Antibiotic resistance of ESKAPE bacteria in acute pharyngitis patients from private clinics in central Malaysia

Christina Shook Cheng Chong^a, Zhuang Mian Bo^a, Wei Keat Tan^a, Seshatharran Parmasivam^a, Shu Ting Pang^a, Benedict Lim Heng Sim^b, Christopher Kwong Chong Lee^b, Renee Lay Hong Lim^a, Crystale Siew Ying Lim^{a*}

^aDepartment of Biotechnology, Faculty of Applied Sciences, UCSI University, No. 1, Jalan Menara Gading, UCSI Heights, Taman Connaught, 56000 Cheras, Kuala Lumpur, Malaysia

^bDepartment of Medicine, Hospital Sungai Buloh, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia

Received 4th November 2019 / Accepted 8th June 2020

Abstract. Worldwide, the ESKAPE group of pathogens - *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species - are emerging as important pathogens which have acquired resistance towards different classes of antibiotics. Malaysia has also reported high levels of antibiotic resistance among these pathogens, based on prevalence data from hospital patients. However, the prevalence and antibiotic resistance rates of ESKAPE group members in the community are largely unknown. Therefore, this study focuses on acute pharyngitis (AP) patients from private primary care clinics in the Klang Valley, central Malaysia, as AP is the most common infection-associated reason for contact with private primary healthcare providers. Out of 205 patients, 119 were found to harbor ESKAPE group bacteria, where a total of 175 isolates were subjected to antibiotic susceptibility testing. Our results show that the most prevalent ESKAPE group member in this cohort is *S. aureus*, with one isolate found to be multidrug-resistant towards penicillin V, cefoxitin, erythromycin and azithromycin. We also report the first finding of community acquired resistance to cefotaxime in *K. pneumoniae*, imipenem in *Enterobacter* spp. and tetracycline, also in *Enterobacter* spp., in Malaysia, which were not derived from samples from a hospital setting. In conclusion, this study, which describes antibiotic resistance of community acquired ESKAPE pathogens in the Malaysian private primary healthcare setting highlights the need for a comprehensive centralized reporting system for community acquired antibiotic resistance to complement the Malaysian National Surveillance of Antibiotic Resistance.

Keywords: Acute pharyngitis, antibiotic resistance, community acquired, ESKAPE, private primary healthcare

INTRODUCTION

Antibiotic resistance has been recognized as a global healthcare crisis resulting in 700,000 deaths annually and it has been estimated that antibiotic resistant infections will cause 10 million annual deaths by 2050 (United Nation, 2019; World Health Organization, 2019). Previous studies have

shown that the inappropriate use of antibiotics is highly correlated to the emergence of antibiotic resistance, where even multidrug-resistant bacterial infections have been reported (Karam *et al.*, 2016; Aslam *et al.*, 2018).

*Author for correspondence: Crystale Siew Ying Lim, Department of Biotechnology, Faculty of Applied Sciences, UCSI University, No. 1, Jalan Menara Gading, UCSI Heights, Taman Connaught, 56000 Cheras, Kuala Lumpur, Malaysia. Email – crystalelim@ucsiuniversity.edu.my

The World Health Organization (WHO) published the first global priority pathogens list (Global PPL) of antibiotic-resistant bacteria to help in prioritizing the research and development of new and effective antibiotic treatments (WHO, 2017). The ESKAPE group of bacteria, defined by the Infectious Diseases Society of America as comprising of the members *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp., features prominently in the Global PPL due to the high prevalence of multidrug resistance (WHO, 2017). ESKAPE infections are also the leading cause of nosocomial infections, which in turn result in greater healthcare costs and high risk of mortality (Santajit and Indrawattana, 2016; Founou *et al.*, 2017; Mulani *et al.*, 2019).

In Malaysia, the National Surveillance of Antibiotic Resistance (NSAR) report provides annual surveillance data on the antibiotic resistance of bacteria that are isolated from clinical samples of patients from hospital settings, including 37 government hospitals and 2 university hospitals throughout Malaysia (Ministry of Health Malaysia, 2019). In the latest NSAR report, the trend of antibiotic resistance prevalence amongst the ESKAPE pathogens has slightly decreased compared to 2017 (Ministry of Health Malaysia, 2019).

However, as the NSAR reports do not specify whether bacterial isolates are hospital-acquired or community-acquired (McNeil *et al.*, 2016), currently there is no distinct data on the prevalence and antibiotic resistance of ESKAPE group members among the general community in Malaysia, especially patients who receive medical care from private primary healthcare providers for infectious diseases. The National Medical Care Statistics (NMCS) reported that upper respiratory tract infections, the most common of which is acute pharyngitis (AP), are the most prevalent diagnosis managed in private clinics (Sivasampu *et al.*, 2014). However, AP was also found to be the affliction with one of the highest rates of inappropriate antibiotic prescription (Ab Rahman *et al.*, 2016). Therefore, this study is aimed at investigating the prevalence of ESKAPE group members and their antibiotic resistance profiles in a cohort of acute pharyngitis (AP) patients from

private clinics in the Klang Valley area of central Malaysia.

MATERIALS AND METHOD

Ethics approval and consent to participate

Informed consent was obtained from all acute pharyngitis patients and private primary healthcare providers (general practitioners - GPs) at private clinics and formal approval for the study was granted by the Medical Research and Ethics Committee of Malaysia (reference number KKM/NIHSEC/P15-847), with the National Medical Research Register (NMRR) Approval No. NMRR-15-928-25596. Throat swabs were obtained by GPs via convenience sampling from patients exhibiting symptoms of sore throat between 3rd January 2016 to 30th November 2016.

Bacterial clinical isolates

Throat swabs were subjected to bacterial cultures and isolates were identified via Matrix-Assisted Laser Desorption/Ionization-Time Of Flight (MALDI-TOF) mass spectrometry (MS).

Antibiotic susceptibility testing

All bacterial clinical isolates were subjected to antibiotic susceptibility testing (AST) using Kirby-Bauer disc diffusion protocols according to specifications in the Clinical and Laboratory Standards Institute guidelines (CLSI, 2018). The ATCC strains *S. aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) were used as the reference strains for the antibiotic susceptibility tests in this study. Briefly, 3 to 5 single colonies of each isolate were selected from LB agar streak plates (Merck, Germany) after overnight incubation at 37°C and transferred to 2 ml of 0.9% saline solution. For inoculum density standardization to yield bacteria suspensions equivalent to approximately 1.5×10^8 CFU/ml of *E. coli* ATCC 25922 for disc diffusion assays, the turbidity of the suspensions of bacterial isolates was adjusted to be equivalent to 0.5 McFarland. The antibiotics used in this study were based on common antibiotics used for upper respiratory tract infections (Teng *et al.*, 2011), antimicrobial therapy list recommended for bacterial

pharyngitis in Malaysian National Antibiotic Guideline (NAG) 2019 (Ministry of Health, 2019) and recommended antibiotics used against ESKAPE for disc diffusion test (CLSI, 2018). The antibiotics used in this study were azithromycin (15 µg), penicillin V (10 U) and erythromycin (15 µg) (Kotra Pharma, Malaysia); cefepime (30 µg), cefotaxime (30 µg), ceftazidime (30 µg), ceftriaxone (30 µg), imipenem (10 µg), meropenem (10 µg) ciprofloxacin (5 µg), levofloxacin (5 µg), chloramphenicol (30 µg) and tetracycline (30 µg) (all from Oxoid, UK). All antibiotic susceptibility tests were carried out in duplicates using Mueller Hinton agar (Oxoid, UK) at 37°C.

Data analysis

The frequency and antibiotic resistance patterns of bacterial clinical isolates were analyzed using descriptive statistics and reported as counts.

RESULTS

ESKAPE group bacteria were detected in the throat swabs of 119 (58.0%) out of a total of 205 patients with acute pharyngitis. Figure 1 shows the distribution of ESKAPE group bacteria among the 119 patients, where *S. aureus* is the most prevalent ESKAPE group member found in this cohort. No *Enterococcus faecium* was found. More than one ESKAPE group member was identified in 19 patients.

Within these 119 patients, 175 isolates of ESKAPE group bacteria were identified, where 89 isolates are *S. aureus* (50.9%), 49 are *K. pneumoniae* (28%), 24 are *Enterobacter* spp (13.7%), 7 are *A. baumannii* (4%) and 6 are *P. aeruginosa* (3.4%). The antibiotic susceptibility test (AST) results of all these isolates are summarized in Table 1.

Figure 1. Number of patients with ESKAPE isolates found in their throat swabs.

Table 1. Antibiotic susceptibility patterns of ESKAPE pathogens.

Antibiotics	Bacteria antibiotic susceptibility, n (%)														
	<i>S. aureus</i> (n=89)			<i>K. pneumoniae</i> (n=49)			<i>A. baumannii</i> (n=7)			<i>P. aeruginosa</i> (n=6)			<i>Enterobacter</i> spp (n=24)		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Penicillins (Cell wall synthesis inhibitors)															
Penicillin V	37(41.6)	NA	52(58.4)	-	-	-	-	-	-	-	-	-	-	-	-
Cephalosporins (Cell wall synthesis inhibitors)															
Cefepime	-	-	-	49(100)	0(0)	0(0)	7(100)	0(0)	0(0)	6(100)	0(0)	0(0)	-	-	-
Cefotaxime	-	-	-	42(85.7)	6(12.2)	1(2.0)	1(14.3)	5(71.4)	1(14.3)	-	-	-	23(95.8)	1(4.2)	0(0)
Cefoxitin	84(94.4)	NA	5(5.6)	-	-	-	-	-	-	-	-	-	-	-	-
Ceftriaxone	-	-	-	49(100)	0(0)	0(0)	1(14.3)	6(85.7)	0(0)	-	-	-	24(100)	0(0)	0(0)
Carbapenems (Cell wall synthesis inhibitors)															
Imipenem	-	-	-	-	-	-	7(100)	0(0)	0(0)	6(100)	0(0)	0(0)	9(37.5)	14(58.3)	1(4.2)
Meropenem	-	-	-	-	-	-	7(100)	0(0)	0(0)	6(100)	0(0)	0(0)	24(100)	0(0)	0(0)
Macrolides (Protein synthesis inhibitors)															
Azithromycin	84(94.4)	0(0)	5(5.6)	49(100)	0(0)	0(0)	-	-	-	-	-	-	-	-	-
Erythromycin	84(94.4)	0(0)	5(5.6)	-	-	-	-	-	-	-	-	-	-	-	-
Fluoroquinolones (DNA synthesis inhibitors)															
Ciprofloxacin	-	-	-	-	-	-	7(100)	0(0)	0(0)	-	-	-	-	-	-
Levofloxacin	85(95.5)	3(3.4)	1(1.1)	-	-	-	7(100)	0(0)	0(0)	6(100)	0(0)	0(0)	24(100)	0(0)	0(0)
Phenicols (Protein synthesis inhibitors)															
Chloramphenicol	-	-	-	49(100)	0(0)	0(0)	-	-	-	-	-	-	-	-	-
Tetracyclines (Protein synthesis inhibitors)															
Tetracycline	68(76.4)	4(4.5)	17(19.1)	-	-	-	7 (100)	0(0)	0(0)	-	-	-	23(95.8)	0(0)	1(4.2)

Note. S: Susceptible; I: Intermediate; R: Resistant; NA: Not available in CLSI guidelines; -: Antibiotics not tested in this study.

Five out of 89 *S. aureus* isolates were identified as methicillin-resistant *S. aureus* (MRSA) as they are resistant to cefoxitin, where all were also found to be resistant to another beta-lactam antibiotic, penicillin V. Notably, one MRSA isolate (#206-5) was identified as multidrug-resistant not only to cefoxitin but also to penicillin V, azithromycin and erythromycin. Overall, isolates of *S. aureus* exhibited the highest antibiotic resistance to penicillin V (58.4%, n=52/89), followed by tetracycline (19.1%, n=17/89). Among the 82 isolates of methicillin-susceptible *S. aureus* (MSSA), only 5% (n=4/82) were found to be erythromycin-resistant.

One isolate each of *K. pneumoniae* (#009-5) and *A. baumannii* (#192-2) was found to be resistant to the 3rd generation cephalosporin cefotaxime, where the former is the first reported in Malaysia for community acquired *K. pneumoniae* from non-hospital settings. In addition, intermediate resistance to cefotaxime was observed for six out of 49 *K. pneumoniae* isolates. All *K. pneumoniae* isolates were found to be susceptible to other members of the cephalosporin family tested in this study (3rd generation cephalosporin ceftriaxone and 4th generation cefepime). On the other hand, the majority of the *A. baumannii* isolates in this study exhibited intermediate

resistance to ceftriaxone (n=6/7) and cefotaxime (n=5/7).

None of the six identified *P. aeruginosa* isolates were found to be resistant or intermediately resistant to any of the tested antibiotics in this study. However, a total of two *Enterobacter* spp. isolates were found to exhibited resistance to imipenem (#224-1) while another is resistant to tetracycline (#103-3), a first for *Enterobacter* spp. in the Malaysian community.

Patients found with non-susceptible ESKAPE group bacteria are listed in Table 2. The multidrug-resistant MRSA in this study was isolated from patient #206. Four acute pharyngitis patients in this cohort were found to harbor more than one ESKAPE group members with antibiotic non-susceptibility: #103 (*Enterobacter* spp. – tetracycline resistant and imipenem intermediate; *A. baumannii* – cefotaxime and ceftriaxone intermediate), #120 (*Enterobacter* spp. – cefotaxime and imipenem intermediate; *A. baumannii* – cefotaxime and ceftriaxone intermediate) and #127 (*K. pneumoniae* – cefotaxime intermediate; *Enterobacter* spp. – imipenem intermediate) and #234 (*S. aureus* – penicillin V, azithromycin and erythromycin resistant; *K. pneumoniae* – cefotaxime intermediate).

Table 2. Non-susceptible ESKAPE group bacteria found in throat swabs from acute pharyngitis patients.

Bacteria species	Antibiotics (R/I)	Number of patients	Patient identifier number
<i>S. aureus</i>	Penicillin V (R)	39	005, 008, 024, 089, 099, 100, 107, 119, 125, 151, 159, 170, 171, 173, 178, 181, 186, 188, 189, 191, 199, 206, 214, 217, 222, 226, 230, 232, 233, 234, 237, 258, 260, 263, 266, 270, 501, 502, 508
	Cefoxitin (R)	5	024, 181, 186, 206, 501
	Azithromycin (R)	4	170, 206, 226, 234
	Erythromycin (R)	4	170, 206, 226, 234
	Levofloxacin (R)	1	100
	Levofloxacin (I)	3	087, 107, 151
	Tetracycline (R)	11	005, 008, 087, 089, 107, 171, 173, 188, 214, 263, 508
	Tetracycline (I)	4	088, 177, 206, 260
<i>K. pneumoniae</i>	Cefotaxime (R)	1	009
	Cefotaxime (I)	6	127, 234, 238, 239, 250, 280
	Cefotaxime (R)	1	192
<i>A. baumannii</i>	Cefotaxime (I)	5	015, 103, 120, 138, 277
	Ceftriaxone (I)	6	015, 103, 120, 138, 192, 277
	Imipenem (R)	1	224
<i>Enterobacter</i> spp.	Tetracycline (R)	1	103
	Cefotaxime (I)	1	120
	Imipenem (I)	11	025, 061, 092, 098, 103, 120, 127, 162, 167, 202, 275

Note. R = resistant; I = intermediate

DISCUSSION

We report the prevalence and antibiotic resistance profiles of ESKAPE pathogens from throat swabs of a cohort of community-based acute pharyngitis patients in private clinics in the Klang Valley area of central Malaysia, where *S. aureus* is the predominant ESKAPE group member found in this cohort. In terms of antibiotic resistance, 58.4% of all ESKAPE isolates are resistant towards penicillin V. Beta-lactams are the most widely-used antibiotic to treat bacterial infections, where penicillins are among the most common beta-lactams prescribed for upper respiratory tract infections (URTIs) by both public and private primary care providers (Teng *et al.*, 2011; Pandey and Cascella, 2019). Generally, the prevalence of methicillin-resistant *S. aureus* (MRSA) among the *S. aureus* isolates in the present study (5.6%, n=5/89) is still lower than the 19.4% reported in the latest NSAR report (Ministry of Health, 2019) and the 9% reported by Sit *et al.* (2018). Nonetheless, we present the first report of MRSA isolated from community-based throat swabs.

Klebsiella pneumoniae ranks high as a cause of community-acquired pneumonia (CAP) in hospitalized patients in Malaysia (Loh *et al.*, 2007). Although the prevalence of antibiotic resistance among *K. pneumoniae* isolates in this cohort in the present study is very low (only 2%, n=1/49), this sole isolate (#009-5) is resistant to the 3rd generation cephalosporin, cefotaxime, and is thus also a putative extended spectrum β -lactamases (ESBL) producer. Similarly, one *A. baumannii* isolate (#192-2) resistant to the 3rd generation cephalosporin cefotaxime was also found in this study. The national resistance rates for *A. baumannii* to cefotaxime was ~70% between 2009-2014, with a dearth of data thereafter (Mohd. Rani *et al.*, 2017; Asif *et al.*, 2018). *Acinetobacter baumannii*, which was once considered a low-category pathogen, has now emerged as a stubborn infectious agent and the existence of antibiotic resistance in isolates of this species as well as *K. pneumoniae* in the community, is a cause for concern.

Carbapenem resistance is defined in this study as resistance to at least one of the carbapenem members of this antibiotic class. Although only one out of 24 (4.2%) *Enterobacter* spp. was found

to be imipenem-resistant, 14 more isolates (58.3%) were determined to be carbapenem-intermediate due to intermediate resistance to imipenem. Interestingly, the prevalence of carbapenem-resistant *Enterobacter* spp. in this community-based cohort is higher than the 1.3% and 1% of imipenem and meropenem resistance, respectively, as reported by NSAR 2014 for *Enterobacter cloacae* in hospital-based settings (Ministry of Health Malaysia, 2015). On the other hand, no carbapenem-resistant *P. aeruginosa* was found in the present study, although generally, in hospital acquired *P. aeruginosa*, the resistance rates to imipenem and meropenem are about 10% and 7%, respectively (Fazlul *et al.*, 2011; Ministry of Health, 2019).

Comparisons between hospital- and community-acquired ESKAPE group members NSAR reports is challenging as there is no differentiation of isolates between those from hospital-acquired or community-acquired infections (or colonizations). NSAR reports prior to 2015 also do not state the source of the bacterial isolates (e.g. blood, pus, swabs or other clinical samples). It is possible that the prevalence of antibiotic resistance in the general community is much higher than current estimates in literature. A study by Ejike *et al.* (2018) found that 44 out of 50 (88%) healthy Malaysian young adults harbored bacteria that were resistant to at least one antibiotic tested from a set of antibiotics commonly prescribed by primary care providers for patients with sore throat, although none of the resistant bacteria were ESKAPE group members. Thus, we recommend that NSAR should be improved to reflect these important points for better management of antibiotic resistance not only in hospitals but also in the community.

CONCLUSION

In conclusion, this study reports the antibiotic resistance profiles of community acquired ESKAPE group bacteria among a cohort of acute pharyngitis patients in the Malaysian private primary healthcare setting. Our results highlight the need for a more comprehensive centralized reporting system for community acquired

antibiotic resistance to complement the current Malaysian NSAR.

ACKNOWLEDGEMENTS

This study was funded by the Kotra Pharma Educational Grant (Proj-In-KOTRA-FAS-001), Kotra Pharma (M) Sdn Bhd, Vertical Business Suite, Unit 35-01, Level 35, Tower A, Avenue 3, Bangsar South, 8, Jalan Kerinchi, Bangsar South, 59200 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur. The authors thank all GPs and patients who were involved in this study.

REFERENCES

- Ab Rahman, N., Teng, C. L., & Sivasampu, S. 2016. Antibiotic prescribing in public and private practice: a cross-sectional study in primary care clinics in Malaysia. *BMC Infectious Diseases* 16(1): 208.
- Asif, M., Alvi, I. A., & Rehman, S. U. 2018. Insight into *Acinetobacter baumannii*: pathogenesis, global resistance, mechanisms of resistance, treatment options, and alternative modalities. *Infection and Drug Resistance* 11: 1249.
- Aslam, B., Wang, W., Arshad, M. I., Khurshid, M., Muzammil, S., Rasool, M. H., Nisar, M. A., Alvi, R. F., Aslam, M. A., Qamar, M. U., & Salamat, M. K. F. 2018. Antibiotic resistance: a rundown of a global crisis. *Infection and Drug Resistance* 11: 1645.
- CLSI, Performance Standards for Antimicrobial Susceptibility Testing, 28th ed. CLSI Supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute, 2018.
- Ejike, U. C., Bo, Z. M., Lim, C. S. Y., & Lim, R. L. H. 2018. Antibiotics resistance of commensal throat bacteria from healthy subjects. *Malaysian Journal of Biochemistry and Molecular Biology* 21(1): 1-8.
- Fazlul, M. K. K., Zaini, M. Z., Rashid, M. A., & Nazmul, M. H. M. 2011. Antibiotic susceptibility profiles of clinical isolates of *Pseudomonas aeruginosa* from Selayang Hospital, Malaysia. *Biomed Research* 22(3): 263.
- Founou, R. C., Founou, L. L., & Essack, S. Y. 2017. Clinical and economic impact of antibiotic resistance in developing countries: a systematic review and meta-analysis. *PloS ONE* 12(12).
- Karam, G., Chastre, J., Wilcox, M. H., & Vincent, J. L. 2016. Antibiotic strategies in the era of multidrug resistance. *Critical Care* 20(1): 136.
- Loh, L. C., Chin, H. K., Chong, Y. Y., Jeyaratnam, A., Raman, S., Vijayasingham, P., Thayaparan, T., & Kumar, S. 2007. *Klebsiella pneumoniae* respiratory isolates from 2000 to 2004 in a Malaysian hospital: characteristics and relation to hospital antibiotics consumption. *Singapore Medical Journal* 48(9): 813-8.
- McNeil, H. C., Lean, S. S., Lim, V., & Clarke, S. C. 2016. The state of ESKAPE in Malaysia. *International Journal of Antimicrobial Agents*: 1-4.
- Ministry of Health Malaysia. 2015. *National Antibiotic Resistance Surveillance Report 2014*. Available at: https://www.imr.gov.my/images/uploads/NSAR/NSAR_2014/Summary_of_Antibiotic_Resistance_2014_report.pdf
- Ministry of Health Malaysia. 2019. *National Antimicrobial Guideline 2019*. Available at: https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/national-antimicrobial-guideline-2019-full-version-3rd-edition_0.pdf
- Ministry of Health Malaysia. 2019. *National Antibiotic Resistance Surveillance Report 2018*. Available at: <https://www.imr.gov.my/images/uploads/NSAR/2018/260619-NATIONAL-ANTIBIOTIC-RESISTANCE-SURVEILLANCE-REPORT-2018-1.pdf>
- Mulani, M. S., Kamble, E. E., Kumkar, S. N., Tawre, M. S., & Pardesi, K. R. 2019. Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review. *Frontiers in Microbiology*: 10.
- Pandey, N., & Cascella, M., 2019. Beta Lactam Antibiotics. In StatPearls [Internet]. StatPearls Publishing.
- Rani, F. M., Rahman, N. I. A., Ismail, S., Alattraqchi, A. G., Cleary, D. W., Clarke, S. C., & Yeo, C. C. 2017. *Acinetobacter* spp. infections in Malaysia: a review of antimicrobial resistance trends, mechanisms and epidemiology. *Frontiers in Microbiology*: 8.
- Santajit, S., & Indrawattana, N. 2016. Mechanisms of antimicrobial resistance in ESKAPE pathogens. *BioMed Research International*, 2016.
- Sivasampu S., Wahab Y.F., Ong S.M., Ismail S.A., Goh P.P., Jeyandran S., 2014. *National Healthcare Statistics Initiative: National Medical Care Statistics Primary Care 2014*. Available at: http://www.crc.gov.my/nhsi/wp-content/uploads/publications/nmcs2014/NMCS_2014_fullreport.pdf
- Sit, P. S., Teh, C. S. J., Idris, N., & Ponnampalavanar, S. 2018. Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia: Correlations between clinical, phenotypic, genotypic characteristics and mortality in a tertiary teaching hospital in Malaysia. *Infection, Genetics and Evolution* 59: 132-141.
- Teng, C. L., Tong, S. F., Khoo, E. M., Lee, V., Zailinawati, A. H., Mimi, O., Chen, W. S., & Nordin, S., 2011. Antibiotics for URTI and UTI prescribing in Malaysian primary care settings. *Australian Family Physician* 40(5): 325-329.
- United Nation. 2019. UN, global health agencies sound alarm on drug-resistant infections; new recommendations to reduce 'staggering number' of future deaths. Available at: <https://news.un.org/en/story/2019/04/1037471>
- World Health Organization. 2017. *WHO publishes list of bacteria for which new antibiotics are urgently needed*. Available at: <https://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>
- World Health Organization. 2019. *New report calls for urgent action to avert antimicrobial resistance crisis*. Available at: <https://www.who.int/news-room/detail/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis>