SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Trends in antimicrobial resistance in Malaysia

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ABSTRACT

Introduction: Antibiotic resistance is a burgeoning problem worldwide. The trend of bacterial resistance has increased over the past decade in which more common bacteria are becoming resistant to almost all the antibiotics currently in use, posing a threat to humans and even livestock.

Methods: The databases used to search for the relevant articles for this review include PubMed, Science Direct, and Scopus. The following keywords were used in the search: Antimicrobial resistance, Malaysian action plan, antibiotic-resistant bacteria, and Malaysian National Surveillance on Antimicrobial Resistance (NSAR). The relevant articles published in English were considered.

Results: The antibiotic-resistant bacteria highlighted in this review showed an increase in resistance patterns to the majority of the antibiotics tested. The Malaysian government has come up with an action plan to create public awareness and to educate them regarding the health implications of antibiotic resistance.

Conclusion: Antimicrobial resistance in Malaysia continues to escalate and is attributed to the overuse and misuse of antibiotics in various fields. As this crisis impacts the health of both humans and animals, therefore a joined continuous effort from all sectors is warranted to reduce the spread and minimize its development.

KEYWORDS:
Antimicrobial resistance, Malaysian action plan, antibiotic-resistant bacteria

INTRODUCTION

Antimicrobial resistance arises as microorganisms survive and reproduce when exposed to antimicrobial drugs. Back in 1907, Paul Ehrlich, the father of modern chemotherapy observed that the organism in trypanosome infections sometimes appears to be resistant to the agent used. Due to specific resistance, he observed that fuchsin dye-resistant strain was still susceptible to an arsenic compound, while a strain resistant to the arsenic compound retained sensitivity to the dye. Later in 1908, he proposed that the resistance can be steadily inherited once it is acquired.[1]

This review provides a general overview of the antimicrobial resistance trends of selected clinical isolates in Malaysia which were obtained from various studies, as well as the Malaysian National Surveillance on Antimicrobial Resistance (NSAR) annual reports.

Antibiotic Resistance Trends

The emergence of antibiotic-resistant microorganisms is a serious public health problem.[2] Developed countries have shifted their drugs towards more expensive one due to the lack of potency of the drugs towards common pathogens. Meanwhile, the developing and least developed countries opt for alternative drugs due to financial constraints which has led to the increased morbidity and mortality.[3]

The World Health Organization (WHO) has come up with a surveillance system called the Global Antimicrobial Surveillance System or GLASS. An early release of the data has shown that there was high antibiotic resistance incidence in both high-income and low-income countries with the occurrence of up to 500,000 cases across 22 countries.[4]

A report by World Bank in 2016 on antimicrobial resistance had predicted that financial burden will mostly be felt by low-income and middle-income countries.[5] The antimicrobial resistance rate has increased by two folds in the last 20 years and has killed approximately 700,000 people per year globally. The number is estimated to escalate to 10 million deaths annually by 2050 whereas the financial burden could cost up to US$100 trillion (RM416.65 trillion).[6] This situation highlights the urgency of an action plan to combat the issue comprehensively.

Prevalence of Antibiotic-Resistant Bacteria in Malaysia

Escherichia coli

The urinary tract infections caused by *Escherichia coli (E. coli)* is the most common bacterial infection in patients worldwide[7] and its occurrence is estimated to be up to 88.0%.[8] Malaysia is one of the countries with higher *E. coli* resistance towards aminopenicillin.[9] Data from various public hospitals in Malaysia revealed that the majority of the tested *E. coli* isolates showed the highest resistance rate to penicillins ranging from 68-100% (Table I). This resistance pattern remains for years and in fact, some of the isolates were also resistant to two or more antibiotics (multidrug-resistant).[10] Data also showed that from the year 2004 to 2018, the resistance of *E. coli* to carbapenems remains low within the range of 0-5%, with a steady increment reported over the years.[11-16]

This article was accepted: 11 June 2021
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Additionally, an imipenem-resistant *E. coli* was reported between 2006 and 2009 and were among the first resistant isolates reported in the country.[12] Resistance rates of more than 85% for ciprofloxacin and cefuroxime were also reported between 2017 and 2018.[15] The data presented showed that *E. coli* is resistant to antibiotic groups that have been widely used for the longest time, although some fluctuations were observed which is due to the number of isolates tested in the individual hospitals. Many studies have suggested that the intrinsic resistance and the expression of numerous efflux pumps could be the major contributors to the resistance patterns observed in this organism.

Acinetobacter baumannii

Acinetobacter baumannii (A. baumannii) is an opportunistic pathogen that can easily acquire resistance elements such as plasmids and conjugative transposons.[17] The broad-spectrum carbapenems are the antibiotic of choice for complications associated with *A. baumannii* although the resistance rate has been increasing in the last two decades.

A report by University Malaya Medical Centre (UMMC) between 1996 and 1998 showed a 100% carbapenems-resistant *Acinetobacter baumannii* (CRAB) resistance towards amoxicillin-clavulanate, ampicillin, cefoperazone, and cefuroxime. Additionally, more than 90% resistance was observed for cephalosporins, gentamicin, and ciprofloxacin.[18] Over the years, the resistance rates for penicillins showed a decrement up to 50%.[13,16,19-23]

The resistance rates for cephalosporins do not show substantial change, although in 2018 for the first time in several years, the resistance rate plummeted to 37.9% (Table II). Conversely, the resistance rates to carbapenems and aminoglycosides fluctuated with the highest rates reported between 2017 and 2018. The data also showed an increasing trend of resistance to fluoroquinolones with an average of 93% in the last two years.[16,23]

Klebsiella pneumoniae

Klebsiella sp. are a reservoir for antibiotic-resistant genes and can transfer the gene to other Gram-negative bacteria. Studies on *Klebsiella pneumoniae (K. pneumoniae)* infections and antibiotic resistance in Malaysia are scanty. Between 2010 and 2012, the majority of the *K. pneumoniae* isolates tested were resistant to second and third generations cephalosporins (97-100%).[24,25] As shown in Table III, the ampicillin, amoxicillin-clavulanate acid and aztreonam resistances were high among *K. pneumoniae* species with an average of 94-100%.[25] The trends plunged drastically in 2013 and 2017 [13] with the lowest resistance rates recorded that is possibly due to the significant number of isolates tested as compared to the earlier years. The resistance rate to gentamicin was recorded between 2010 and 2017, with the lowest resistance rate recorded in 2017 (8.5%).[13] Data also revealed a steady increase in the resistance pattern to carbapenems.[13]

Staphylococcus aureus

Staphylococcus aureus (S. aureus) possesses the ability to develop a resistance mechanism to various antibiotics [26] and its resistance towards β-lactams is due to the presence of the mecA gene.[27] One of the earliest reports from Hospital Kuala Lumpur (HKL) recorded all 539 MRSA isolates were resistant to penicillin.[28] The resistance rates remained constant until 2018 with 100% isolates were resistant (Table IV). Likewise, the resistance rates to gentamicin persisted over the years with the highest rates reported between 1990-1991 and 2002-2007.[28,29] Resistance to erythromycin showed a steady declined over the years, while the isolates showed an increase in resistance patterns to clindamycin, from 0% in 2006-2007 to an average of 83% in 2011-2013.[30-32] Until 2018, none of the *S. aureus* isolates is resistant to linezolid or vancomycin.[28-33]

Enterococcus sp.

Enterococcus sp. are part of the normal flora and are natural inhabitants of nature. They are also opportunistic pathogens that can pose serious threats to human life. Treatment for enterococci infections is challenging as they are intrinsically resistant to multidrug and can develop resistance to other classes of antibiotics. From the year 2007 to 2008, *Enterococcus faecium (E. faecium)* isolates showed complete resistance to vancomycin, ampicillin, and teicoplanin.[34] Although ampicillin-resistant *Enterocccus faecalis (E. faecalis)* was also reported, the rates were much lesser than the ones reported in *E. faecium*.[13,35-36]

Despite that 100% vancomycin-resistant *E. faecium* was reported between 2007-2008, the rates fall to 14.1% in 2018. Unlike *E. faecium*, the number of vancomycin-resistant *E. faecalis* isolates were very less, with the highest rate of 6% reported over the years.[13,35-36] The resistance rates for gentamicin and linezolid were reasonably constant over the years for both *E. faecium* and *E. faecalis* isolates.[13,16,34-36] Conversely, the resistance rates of erythromycin and tetracycline among the enterococci isolates were high with an average of 98% (Table V).[36]

The Contributing Factors

According to WHO, misuse and overuse of antimicrobial agents are the main causes of antibiotic resistance.[4] As of 2016, the National Medical Care Survey (NMCS) has gathered data of 27,587 patients from 545 healthcare clinics and 5810 (21.1%) patients that received antibiotic prescriptions through which 197 (3.4%) of them were prescribed with more than one antibiotic.[37]

Another observation revealed that the rate of antibiotic prescriptions in private clinics (30.8%) is higher than in public or government clinics (6.8%). Almost half of the prescribed antibiotics are for acute upper respiratory tract infections (URTI) followed by other diagnoses such as fever and gastroenteritis.

Consumption of foods contaminated with pathogenic *E. coli* may lead to bacterial infections and many studies on *E. coli* are concerned with beef samples. A study isolated 55 *E. coli* strains from ducks in Penang and showed that they are completely resistant to vancomycin and more than 60% are resistant to tetracycline, ampicillin, and streptomycin.[38] Another study reported that out of 40 beef samples taken from two local abattoirs in Selangor contains Enterobacteriaceae (82.5%) and *E. coli* (55%).[39] Although a total of 97 antibiotics have been approved in Malaysia and

Table I: The Prevalence of Antibiotic-Resistant *Escherichia coli* in Malaysia

Year	Type of Antibiotics												Source*
	Ampicillin %	Piperacillin %	Amoxicillin %	Cefuroxime %	Ceftazidime %	Cefepime %	Imipenem %	Meropenem %	Amikacin %	Gentamicin %	Ciprofloxacin %	Trimethoprim-sulfamethoxazole %	
2004	77 (47)	64 (47)	17 (47)			6 (47)	0 (47)		2 (47)	21 (47)	33 (47)		10
2006-2008		48.9 (45)					0 (45)		11.1 (45)	56 (45)	71.1 (45)	97.8 (45)	11
2006-2009	71.7 (1642)			5.6 (1642)	5.6 (1642)		4.9 (1642)		3.8 (1642)	8.4 (1642)	9.7 (1642)		12
2013	68.9 (28720)			22.6 (12974)			0.3 (28696)	0.3 (27759)	0.8 (11924)		23.4 (29400)		13
2014	69.8 (149)						0 (149)	0 (149)	0 (149)				14
2016							0.8 (29312)	0.9 (28602)	1.5 (28139)				13
2017-2018	100 (100)			95 (100)							86 (100)		15
2018				24.5 (31817)				0.7 (30153)			23.0 (31150)		16

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

Table II: The Prevalence of Antibiotic-Resistant *Acinetobacter baumannii* in Malaysia

Year	Type of antibiotics														Source*
	Amoxicillin-Clavulanate %	Ampicillin %	Piperacillin %	Cefoperazone %	Cefuroxime %	Ceftazidime %	Ceftriaxone %	Cefotaxime %	Imipenem %	Ciprofloxacin%	Amikacin %	Gentamicin %	Netilmicin %	Colistin %	
1996-1998	100 (88)	100 (88)		100 (88)	100 (88)	97.7 (88)	97.7 (88)	97.7 (88)	36.4 (88)	90.9 (88)		95.5 (88)			18
2008-2009		92 (100)	60 (100)			59 (100)			55 (100)			48 (100)		0 (100)	20
2009	63 (111)	90 (111)	68 (111)	95 (111)	79 (111)			87 (111)		22 (111)			21 (111)		21
2010-2011						78.4 (162)			79 (162)	79.6 (162)					22
2017		57.1 (7627)		46.8 (5655)		58 (8183)			61.7 (7795)		49.8 (8155)	53.2 (7860)			13
2017-2018						99.06 (102)			100 (102)	95.6 (102)	63.73 (102)	81.11 (102)			23
2018		56.0 (7272)				37.9 (7377)			41.3 (7261)	90.9 (88)	31.5 (7348)	31.5 (7202)			16

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

Table III: The Prevalence of Antibiotic-Resistant *Klebsiella pneumoniae* in Malaysia

Year	Type of antibiotics											Source*
	Ampicillin %	Amoxicillin + clavulanic acid %	Aztreonam %	Cefepime %	Ceftriaxone %	Cefuroxime %	Cefoperazone %	Cefotaxime %	Ceftazidime %	Imipenem %	Gentamicin %	
2010-2012		86.7 (321)									61.5 (321)	24
2010-2012	100 (93)	94.6 (93)	98.9 (93)		100 (93)	100 (93)	100 (93)	100 (93)	97.8 (93)	1.1 (93)	74 (93)	25
2013		18.3 (25916)		15.5 (19158)		25.9 (26127)		27 (21453)	24.2 (24691)	1.5 (24477)		13
2017		20.1 (30470)		16.4 (29798)		25.1 (31104)		22.2 (30840)		1.7 (31143)	8.5 (30801)	13

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

Table IV: The Prevalence of Antibiotic-Resistant *Staphylococcus aureus* in Malaysia

Year	Type of antibiotics												Source*
	Penicillin %	Oxacillin %	Ampicillin %	Cefoxitin %	Amikacin %	Gentamicin %	Erythromycin %	Ciprofloxacin %	Co-Trimoxazole %	Clindamycin %	Linezolid %	Vancomycin %	
1990-1991	100 (539)					92 (539)	98 (539)		94 (539)			0 (539)	28
2002-2007	100 (1979)					92 (1979)	98 (1979)		94 (1979)			0 (1979)	29
2006-2007	100 (32)	100 (32)	100 (32)	100 (32)	78.1 (32)	78.1 (32)				0 (32)	0 (32)	0 (32)	30
2011-2012	100 (175)	100 (175)				88 (175)	93.7 (175)			88 (175)	0 (175)	0 (175)	31
2013	100 (66)	87.9 (66)				59.1 (66)	87.9 (66)	83.3 (66)		78.8 (66)		0 (66)	32
2018	100 (36)	100 (36)				88.8 (36)	33.3 (36)					0 (36)	33

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

Table V: The Prevalence of Antibiotic-Resistant Enterococci in Malaysia

Year	Type of antibiotics								Source*
	Ampicillin %	Vancomycin %	Teicoplanin %	Gentamicin %	Linezolid %	Tazobactam-piperacillin %	Erythromycin %	Tetracycline %	
					Enterococcus faecium				
2007-2008	100 (3)	100 (3)	100 (3)	50 (3)	0 (3)				34
2009-2010	92.9 (28)	0 (28)	0 (28)	82.1 (28)		96.4 (28)			35
2013	84 (25)			84 (25)	0 (25)		100 (25)	100 (25)	36
2013	83.3 (653)	8.4 (667)		43 (393)	1.1 (540)				13
2017	87.5 (1050)	15.6 (1033)		42.7 (655)	1.5 (876)				13
2018	89.8 (996)	14.1 (1037)		43.5 (614)	1.0 (878)				16
					Enterococcus faecalis				
2009-2010	3.2 (31)	0 (31)	0 (31)	38.7 (31)		3.2 (31)			35
2009-2010	24 (50)	6 (50)		48 (50)	0 (50)		96 (50)	98 (50)	36
2013	5.5 (1356)	1.4 (1359)		19.4 (806)	4.7 (1029)				13
2017	6 (2374)	1.3 (2313)		23.7 (1513)	2.2 (1905)				13

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

registered with the Ministry of Health for food and animal practice, the majority of these antibiotics are not advisable for veterinary purposes by WHO. It was suggested that the growth of promoter agents that are not used for human therapeutic reasons should be used in livestock farming instead of antibiotics used in human therapy.

Malaysian Action Plan on Antimicrobial Resistance

The Malaysian government has revised several strategies to curb the spread of fatal diseases and minimize the threat of antimicrobial resistance. The action plan on antimicrobial resistance (MyAP-AMR) is structured based on four key areas: (1) public awareness and education, (2) surveillance and research, (3) infection prevention and control, and (4) appropriate use of antimicrobials.

Significant measures have been developed to slow down the emergence of antimicrobial resistance and to avert its spread. This includes increasing public awareness and understanding regarding antimicrobial resistance, particularly among healthcare workers, those under nursing care, in food and livestock production, and aquaculture. It is important to comprehend the emergence of antimicrobial resistance through surveillance, monitoring and research thus, providing information on antimicrobial issues and the proposed risk of antimicrobial resistance. The government is also focused on infection prevention and control through enforcement of appropriate antimicrobial uses to reduce antibiotic-resistant bacteria.[40]

Research findings have suggested that more educational campaigns need to be organized to improve public awareness and promote the rational use of antibiotics as many Malaysians were found to have inadequate knowledge and attitudes concerning both antibiotic use and antibiotic resistance. Aside from that, antimicrobial stewardship and infection control programs have been designed to optimize the appropriate use of antimicrobials by ensuring that every patient receives an antibiotic only when one is needed, with the right dose and within the exact duration. This is to optimize clinical outcomes and minimize unintended consequences of antimicrobial use.

CONCLUSION

Antimicrobial resistance is a serious threat to human health and this review has revealed the trends of antibiotic resistance in Malaysia over the years. Major drivers of antimicrobial resistance include inappropriate uses of antibiotics in healthcare practices as well as in animal production. A continuous effort from the related agencies to combat antimicrobial resistance in every aspect is essential to prevent bacteria from becoming resistant, henceforth causing severe impacts on human health and the future economy.

FUNDING

None to declare.

CONFLICTS OF INTEREST

None to declare.

ETHICAL APPROVAL

This review article does not contain any studies related to human participants or animals performed by any of the authors.

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