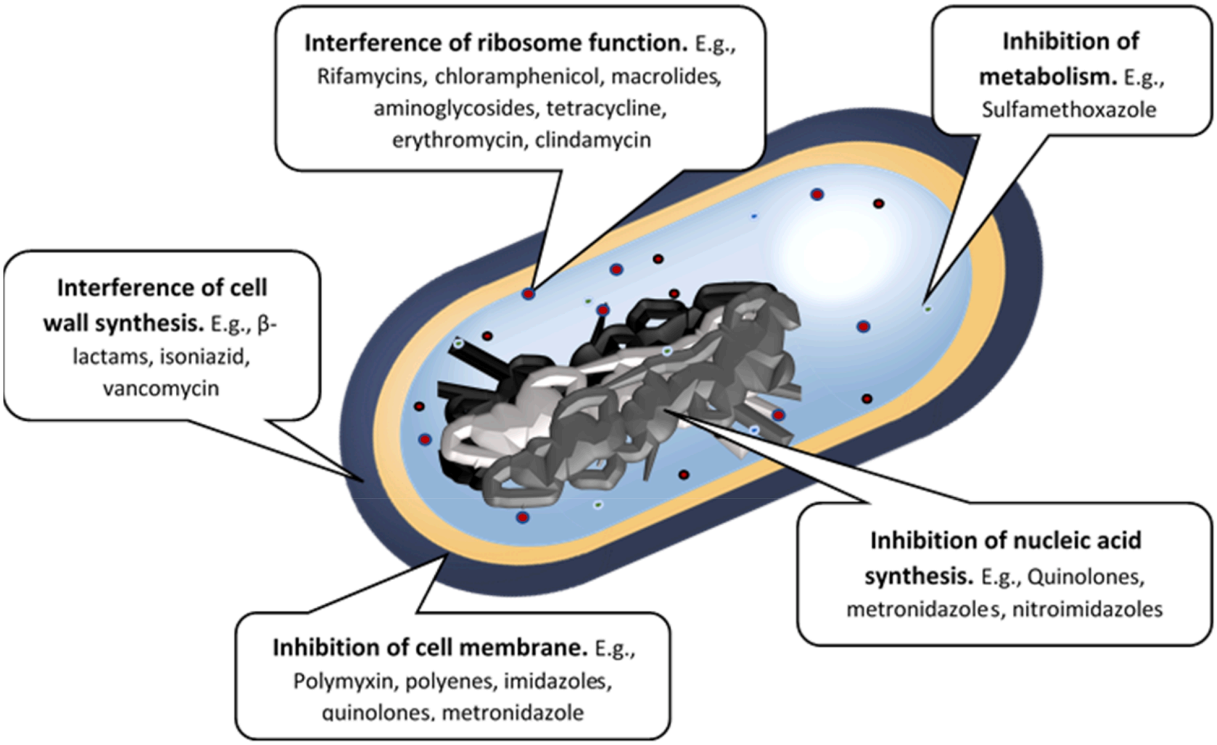

Fig. 3. A brief description of five major mechanisms of action of antibiotics from several antibiotic classes against bacteria.

antibiotic interferes a particular pathway, a sophisticated alternative mechanism will be activated by the microorganism to avoid the bacteriostatic or bactericidal activity of the agent (Munita and Arias, 2016). The antimicrobial resistance is usually driven by natural biological factors including biochemical and genetic aspects. However, the excessive use of antimicrobial agents in agriculture and as disinfectants in household chores as well as poor infection control and hygiene in health care settings have further catalysed this crisis.

5. Biochemical aspects of resistance

Microorganisms have evolved to avoid killing by antimicrobial agents and gain resistance through various biochemical routes. Although the biochemical routes of resistance are diverse as shown in Fig. 4, they can be clustered as follows based on the prevalence of medically important pathogens (Džidić et al., 2008; Munita and Arias, 2016).

5.1. Antibiotic inactivation

Antibiotic inactivation is an enzyme-based process where the active antibiotic molecule will be rendered inactive by enzymes produced by the resistant bacterial cells. The strategies to deactivate antibiotic molecules include hydrolysis, group transfer and redox process. One of the well-studied examples of hydrolysis inactivation is the destruction of the β-lactam ring of penicillin, cephaloporin and carbapenem by bacteria that produce β-lactamase, such as *E. coli, K. pneumoniae*, and *Enterobacter* spp (Davies, 1994) and enzymes such as acyltransferase, phosphotransferases, and thioltransferases (Wright, 2005). The redox process is an inactivation through oxidation or reduction of a drug molecule (Wright, 2005). However, this pathway is not often encountered in medical practice compared to hydrolysis and group transfer mechanisms (Džidić et al., 2008).

5.2. Decreased antibiotic penetration

As most of the antibiotics in the clinical practice have intracellular targets, bacteria have evolved to limit the penetration of the antibiotics through decreased permeability of the cell membrane. For example, the outer cell wall layer of *Mycobacterium tuberculosis* is extremely lipophilic as it is made of mycolic acids, a long fatty acid chain (Jackson, 2014). The penetration of hydrophilic drugs is dependant on the porin channels and it has been reported that the penetration via mycobacterial porin happen to be slower as it exists in a low concentration (Jarlier and Nikaido, 1994). The mycobacterial cell wall therefore creates a permeability barrier towards antibiotics which leads to natural resistance to a variety of antibiotics. Studies have been reported that the activity of hydrophilic molecules (i.e. isoniazid) could be improved by chemically modifying it into a lipophilic compound to enhance the antibiotic's permeation through the lipid bilayer membrane (Parumasivam et al., 2013a, 2013b).

5.3. Activation of efflux pump

The role of efflux pumps in enhancing antibiotic resistance has gained significant attention over the years. Efflux pumps are transport protein found in the membrane of the bacterial cell wall that transport nutrient and extrude toxic compounds from the cellular environment. However, the efflux mechanism has become increasingly recognised as the major component of resistance to many classes of antibiotics (Soto, 2013; Varela et al., 2013). Efflux pumps can be specific to one particular antibiotic while multidrug efflux pumps (MEPs) can extrude out a variety of structurally and functionally different antibiotics (Fiamegos et al., 2011). The major classes of antibiotics that are known to be effluxed by intrinsic bacterial efflux pumps are macrolides, β-lactams, fluoroquinolones, oxazolidinones, and fourth generation cephalosporins and carbapenems (Li and Nikaido, 2009; Li et al., 2015).

5.4. Target bypass

Bacteria produce alternatives proteins to adopt the role of native protein which allows the cells to gain resistance to an antibiotic (Giedraitienė et al., 2011). The *mecA* gene encodes for a novel penicillin-binding protein (PBP), PBP-2A which allows methicillin resistance in *S. aureus* (Wielders et al., 2002). Upon exposure to methicillin, the high-affinity PBPs were shuttled down while the low-affinity PBP-2A takes over the role of these PBPs for the bacteria to propagate (Enright, 2003; Hartman and Tomasz, 1984). The *mecA* also contains gene structures, such as Tn554, pUB110, and pT181, that are encoded for resistance to non-β-lactam antibiotics (Ito and Hiramatsu, 1998). Though antibiotics with high affinity for PBP-2a have been investigated for the treatment of MRSA, none has made to the clinical trial.

6. Genetic aspects of resistance

It is well-known that antimicrobial resistance is not only driven by biochemical factors, but also predominantly caused by genetic aspects in the clinical settings. Nonetheless, the origin of genetic mutations has begun with the antibiotic era in 1940s with the discoveries of bacterial strains that are resistant to antibiotics (Džidić et al., 2008). Various studies have identified numerous genetic loci in pathogenic microbes that contribute to antibiotic resistance (Beceiro et al., 2013; Giedraitienė et al., 2011). Several genes can be involved in antibiotic resistance due to several targets or pathways in the bacterial cells or the mechanism of action of an antibiotic may involve the expression of several genes. Hence, the genetic factors of bacterial resistance include mutational resistance and horizontal gene transfer.

6.1. Mutational resistance

6.1.1. Spontaneous mutation

Spontaneous mutation could be driven by various factors, especially via interference with the DNA replication. For example, majority of resistance against rifampicin is nearly always in the *rpoB* gene that encodes for RNA polymerase in *M. tuberculosis, P. aeruginosa* and *E. coli* (Goldstein, 2014; Hall et al., 2011; Kumar and Jena, 2014; Rodríguez-Verdugo et al., 2013). The types of mutations that have been reported are single and multiple nucleotide changes including insertion and deletion. The alteration at codons 513, 526 or 531 results in high-level rifampicin resistance while alteration at positions 511 and 533 lead to low-level resistance in *M. tuberculosis* (Ohno et al., 1996; Somoskovi et al., 2001). On the other hand, Jin and Gross (1988) showed that mutation within 225 base pair region of *rpo* gene gave rifampicin resistance in *E. coli* (Jin and Gross, 1988). These mutations result in weaker binding affinity of rifampicin with RNA polymerase and retards the activity of the drug. Similarly, resistance to ethambutol was mediated by mutations in *embCAB* gene which is encoded for membrane-associated arabinosyl transferase enzymes in the synthesis of the arabinogalactan of the mycobacterial cell wall (Zhao et al., 2015). Mutations at *embB* cause alterations in EmbB protein and alters the antibiotic target. Furthermore, sequence analysis of ethambutol resistant *M. tuberculosis* strains showed that the substitution of methionine with valine or leucine at codon 306 demonstrates high level of resistance compared to substitution of methionine with isoleucine (Rattan et al., 1998). There are also several mycobacteria strain which lacks mutations at gene *embCAB* but non-susceptible to ethambutol (Das et al., 2006; Ramaswamy et al., 2000). The rationale for this scenario is still unknown (Ramaswamy et al., 2000).

6.1.2. Hypermutation

Studies have shown that hypermutation has a crucial role in the evolution of antibiotic-resistance which imposed a significant negative impact on the antimicrobial therapy. Hypermutators are microorganisms with an increased affinity to go through spontaneous mutation due to defects in DNA repair or error in avoidance system (Oliver and Mena, 2010). The increased mutation rate allows the bacteria to adapt rapidly to antimicrobial agents, host immunity or viral parasites. Hypermutation has been shown to confer evolutionary advantages in the adaptation of bacteria to a new environment. These hypermutations are identified to be regulated by SOS-inducible mutator DNA polymerase IV which has been reported in *E. coli, Salmonella enterica, Neisseria meningitis* and *Haemophilus influenza* (Janion, 2008; Oliver and Mena, 2010; Tompkins et al., 2003). The involved genes are referred to as mutator genes. The first evidence to reveal the role of hypermutation in clinical antimicrobial-resistant was obtained from a study conducted in cystic fibrosis patients infected with *P. aeruginosa* in Spain (Oliver et al., 2000).

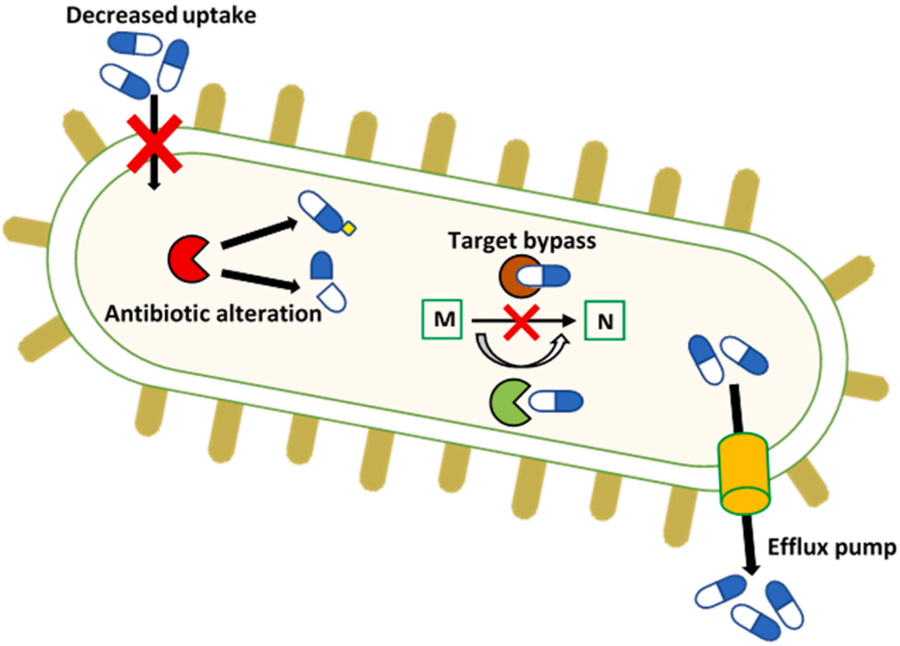

Fig. 4. Common mechanisms of bacterial antibiotic resistance including decreased antibiotic uptake, antibiotic inactivation by alteration mechanisms, bypass of antibiotic target through production of alternative protein and activation of the efflux pumps.

Hypermutation also allows *P. aeruginosa* to establish a pulmonary infection via a plethora of phenotypic adaptation including biofilm formation and genetic mutations for long-term persistence (Oliver and Mena, 2010; Smith et al., 2006; Ventre et al., 2006).

6.1.3. Adaptive mutation

Though the adaptive mutation is a relatively unexplored area, it is undeniable that the adaptive mutation is one of the main sources of antimicrobial resistance in the clinical environment (Fernández and Hancock, 2012). The distinctive feature of adaptive mutation is that it arises in non-dividing microorganisms that are exposed to non-lethal selective pressure, e.g. nutrient conditions, growth state, and sub-inhibitory levels of antibiotics concentration (Džidić et al., 2008; Tello et al., 2012). This mutation is also transient in nature and can revert to the original condition in the absence of triggers (Fernández and Hancock, 2012). Hence, the adaptive mutation is also known as directed, stationary-phase or selection-induced mutation. The adaptive mutation has been shown to be regulated by SOS response, a response towards DNA damage where the cell cycle is arrested where DNA repair and emergence of resistance are increased (Džidić et al., 2008; McKenzie et al., 2000). For example, *E. coli* that has been exposed to sublethal concentration of streptomycin induces the expression of recA- and *u*muDC-independent mutator phenotype on transfected M13 single-stranded DNA (Ren et al., 1999). The drastic increase in MDR and XDR *M. tuberculosis* strains during an infection treatment therapy period is also contributed by adaptive mutation (Gillespie, 2002).

6.2. Horizontal gene transfer

Another well-studied mechanism of antibiotic-resistance is horizontal gene transfer which is also known as lateral gene transfer. The lateral gene transfer can occur between two different prokaryotes or between a prokaryote and a eukaryote. The transmission of resistant genes between different genomes is usually mediated through conjugation, transformation or transduction mechanism (Baharoglu et al., 2010). Conjugation is a transient fusion between two bacteria where the transfer of genetic material including the genes that encode for antibiotic resistance is transferred from donor to recipient via a conjugation bridge. The transformation mechanism involves uptake of free genetic material released from a donor bacterium by a recipient bacterium. Transduction is a gene transfer mechanism mediated by bacteriophages and integrons (a gene capture system) and this transfer of resistant genes often occurs via transposons or plasmids. Gene conferring methicillin resistance, *mecA*, is usually disseminated by conjugation, transformation or transduction in methicillin-susceptible *S. aureus* and lead to the emergence of MRSA (Bitrus et al., 2017; Giedraitienė et al., 2011). MRSA has been identified to acquire vancomycin-resistant genes via conjugation from vancomycin-resistant enterococci (VRE) during co-infection (Malachowa and DeLeo, 2010). MRSA and VRE are amongst the most important global cause of nosocomial infections that are mainly responsible for increased treatment cost and healing period for patients and hospitals.

6.3. External factors

6.3.1. Pharmacological aspects

The effective dose of an antibiotic for antimicrobial therapy are determined by pharmacokinetics (PK) and pharmacodynamics (PD) parameters. The PK/PD models are used to bridge the pre-clinical and clinical evaluations (Velkov et al., 2013). These PK/PD models have been extensively employed as a tool in the development of new antibiotics, estimation of optimal dosing as well as in the in the understanding on the development of resistance (Velkov et al., 2013). The pharmacological factors influencing the emergence of drug-resistant can be: (1) drug-specific, the knowledge on a drug including the bioavailability after administration, the mechanism of action and its MIC against targeted microorganisms (Elizabth and Angela, 2017), (2) organism-specific, the pathogenicity of a microorganism to acquire resistance upon exposure to a drug (Elizabth and Angela, 2017), and (3) host-specific, covers genetic makeup of a patient that influences the PK/PD of drugs and consequently the development of resistance (Elizabth and Angela, 2017). The pharmacological factors of microbial resistance were systematically revied by Elizabeth and Angela (Elizabth and Angela, 2017) and Zdanowicz (Zdanowicz, 2006).

6.3.2. Food chain aspects

Overuse of antibiotics in the agricultural sector has resulted in the emergence of new strains of antibiotic-resistant bacteria. It is undeniable that antibiotics are widely used in the livestock to promote faster growth, better yield and prevent infection (Ventola, 2015). Antibiotics are also used as herbicides and pesticides for vegetations to control weeds and pests that infest the cultivated plants (Ventola, 2015). Theoretically, the antibiotics used above are ingested by humans as food (Ventola, 2015) and therefore, there are chances that the resistant genes may be transferred from the animal through zoonotic diseases or as a direct exposure from the food. The transfer of resistant bacteria from animal to human is not new as it has been identified in the 80 s itself (Bartlett et al., 2013; Ventola, 2015). Indeed, scientists have thought that new dangerous superbugs and viruses are triggered by overuse of antibiotics in the agriculture (Guglielmi, 2017). Reducing excessive or unnecessary use of antibiotics in the agriculture should be achieved to combat the burden of antimicrobial resistance and this requires a global implementation of strict policies on the use of antibiotics in these sectors.

6.3.3. Educational aspects

Misuse of an antibiotic is a serious public health threat in the Southeast Asian countries. For example, prescription of antibiotics for viral infections such as fever and flu are self-limiting as many are still unaware that antibiotics treat bacterial infection only and exposure to unnecessary antibiotics may also lead to antibiotic resistance. In a cross-sectional study conducted at a hospital in Malaysia by Tan et al. (2017), 80% of the antibiotic prescription for treatment of upper respiratory tract infections were inappropriate due to the prescribers who were unaware of the current regimen (Tan et al., 2017). This study also revealed the overdosing of antibiotics for treatment of upper respiratory tract and urinary tract infections and long medication period for treatment of leptospirosis and ocular infections (Tan et al., 2017). Though Malaysia has National Antibiotic Guidelines (NAG) launched in 2014, awareness of appropriate medications for infectious diseases are still lacking. Therefore, a systemic approach is needed to educate the health sector practitioners to further improve antibiotic prescribing practice in Malaysia as well as other countries facing similar situation.

6.3.4. Economic/financial aspects

Economic and financial standings limit the accessibility of essential antibiotics to patients, pharmacies and to healthcare administrators (Pécoul et al., 1999). This phenomenon has been implicated in inadequate treatment options or abandonment of treatment and made worse by the outbreak of antibiotic-resistant pathogens which require second- or third-line antibiotics. These antibiotics are often expensive and not easily accessible. This scenario is a widespread threat for developing countries especially in the Southeast Asian and African countries which has a higher burden of communicable diseases and inferior financial status (Dhillon et al., 2012; Fonkwo, 2008). The obstacles to acquire an appropriate treatment also occur in the form of inadequate infrastructure, i.e. diagnostic tools and insufficient number of trained personnel (McNerney, 2015; Wertheim et al., 2010). These difficulties occasionally delay the treatment and possibly a global mutual partnership between the developing and developed countries as well as world organisations may mitigate these hurdles.

7. Strategies to overcome antibiotic resistance

The efforts to improve the activity of available antibiotics and discovery of new agents are being carried out worldwide to reduce the development of antibiotic resistance. Good efficacy, superior activity than present antibiotics and optimal safety profile are the main criteria of a new antibiotic. However, the discovery of new antibiotic has long been overdue and experts in the health sector have witnessed the emergence of antibiotic resistant bacteria even on the final line of antibiotics. Therefore, available steps to overcome antimicrobial resistance and reports on present advancement in the discovery and development of antimicrobials have been discussed in this section. Chemical and biological methods coupled with advanced technological improvements are considered to have an advantage in the advancement of antimicrobial chemotherapy. Some of these approaches are already under investigation for more than a decade, though the advancement and production of useful antimicrobials are relatively slow.

7.1. Chemical structure modifications

Structure modifications of currently available antibiotics is one of the possible approaches to overcome the problem of antibiotic resistance. Vancomycin as an example, is an effective antimicrobial agent against Gram-positive bacteria. The resistant strain of bacteria to vancomycin has now developed after nearly 60 years since the discovery of this antimicrobial and one example is the Vancomycin-Resistant Enterococcus (VRE). Research has been conducted to modify the peripheral components of this glycopeptide-based antibiotic and this subsequently has overcome the developed mechanism of resistance, with two additional bacterial-killing mechanisms – (1) modifications on the binding pocket and (2) induced bacterial cell membrane permeability. This gives a 6000-fold increase in its potency against Van-A (resistant to vancomycin and teicoplanin) VRE and a reduced susceptibility to resistance (Okano et al., 2017).

7.2. Combinational therapy of antibiotics

Combinational therapy of antibiotics was also found to be an effective way to restore the susceptibility of bacteria towards antibiotics. Two or more agents may be combined according to the susceptibility pattern of the infectious microbes where a synergistic effect may be observed to enhance the treatment effectivity. In essence, there are three possible mechanisms of action in combinational therapy of antibiotics as described by Fischbach (2011): (i) inhibition of target in different pathways (i.e., antibiotics in combination for antituberculosis therapy), (ii) inhibition of distinct target in the same pathway (i.e., combination of trimethoprim and sulfamethoxazole) and (iii) inhibition of the exact same target through different mechanism (i.e., the use of streptogramins) (Fischbach, 2011; Worthington and Melander, 2013). In the treatment of several infectious diseases such as HIV/AIDS, malaria and tuberculosis, antibiotics in combination is always the choice to augment the efficacy of the treatment (Worthington and Melander, 2013). Unless a powerful antibiotic is discovered in the near future, combinational antibiotic therapy is the first approach that will be taken to combat MDR infections in current clinical settings. As an example, polymyxin and colistin are used in combination to treat infection caused by MDR Gram-negative infections.

Another useful approach under combinational therapy of antibiotics is called the sequential dose regiment. Through this way, the use of two (or more) drugs is being alternated over time and the collateral sensitivity of bacteria will be maximized. Hence, the antibiotics – that are supposed to be ineffective to the target bacteria – will work synergistically to inhibit the bacteria. This approach however is not easily applied and need thorough evaluation and screening of possible antibiotics (Richardson, 2017). However, there is one major drawback to this approach – the possibility of interactions between the antibiotics. This is an important issue especially if the interaction will lead to reduced efficacy or increased toxicity of the treatment. Although this is of concern, combining multiple drugs, in general, has been the chosen approach in the treatment of other medical conditions as well such as in cardiovascular disease and cancer (Worthington and Melander, 2013).

7.3. Drug-adjuvant combinations

Adjuvants are other molecules that may help to increase the activity of an antibiotic. These molecules are usually not lethal to microorganism on their own. A classic example is Augmentin® which is a combination of amoxicillin (β-lactam antibiotic) and clavulanic acid (β-lactamase inhibitor). The presence of clavulanic acid helps to augment the efficacy of amoxicillin by inhibiting the β-lactamase enzyme which will usually cause the inactivation of the antibiotic (Worthington and Melander, 2013). This approach is useful to delay the onset of resistance, however, not all β-lactamase enzyme produced by microorganisms are sensitive to the β-lactamase inhibitors. Hence, scientists are working towards producing newer generation of β-lactamase inhibitors such as BLI-489 and LK-157 molecules which have shown good *in vitro* result for the inhibition of the extended-spectrum β-lactamase (ESBL) microorganisms (Worthington and Melander, 2013).

Additionally, as reported by Levasseur et al. (2011), the susceptibility of *P. aeruginosa* towards ceftazidime (cephalosporin group of antibiotics) was reported to increase from 65% (when used alone) to 94% when used in combination with avibactam. It was found that the resistance developed by *P. aeruginosa* against cephalosporin antibiotics is mainly because of the overexpression of the chromosomally encoded AmpC B-lactamase (Lister et al., 2009) and there are reports on the ability of avibactam to overcome the ceftazidime resistance (Mushtaq et al., 2010). The activity of avibactam as a potent inhibitor of AmpC hydrolytic activity may be the main reason behind its effectiveness when in combination with ceftazidime against *P. aeruginosa* (Levasseur et al., 2012).

In order to discover more adjuvants to antibiotics, currently available drugs are screened for their potential as an adjuvant. A number of compounds from other classes of drugs such as antihistamine, anti-inflammatory and antihypertensive were found to have activities against broad spectrums of microorganisms. As reported by Ejim et al. (2011), 69 non-antibiotics were found to potentiate the activity of minocycline against various microorganisms including MRSA and several MDR species such as *P. aeruginosa* (Ejim et al., 2011; Worthington and Melander, 2013).

7.4. Aminoglycosides and derivatives

The first aminoglycoside antibiotic, streptomycin, was discovered in 1943 and its activity covers Gram-negative and Gram-positive bacteria. Each aminoglycosides antibiotic has different activity profiles due to their diversified molecular structure and this class of antibiotics are usually used as the second- or third-line agents in the treatment of infectious diseases including MRSA and MDR-TB. Hence, the development of resistance towards aminoglycoside is considered to be very alarming (Labby and Garneau-Tsodikova, 2013).

The main factor that plays an important role in the development of resistance towards aminoglycoside is related to the activity of aminoglycosides-modifying enzymes (AMEs). As reviewed by Labby and Garneau-Tsodikova (2013), there are five main mechanisms identified to be potentially effective; (1) drug combination and repurposing, (2) regulating the expression of AME, (3) discovery of new aminoglycoside to evade the action of AME, (4) by using AME inhibitor and (5) by using high-throughput methods to access the activity of new aminoglycosides (Labby and Garneau-Tsodikova, 2013).

Hence, research has been directed towards producing newer aminoglycoside and as an example, plazomicin was developed with improved activity against the resistant strains of MDR Gram-negative bacteria and MRSA. This antibiotic is not affected by most of the AMEs commonly produced by the resistant bacteria (Tillotson and Theriault, 2013). Galani et al. (2012) described the evaluation of this agent against 300 MDR isolates consisting of *E. coli, K. pneumonia* and *Enterobacter* sp. from hospitals in Athens, Greece. Most of the isolates showed resistance towards other available aminoglycosides (amikacin, tobramycin, gentamicin) and interestingly, it was found that plazomicin was effective against all isolates of *E. coli, K. pneumonia* and *Enterobacter* sp. with low MIC values (Galani et al., 2012).

7.5. Alternatives to antibiotics

Several researchers are switching their attention to biopharmaceuticals as an alternative to antibiotics, as a newer way of combating antimicrobial resistance. Czaplewski and co-workers have identified 19 approaches that are already under development in the academia and industry, with 10 having a good potential clinical impact, feasibility and safety. Among these agents, seven (antibodies, lysins, vaccines, engineered phages, wildtype phages, probiotics and immune stimulation) are already in clinical trials whereas the remaining three (antimicrobial peptides, host defence peptides and antibiofilm peptides) are in pre-clinical phase. There is no one agent that is already in the market, hence the success of the seven agents in the clinical trials will give a good connotation to the application of antibiotic alternatives as antimicrobial agents (Czaplewski et al., 2016).

The discovery of quorum sensing (QS) as an antibacterial target is one of the approaches that may have a benefit in antimicrobial chemotherapy. By using alternatives such as antibodies as described by Czaplewski et al. (2016), the QS of virulent bacteria can be targeted. QS is a complex regulatory communication system through the release of low-molecular weight molecules by bacteria. Que et al. (2011) hypothesized that by using anti-QS-inhibitors, the infection caused by *P. aeruginosa* and other MDR bacteria can be inhibited. QS may be a potential target for future drug development and the development of resistance may be reduced by targeting such non-essential functions (Que et al., 2011; Tillotson and Theriault, 2013).

Bacteriophages as an antibacterial agent in combating antibiotic resistant microorganism have been considered as a possible step to overcome antibiotic resistance. As an example, Phico Therapeutics is developing a technology, SASPject™, which could be used to target selected bacteria and destroy them rapidly (99.9% of bacteria in 2 min) while leaving the normal flora unharmed. SASPject™ consist of bacteriophages (modified and disabled bacterial viruses) that carries the gene for antibacterial protein. This gene will be injected into the target bacteria and expression of this gene will subsequently cause inactivation of the bacterial DNA (Fairhead, 2009). Currently, there are no known mechanism of possible resistance that could develop following the application of this technology. The application of phage in combination with antibiotic is also of interest as this could reduce the chances of resistance to develop and at the same time provides good antimicrobial activity as compared to either agent used on its own (Tillotson and Theriault, 2013).

Efforts to develop newer antibacterial agents have shifted towards using naturally occurring or synthetic antimicrobial peptides as a model, due to the potential of these group of molecules as effective antibacterial agents. They were shown to have the ability to cause disruption on the bacterial membrane that may cause the complete dissolution of the membrane (Tillotson and Theriault, 2013). As reviewed by Marr et al. (2006), there are several antimicrobial peptides that were shown to be effective and have been used in the clinics, (i.e., the polymyxin B and E and the gramicidin S). These antibiotics are known to be effective against bacterial infections, low resistance was found to develop over the years and is still effective against Gram-negative bacteria. To date, the antimicrobial peptides that were developed and used in the clinics showed a very low rate of resistance as compared to other group of antibiotics (El Shazely et al., 2020). Hence, this gives an indication of their effectiveness and potential, despite some hurdles such as high production cost and toxicity which are commonly associated with these peptides (Marr et al., 2006).

8. Conclusion and future perspectives

The devastating effect of antibiotic resistance is gradually being witnessed through the sharp increase in the number of cases related to resistance in bacteria towards commonly prescribed antibiotics in the clinical settings. Although, antibiotic has been saving countless lives since the 1940s, its effects may not last long with its current non-judicial practice in the clinical, agricultural, animal husbandry and several other sectors that misuse and overuse this drug. Increased use of antibiotics has created a high evolutionary pressure for the emergence of antibiotic resistance for the survival of bacteria. Although this is a natural phenomenon where bacteria evolve to resist the antibacterial activity of the natural antibacterial compounds, recent advancements in the scientific field have deepened our knowledge on existing bacterial resistance mechanisms. Moreover, this information should be used as a guidance in the development of new antibiotics to avoid or bypass potential antibacterial compounds that may trigger existing antibiotic resistance mechanism of bacteria. On the other hand, strict guidelines must be implemented to avoid misuse of antibiotics to limit the potential spread of bacterial resistance in both the hospital and community settings. This is mainly due to the increased volume and speed of intercontinental travel which is responsible for the spread of antibiotic resistant bacteria globally. Therefore, it is imperative that events or actions that may trigger antibiotic resistance should be avoided especially for the drugs of last resort that are currently used in the hospitals to treat severe life-threatening bacterial infections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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