Copyright is owned by the Author of the thesis. Permission is given for a copy to be downloaded by an individual for the purpose of research and private study only. The thesis may not be reproduced elsewhere without the permission of the Author.

Epidemiology of antimicrobial resistance in patients presenting at 3 sentinel surveillance hospitals in Chiang Mai province, Thailand, April 2017 – January 2018

A thesis presented in partial fulfilment of
the requirements for the degree of
Master of Public Health at Massey University

Jessada Thanakitjaroenkul

School of Health Sciences, Collage of Health,
Massey University, Palmerston North, New Zealand

December 2022

Contents

Page

1. Abbreviations iv
2. List of Tables vi
3. List of Figures viii
4. Abstract 1
5. Acknowledgements 2
6. Chapter I: Introduction and literature review 3
    6.1 Introduction 3
        6.1.1 Global situation on antimicrobial resistance (AMR) 3
        6.1.2 Antibiotic use related to AMR 6
        6.1.3 The impacts of AMR 8
        6.1.4 Global and Thai action plans on AMR 9
        6.1.5 National surveillance system on AMR in Thailand 11
    6.2 Literature review 13
        6.2.1 Antimicrobial resistance and sepsis 13
        6.2.2 Risk factors for getting infection with AMR bacteria 13
    6.3 Objectives 15
7. Chapter II: Methodology 16
    7.1 Methods 16
        7.1.1 Ethical considerations 16
        7.1.2 Study population 16
        7.1.3 Data source 18
        7.1.4 Data management and analysis 20
    7.2 Study I: Descriptive epidemiology of sepsis patients infected with AMR bacteria in 3 sentinel surveillance hospitals in Chiang Mai, Thailand, April 2017 – January 2018. 21
        7.2.1 Case definition 21
        7.2.2 Data extraction 22
        7.2.3 Data analysis 22
    7.3 Study II: Cross-sectional analytic study of risk factors for infection with an AMR-bacteria and death among patients infected with the eight selected bacterial pathogens in Chomthong hospital, Chiang Mai, Thailand, April – October 2017 23
        7.3.1 Case definition 23

7.3.2 Data extraction 23
7.3.3 Data analysis 23
8. Chapter III: Results 25
8.1 Study I: Descriptive epidemiology of sepsis patients infected with AMR bacteria in 3 sentinel surveillance hospitals in Chiang Mai, Thailand, April 2017 – January 2018 25
8.2 Study II: Cross-sectional analytic study of risk factors for infection with an AMR bacteria and death among infected patients with the eight selected pathogens in Chomthong hospital, Chiang Mai, Thailand, April – October 2017. 33
8.2.1 Analysis of epidemiological characteristics of patients infected with the eight selected pathogens 33
8.2.2 Analysis of risk factors associated with AMR infection 41
8.2.3 Analysis of risk factors associated with death 44
9. Chapter IV: Discussion and conclusions 47
9.1 Discussion 47
9.2 Limitations 51
9.3 Recommendations 51
9.4 Conclusions 52
10. Appendix 54
10.1 Figures and tables related to analysis of Study I 54
10.2 Figures related to analysis of Study II 61
11. References 63

1. Abbreviations

ABR	Antibacterial resistance or antibiotic resistance
AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility testing
BoE	Bureau of Epidemiology
BSI	Bloodstream infection
CDC	Centers for Disease Control and Prevention
CFR	Case fatality rate
CI	Confidence interval
CIA	Critically important antimicrobial
CLSI	Clinical and Laboratory Standards Institute
CRE	Carbapenem-resistant Enterobactericeae
DDC	Department of Disease Control
DMSc	Department of Medical Sciences
ECDC	European Centre for Disease Prevention and Control
ESBL	Extended-spectrum β-lactamase
FIO_2	Fraction of inspired oxygen
GDP	Gross domestic product
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	Hospital-acquired infection
HCUP-NIS	the National (Nationwide) Inpatient Sample – Healthcare Cost and Utilization Project
ICU	Intensive care unit
IHR	International Health Regulations
IPD	Inpatient department
IQR	Interquartile range
JEE	Joint External Evaluation
LR	Likelihood ratio

MAP	Mean arterial pressure
MDR	Multidrug-resistance
MIDAS	Medical Information Data Analysis System
MoPH	Ministry of Public Health
NAMCS	National Ambulatory Medical Care Survey
NARST	National Antimicrobial Resistance Surveillance Center, Thailand
OPD	Outpatient department
OR	Odds ratio
PaO_2	Partial pressure of oxygen
r^2	Coefficient of determination
ROC	Receiver operating characteristic
SD	Standard deviation
SMART	Study for Monitoring Antimicrobial Resistance Trends
SOFA	Sequential Organ Failure Assessment
URI	Upper respiratory tract infection
UTI	Urinary tract infection
WHO	World Health Organization

2. List of Tables

Table 1. Examples of antibiotic resistant mechanisms for specific microorganisms. 8

Table 2. Priority specimens and pathogens for AMR surveillance by GLASS adapted from (WHO, 2015b). 9

Table 3.List of selected pathogens and antibiotic resistance under the AMR surveillance system in Thailand. 12

Table 4. The number of patients reported to BoE from the 3 sentinel hospitals from April 2017 – January 2018. 18

Table 5. Details of variables from the dataset of AMR surveillance in Chiang Mai.................... 19

Table 6 Sequential Organ Failure Assessment (SOFA) score adapted from Vincent et al. (1996). 21

Table 7. Demographic characteristics of sepsis patients infected with a pathogen with AMR in 3 sentinel hospitals in Chiang Mai, April 2017 – January 2018... 26

Table 8. Hospitalisation data of sepsis patients infected with a pathogen with AMR in 3 sentinel hospitals in Chiang Mai, April 2017 – January 2018. 28

Table 9. Demographic data of patients infected with the eight selected pathogens* in Chomthong hospital, Chiang Mai, April – October 2017 (n=455)... 34

Table 10. Hospitalisation data of patients infected with the eight selected pathogens* in Chomthong hospital, Chiang Mai, April – October 2017 (n=455)... 36

Table 11. Resistance prevalence to antibiotic agents of the eight selected pathogens in Chomthong hospital from all specimen types reported to BoE, April – October 2019................ 38

Table 12. Resistance prevalence to antibiotic classes and MDR of the eight selected pathogens in Chomthong hospital from all specimen type reported to BoE, April – October 2019. 40

Table 13. Univariate analysis showing the association between AMR status and potential risk factors.. 42

Table 14. Comparison of logistic regression models which AMR status as the outcome............ 43

Table 15. Multivariate analysis showing the association between AMR status and potential risk factors.. 44

Table 16.Univariate analysis showing the association between dead status and potential risk factors.. 45

Table 17.Comparison of logistic regression models for factors associated with dead status of patients. 46

Table 18. Multivariate analysis showing the association between dead status and potential risk factors. 46

Table 19. Mid-year population classified by age group in each district in Chiang Mai, 2017..... 56

Table 20. Age-adjusted morbidity rates of AMR by district in Chiang Mai, April 2017 – January 2018.......... 60

3. List of Figures

Figure 1. Number of deaths attributable to AMR infections per year by 2050 (O'Neill, 2014). ... 3

Figure 2. Percentage of E. coli isolates resistant to third-generation cephalosporins by country, WHO European Region, 2020 (WHO & ECDC, 2022). ... 4

Figure 3. Percentage of K. pneumoniae isolates resistant to third-generation cephalosporins by country, WHO European Region, 2020 (WHO & ECDC, 2022). ... 5

Figure 4. Framework of the national strategic plan on AMR (2017-2021) of Thailand adapted from Sumpradit et al. (2017). ... 10

Figure 5. Map of Chiang Mai province, Thailand. ... 17

Figure 6. The percentages of sepsis patients infected with a pathogen with AMR by type of organism in 3 sentinel hospitals in Chiang Mai province, April 2017 – January 2018 (n = 148). 29

Figure 7. The percentages of sepsis patients infected with a pathogen with AMR by type of organisms and HAI status in 3 sentinel hospitals in Chiang Mai, April 2017 – January 2018. ... 30

Figure 8. The number of sepsis patients infected with a pathogen with AMR by week of specimen collection in Chiang Mai, April 2017 – January 2018 (n = 148). ... 31

Figure 9. Age-adjusted morbidity rates and 95% confidence intervals of sepsis AMR by districts in Chiang Mai province (April 2017 – January 2018) for patients admitted to Nakornping, Chomthong, and Sanpatong hospitals. ... 32

Figure 10. Geographical distribution of sepsis patients infected with a pathogen with AMR in Chiang Mai based on data from Nakornping, Chomthong, and Sanpatong hospitals, April 2017 – January 2018. ... 32

Figure 11. Percentage of sepsis cases with AMR by age in Nakornping hospital (n = 106). ... 54

Figure 12. Percentage of sepsis cases with AMR by age in Chomthong hospital (n = 36). ... 54

Figure 13. Percentage of sepsis cases with AMR by age in Sanpatong hospital (n = 6). ... 55

Figure 14.Percentage of bacteria by species for resistant bacteria isolated from sepsis cases in the 3 sentinel hospitals in Chiang Mai ... 55

Figure 15. Percentage of the patients infected with 8 selected pathogens in Chomthong hospital, April – October 2017 (n = 455). ... 61

Figure 16. Figure 16. Percentage of the patients infected with AMR pathogens in Chomthong hospital, April – October 2017 (n = 203). ... 61

Figure 17. Percentage of the patients infected with non-AMR pathogens in Chomthong hospital, April – October 2017 (n = 252). 62

4. Abstract

Antimicrobial resistance (AMR) defined as microorganisms including bacteria, viruses, fungi, and parasites have the ability to resist the effect of antimicrobial drugs is a serious global public health problem which is apparently increasing. The consequences of AMR include health and economic impacts. The World Health Organization has launched a global action plan on AMR to encourage countries to tackle the crisis of AMR urgently. Thailand approved a national strategic plan on AMR and the Bureau of Epidemiology established a surveillance system on AMR at 6 sentinel hospitals in 4 provinces including 3 sentinel hospitals in Chiang Mai.

Study I described the epidemiological characteristics of sepsis patients infected with a pathogen with AMR bacterial infection in 3 sentinel hospitals in Chiang Mai, April 2017 – January 2018. Study II was conducted to examine differences between characteristics of patients by AMR status for all bacterial infections and identify potential risk factors for AMR and for death among the patients in Chomthong hospital, Chiang Mai, April – October 2017. Data from patients infected with bacteria (both AMR and non-AMR) from Chomthong hospital was used in the analyses in Study II.

Descriptive statistics were used to present prevalence, incidence, proportion, mean with standard deviation, median with interquartile range. Age-adjusted morbidity rates were calculated for each district. Univariate and multivariate analysis was performed to examine associations between potential risk factors and the outcome. Results were presented as odds ratio (OR) and adjusted OR. Inferential statistics was done to determine *p*-values and 95% confidence intervals. A backward stepwise approach was performed to select potential risk factors in the multivariate analysis.

The results reveal that there were 148 sepsis patients infected with eight selected AMR pathogen over the study period from 3 sentinel hospitals. Overall prevalence of sepsis patients infected with a pathogen with AMR in Chiang Mai province may be higher than 9.2 cases per 100,000 population and Case fatality rate (CFR) for sepsis patients infected with a pathogen with AMR was 23% (34/148). The percentage of female patients overall was 51.3%. The median of age of the patients in the three hospitals ranged from 64.0 to 68.0 years. The highest percentage of the AMR organisms was *E. coli* accounting for approximately 56.8%. About forty percent (53/132) of sepsis patients infected with a pathogen with AMR were hospital-acquired infection (HAI). About one-third of sepsis patients infected with a pathogen with AMR in Nakornping occurred in rainy season in Thailand.

In Chomthong hospital, 62% (13/21) of *A. baumannii* isolates were multidrug resistant (MDR), which was defined as resistance to ≥ 1 antibiotic agent in ≥ 3 antibiotic classes, following by *E. coli* isolates 42.2% (89/211), *K. pneumoniae* isolates 37% (25/67), and *P. aeruginosa* isolates 31% (13/41). Underlying disease, HAI, and *E. coli* infection were risk factors for AMR infection for which the adjusted ORs were 2.66 (95%CI 1.13 – 6.25), 4.39 (95%CI 1.84 – 10.48), and 10.69 (95%CI 4.47 – 25.55) respectively. HAI, MDR infection, and sepsis were risk factors for death during hospitalisation period which the adjusted ORs were 3.05 (95%CI 1.08 – 8.65), 3.95 (95%CI 1.30 – 12.00), and 4.62 (95%CI 1.51 – 14.11) respectively.

Antimicrobial resistance was still a problem in Chiang Mai. Public health sectors should take an AMR to be an important issue to increase resources including workforce, budget, and equipment support to the surveillance system. Strengthening HAI prevention and control programme could reduce the occurrence of AMR and death during the patients' hospitalisation.

5. Acknowledgements

This 90-credit thesis, which is a part of Master of Public Health (MPH) fulfilment, would not be completed if there was no supports and assistances from all people and organisations listed in this acknowledgement. First of all, I would like to acknowledge my supervisors, Jackie Benschop and Joanna McKenzie for patient guidance, suggestions, encouragement and advice they have provided throughout my time as their student. I could say that I have been lucky to have the supervisors who took care very much about my work and responded to my queries promptly. My supervisors have shown never ending patience in long delay between versions of my thesis. Also, I would like to thank my supervisors for their supports in other issues during my university's life such as coordinating with the College of Health, supporting to get an Australia's Visa for a conference. I also thank Peter Jolly for his ride at the first day I arrived Palmerston North, New Zealand and his supports all the time when I was in Massey University especially in Wool building.

Many thanks are due to Massey University, which is forever a lovely and peaceful place for my MPH studying, for such a memorable experience in abroad. I would like to express my gratitude and appreciation to Rachel Page, the head of school of health sciences, the university's staff, library's staff and all the course coordinators and lecturers involved in my advance English courses and MPH programmes. I also thank my Thai, Chinese, Indonesian, and Kiwi friends in New Zealand for their supports and encouragement when I have any problem during the process of studying. I really appreciated the Baxter hostel on Ranfurly and Kloyjai Cheuyglintase, my friend's mom, for the good and cheap accommodations I stayed in the first and second years respectively.

I would like to thank the Department of Disease Control (DDC), Thailand for a very good opportunity and funding to study in New Zealand (Aotearoa), the land of the long white cloud. I also appreciate Nakornping, Chomthong, and Sanpatong hospitals for approving me to use the patient's data for this thesis and thank to Dr.Thitipong Yingyong and their staff working for Bureau of Epidemiology, DDC who coordinated with the study hospitals. Moreover, I would like to thank all the patients for their useful information although I have not known their name and who they are.

Finally, I would like to thank my family and friends in Thailand who have encouraged and supported my completion of MPH.

6. Chapter I: Introduction and literature review

6.1 Introduction

6.1.1 Global situation on antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) occurs when microorganisms including bacteria, viruses, fungi, and parasites have the ability to resist the effect of antimicrobial drugs which are intended to kill or limit their growth (World Health Organization [WHO], 2021). AMR is a serious global public health problem which is apparently increasing (WHO, 2021). A recent systematic analysis of published literature estimated that around 4.95 million deaths were related to resistant bacterial infection (Murray et al., 2022). Additionally, O'Neill (2014) illustrated the future global problem of AMR with the predicted number of deaths attributable to AMR infections globally at 10 million deaths per year by 2050 if the level of AMR prevalence does not increase (Figure 1). Antimicrobial-resistant microorganisms may contribute to reduced efficacy of antimicrobials which may result in prolonged antimicrobial treatment and an increased risk of death. This can increase the risk of organisms spreading in communities and hospitals. Additionally, infections with resistant organisms may spread globally as infected people (symptomatic or asymptomatic) travel across international borders and boundaries (Shallcross & Davies, 2014).

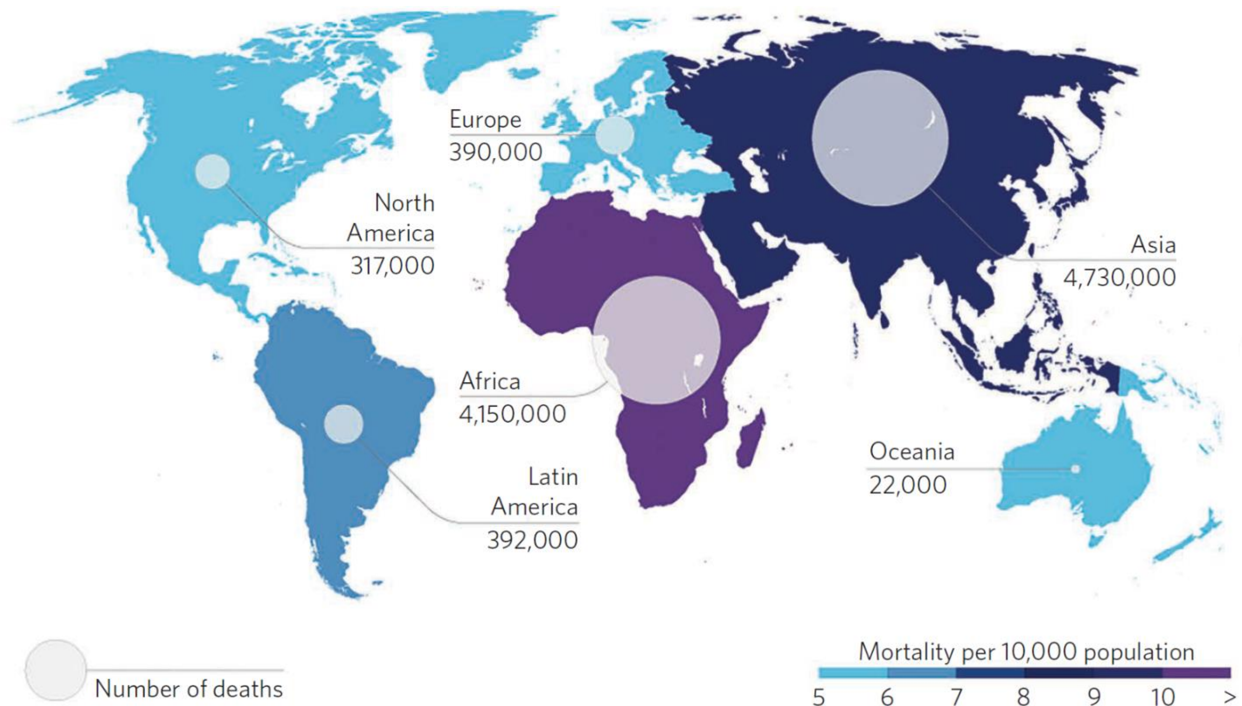

Figure 1. Number of deaths attributable to AMR infections per year by 2050 (O’Neill, 2014).

The United States (US), Centers for Disease Control and Prevention [CDC] (2019) reported that over 2.8 million people were infected with antimicrobial-resistant bacteria with at least 35,000 deaths associated with these infections each year. Similarly, approximately 33,000 patients die from an infection with antimicrobial-resistant bacteria in European countries annually (WHO regional office for Europe & European Centre for Disease Prevention and Control [ECDC], 2022). A particularly concerning situation in Europe is the resistance of gram-negative bacteria, especially *Klebsiella pneumoniae* (*K. pneumoniae*) and *Escherichia coli* (*E. coli*), to third-generation cephalosporins. Specifically, *E. coli* isolates resistant to third-generation cephalosporins percentages 50% or above were observe in 5 (12.5%) of 40 countries in Europe (Figure 2).

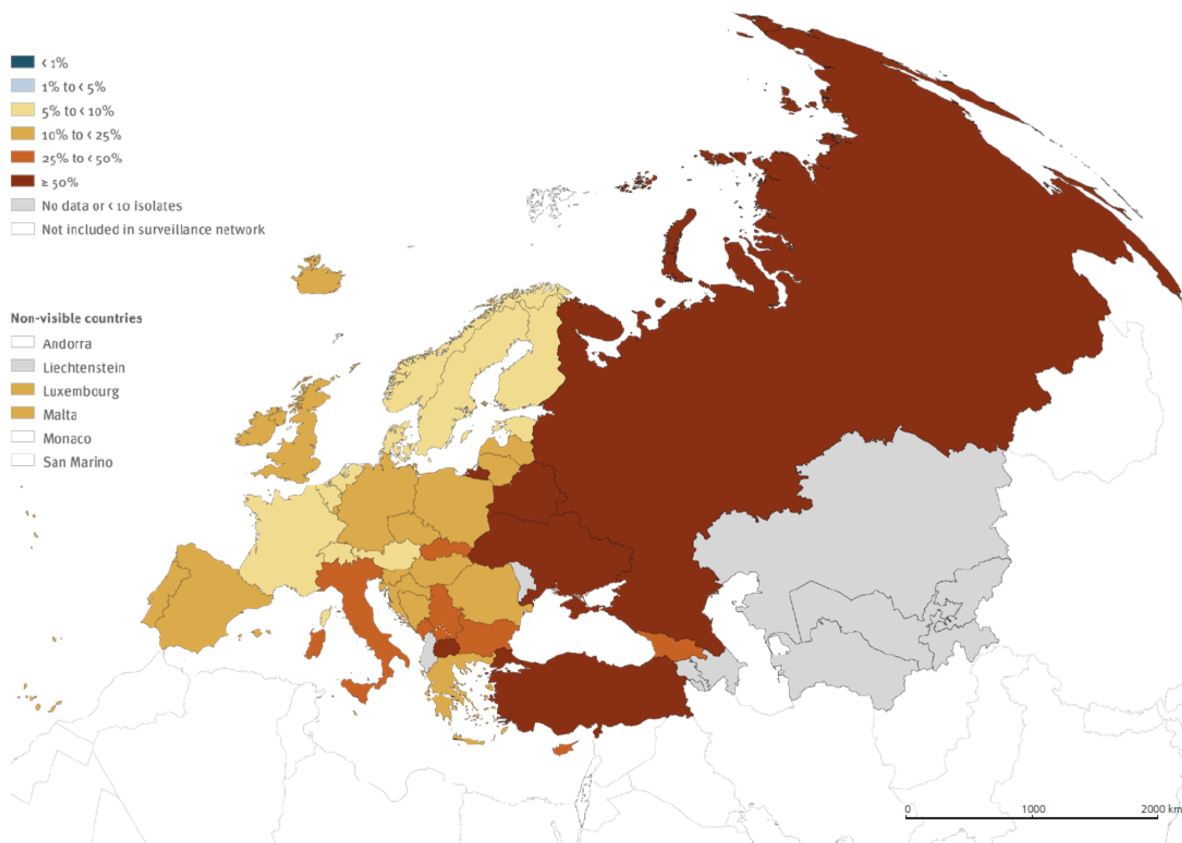

Figure 2. Percentage of E. coli isolates resistant to third-generation cephalosporins by country, WHO European Region, 2020 (WHO & ECDC, 2022).

For third-generation cephalosporins resistance in *K. pneumoniae*, there were 18 (45%) of 40 countries in Europe reported percentages of *K. pneumoniae* isolates resistant to third-generation cephalosporins equal to or above 50% (Figure 3). Third-generation cephalosporins are one of the highest priority antibiotics according to WHO's list of critically important antimicrobials (CIAs) for human medicines. This list is used for developing antimicrobial use guidelines in both animals and humans to preserve the effectiveness of the drugs for further treatment (WHO, 2017). In the US, *Clostridium difficile* (*C. difficile*), carbapenem-resistant Enterobacteriaceae (CRE), and cephalosporin-resistance *Neisseria gonorrhoeae* (*N. gonorrhoeae*) are high-consequence public

health threats that need urgent response. The CDC report these threats have the potential to become epidemics in the future (CDC, 2019).

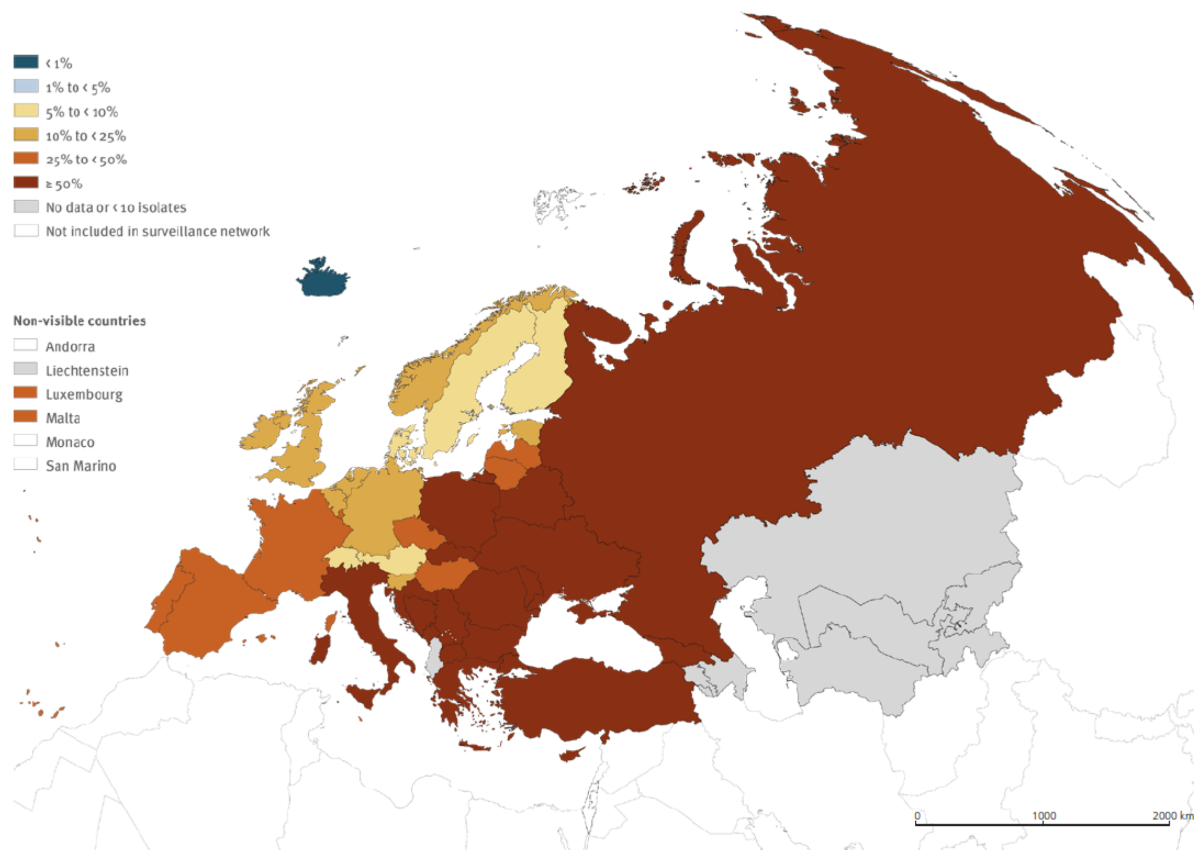

Figure 3. Percentage of K. pneumoniae isolates resistant to third-generation cephalosporins by country, WHO European Region, 2020 (WHO & ECDC, 2022).

There is limited data on the situation of AMR in many countries in Africa owing to the lack of national surveillance systems (Essack, Desta, Abotsi, & Agoba, 2017). Tadesse et al. (2017) systematically reviewed 144 articles on AMR from 30 countries in Africa published from 2013 to 2016 and calculated the median prevalence of resistance to antibiotics. Key findings included that the carriage of cotrimoxazole resistance in gram-negative bacteria and isolation from patients with blood stream infection, wound infection, acute gastroenteritis, and urinary tract infection was high (Median Resistance 75.0%, IQR 49.5%-92.3%). Cotrimoxazole is one of the commonly used drugs in the countries. Moreover, 20% (593/2963) and 19.5% (1051/5395) of *E. coli* isolates from either clinical infection or carriage were resistant to the third-generation cephalosporins including ceftriaxone and cefotaxime, respectively. Similarly, 34.2% (545/1594) and 46.7% (560/1199) of *K. pneumoniae* isolates from either clinical cases or carriage were resistant to ceftriaxone and cefotaxime respectively. Resistant microorganisms are not only prevalent in sick people, but they are also found in healthy people, including children. Specifically, a study in the Central African Republic showed that 59% (79/134) of asymptomatic children aged less than 5 years had *Enterobacteriaceae* that produced extended-spectrum β-lactamases (ESBL)

cultured from stool samples (Farra et al., 2016). These children had no history of diarrhoea or use of antibiotics in last 7 days.

The problem of antimicrobial-resistant microorganisms is a serious problem in Asia and the Pacific (Murray et al., 2022). Specifically, the estimated number of deaths per year by 2050 associated with antimicrobial resistance was 1.39 million in South Asia and 1.02 million in Southeast Asia, east Asia, and Oceania. The countries in the Asia and Pacific region include both high-income countries and low-to-middle-income countries (LMICs) and both are vulnerable to the problem of AMR. More than half of the world's megacities are located in the region and these densely populated cities might be reservoirs for AMR pathogens with high potential to spread due to unplanned urbanisation, poor sanitation and wastewater management particularly in LMICs (Yam et al., 2019).

Thus, all continents of the world face the problem of AMR. The emergence of the problem is reported to be accelerated by an inappropriate use of antibiotics which has become widespread over several decades (WHO, 2018).

6.1.2 Antibiotic use related to AMR

Inappropriate use of antimicrobials is a main driver of AMR (WHO, 2021). Antibiotics are more likely to be used inappropriately in countries where there is little or no legislation and restrictions on the use of antibiotics or lack of public knowledge and awareness (Machowska & Lundborg, 2019). In this context, inappropriate use of antibiotics includes self-medication with antibiotics without medical advice, prescription of antibiotics in viral infections, and prescription of broad-spectrum antibiotics for empirical treatments without laboratory testing for sensitivity.

In India where antibiotics can be purchased without a physician's prescription, a study found that 63/72 (88%) of the respondents purchased antibiotics without any prescription and about 29/55 (53%) of the respondents reported failure to complete the consumption of the course of antibiotics (Kotwani, Joshi, Lamkang, Sharma, & Kaloni, 2021). A systematic review of 7 published studies in Saudi Arabia on factors influencing antibiotics misuse between 2002 and 2015 suggested that low level of education, socio-economic status, and cultural factors are factors contributing to the inappropriate use of antibiotics (Alnemri, Almaghrabi, Alonazi, & Alfrayh, 2016). A cross-sectional survey in 2017 in north-western Ethiopia of 650 participants found that about 50% of the participants used antibiotics purchased from private pharmacies without a prescription or shared leftover antibiotics from their neighbour or family member in a previous year (Erku, Mekuria, & Belachew, 2017). India was the world's biggest user of antibiotics for human health in 2010 with 12.9 billion units measured by sales data for hospitals and retail pharmacies from the Medical Information Data Analysis System (MIDAS®) database (Van Boeckel et al., 2014). A study in India assigned 2 researchers presenting as community customers with clinical scenarios including upper respiratory tract infection (URI) and diarrhoea to visit drug stores for purchasing medicines (Shet, Sundaresan, & Forsberg, 2015). The result of the study demonstrated that about two-thirds of the number of pharmacy visits in 2 simulated patients (n = 261 visits) were given antibiotics especially amoxicillin and ciprofloxacin for the conditions of URI and diarrhoea respectively.

Antibiotics may also be used inappropriately in countries where antibiotic use is regulated by government organisations. For example, in Armenia, about 78% of pharmacists in the study reported that purchasing antibiotics without prescription was still observed at their pharmacy in spite of national regulations and the most important barrier for dispensing antibiotics with a prescription at community pharmacies was lack of patient's awareness of the use of antibiotic (Kazaryan, Sevikyan, Vardanyan, Amirkhanyan, & Melikyan, 2021). In a hospital setting in the US, the National Ambulatory Medical Care Survey (NAMCS) revealed that weighted mean annual rate of antibiotic prescriptions for patients with acute respiratory infection during 2010-2011 was 221 antibiotic prescriptions per 1,000 general population. However, approximately 50% of these prescriptions were estimated to be inappropriate based on national guidelines from professional societies for common diseases (Fleming-Dutra, Hersh, Shapiro, & et al., 2016). In England, a survey using the data from the Health Improvement Network illustrated statistically significant overprescribing of antibiotics used in patients with common infectious conditions including acute cough, sore throat, rhinosinusitis, otitis media, and bronchitis (Pouwels, Dolk, Smith, Robotham, & Smieszek, 2018). Indeed, the actual antibiotic prescribing proportion among patients with acute cough was 0.41 (n = 573,827 consultations) while the ideal proportion of antibiotic prescription based on guidelines and experts' opinion was estimated to be 0.10. Also, the actual antibiotic prescribing proportion among patients with sore throat was 0.59 (n = 386,971 consultations) while the ideal proportion was 0.13.

The inappropriate use of antibiotics could accelerate the process of genetic changes in bacteria resulting in antibacterial resistance (ABR). The most common mechanisms of ABR were antibiotics' enzymatic degradation, mutation in the target site of antibiotics, decreased permeability of bacteria's cell wall to antibiotics, and the active efflux of antibiotics across bacteria's cell membrane (Harbottle, Thakur, Zhao, & White, 2006). For instance, *Enterobacteriaceae* including *E. coli* and *K. pneumoniae* can produce enzymes destroying the molecule of antibiotics especially in the amide bond of antibiotic's β-lactam ring (Munita & Arias, 2016). The important enzyme found in these bacteria is a plasmid-encoded ESBL called CTX-M (CTX as the abbreviation of cefotaxime, -M from Munich where the enzyme was first recognised). This enzyme is the major cause of the emergence of cephalosporin resistance in *Enterobacteriaceae* in the world (Cantón, González-Alba, & Galán, 2012). Moreover, other bacteria have their own individual mechanism to develop ABR as shown in Table 1.

Table 1. Examples of antibiotic resistant mechanisms for specific microorganisms.

Microorganism	Resistance to antibiotic	Mechanism	Reference
Acinetobacter baumannii (A. baumannii)	colistin	Reduced production of antibiotic's binding target, lipid A component of lipopolysaccharide in bacteria's cell wall, due to gene mutations.	Moffatt et al. (2010)
Enterococcus spp.	vancomycin	Alteration of cell wall precursors, peptidoglycan, resulting in poor binding to vancomycin.	(Gold, 2001)
Pseudomonas aeruginosa (P. aeruginosa)	carbapenems	Multifactorial including production of carbapenemases and diminished outer cell membrane permeability, and increased efflux pump systems.	(Rodríguez-Martínez, Poirel, & Nordmann, 2009)
Staphylococcus aureus (S. aureus)	methicillin	The expression of non-native penicillin-binding proteins which are resistant to the action of β-lactam antibiotics including methicillin.	(Stapleton & Taylor, 2002)

6.1.3 The impacts of AMR

The consequences of antimicrobial-resistant organism infections include both health and economic impacts (Cosgrove & Carmeli, 2003). The infections with the resistant organisms cause a delay in treatment with effective specific antibiotics leading to increased length of hospitalisation. This might result in serious adverse outcomes including fatality (Ibrahim, Sherman, Ward, Fraser, & Kollef, 2000). The study by Lautenbach, Patel, Bilker, Edelstein, and Fishman (2001) revealed that patients infected with ESBL-producing *E. coli* and *K. pneumoniae* received effective antibiotics (median of 72 hours after an infection was suspected) slower than patients infected with non-ESBL-producing strains (median of 11.5 hours after an infection was suspected) (p-value < 0.001). The study also found that the patients infected with ESBL-producing strains had greater length of hospitalisation than the patients infected with non-ESBL-producing strains with statistical significance (p-value = 0.01). The results of the report by O'Neill (2014) demonstrate a significant economic impact due to a continued increase in AMR in the world by 2050 which would lead to a reduction of 2% - 3.5% in Gross domestic product (GDP) according to 10 million people dying every year. Also, Shrestha et al. (2018) studied the productivity losses owing to excess mortality, and the incremental cost of treating patients infected with a pathogen with AMR as compared to patients infected with susceptible organisms in Thailand and the US. The results suggest that the total economic cost of the infection with five selected resistant organisms including *S. aureus*, *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* was 0.5 and 2.9 billion USD in Thailand and the US respectively. Accordingly, the health and economic impacts of AMR problem are obviously presented requiring an immediate response to minimise the effects of the problem.

6.1.4 Global and Thai action plans on AMR

WHO (2015a) launched a global action plan on AMR in 2015 in order to encourage countries and member states to tackle the crisis of AMR urgently. The objectives of the plan include improving awareness of AMR, strengthening the evidence base of AMR through surveillance and research, reducing the incidence of AMR infection through infection prevention measures, optimising the use of antimicrobials in both human and animals, and ensuring sustainable investment in countering the problem of AMR. WHO (2015a) suggests that the five key objectives need to be undertaken together with the cooperation of all sectors including patients, health care workers, farmers, animal husbandry, pharmaceutical sector, academics, and governmental organisations. Moreover, the Global Antimicrobial Resistance Surveillance System (GLASS), which is a platform for data sharing on AMR globally, has been implemented by WHO to support the global action plan. Currently, GLASS is focusing on bacteria which cause an illness in humans and gathering the data on resistance in 8 priority bacteria from 4 specimen types collected from patients described in Table 2. In the future, GLASS will expand the system to include gathering data from other types of AMR-associated surveillance such as antimicrobial use, environments, and food supply chains (WHO, 2015b).

Table 2. Priority specimens and pathogens for AMR surveillance by GLASS adapted from (WHO, 2015b).

Specimen	Priority pathogens for surveillance
Blood	*A. baumannii, E. coli*, *K. pneumoniae*, *S. pneumoniae, S. aureus*, and *Salmonella spp.*
Urine	*E. coli* and *K. pneumoniae*
Faeces	*Salmonella spp.* And *Shigella spp.*
Genital swabs	*N. gonorrhoeae*

The Royal Thai Government approved a national strategic plan on AMR (2017-2021) in August 2016 which aims to promote the collaboration of multiple sectors including the Ministry of Public Health, Ministry of Agriculture and Cooperatives, and universities. The aims of the plan are to decrease AMR morbidity, inappropriate antimicrobial consumption, and to raise public awareness (Tangcharoensathien et al., 2017). The national plan comprises six strategic actions including: 1) AMR surveillance using a One Health approach, 2) Regulation of antimicrobial distribution, 3) Infection prevention and control and antimicrobial stewardship, 4) AMR containment and antimicrobial use in agriculture and animals, 5) Public awareness on AMR and appropriate use of antimicrobials, and 6) Governance mechanisms to implement and sustain AMR actions (Figure 4).

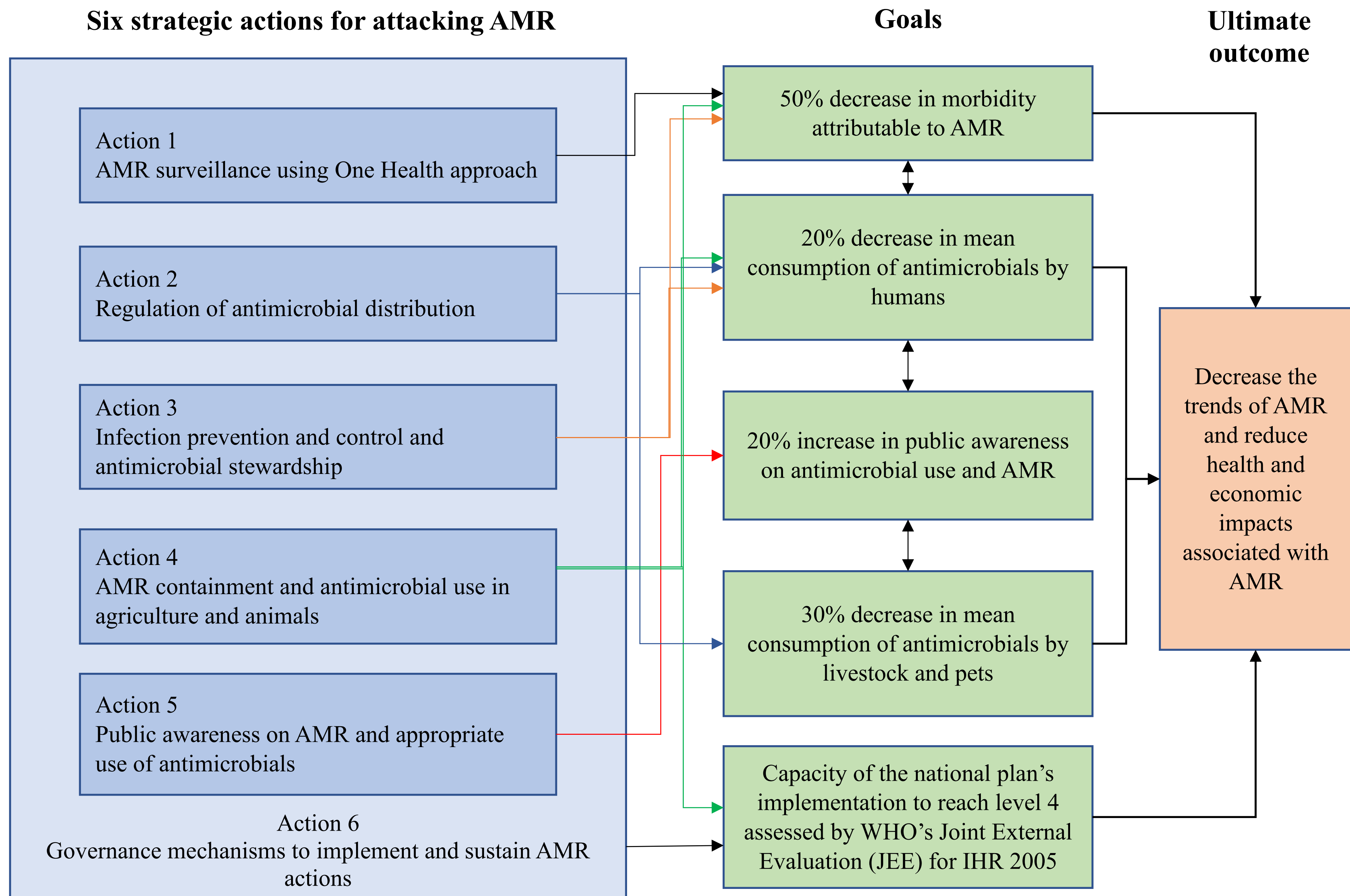

Figure 4. Framework of the national strategic plan on AMR (2017-2021) of Thailand adapted from Sumpradit et al. (2017).

6.1.5 National surveillance system on AMR in Thailand

The National Antimicrobial Resistance Surveillance Center, Thailand (NARST) under Department of Medical Science (DMSc), Ministry of Public Health (MoPH) has been established since 1997. NARST, which has been designated as a WHO collaborating centre for antimicrobial resistance surveillance and training since 2005, is the national AMR reference laboratory. NARST is responsible for supervision of participating hospital laboratories to perform antimicrobial susceptibility testing (AST) and building the capacity of the laboratories. Performance standards for AST by Clinical and Laboratory Standards Institute (CLSI) was recommended to use across laboratories qualified by DMSc (2017). In addition, NARST has collected and analysed the data on AST, and disseminated the results to policy makers for further decision-making and to physicians for providing an evidence-based information of antibiotic use in their hospital. NARST has also participated and shared the information on AST in Thailand to GLASS since it has been implemented. However, only the data on laboratory surveillance is not sufficient to provide the whole picture of AMR in Thailand for public health policy makers who need more information on AMR such as population at risk. So, the surveillance on AMR may need to be strengthened in order to improve understanding of knowledge on AMR in Thailand and to implement specific prevention measures in the future. Thus, the Bureau of Epidemiology (BoE), a governmental organisation under the Department of Disease Control (DDC), MoPH who is responsible for developing national disease surveillance systems, cooperates with some hospitals participating in the surveillance on AMR led by NARST to improve the surveillance program in humans in the country. BoE is leading a surveillance system for AMR in humans in Thailand, beginning in 2017. The surveillance system comprises collecting epidemiological data from patients infected with selected AMR pathogens from 6 sentinel hospitals in 4 provinces including, Nakornping hospital (Chiang Mai province), Chomthong hospital (Chiang Mai province), Sanpatong hospital (Chiang Mai province), Phrapokklao hospital (Chanthaburi province), Suratthani hospital (Suratthani province), and Bamrasnaradura Infectious Disease Institute (Nonthaburi province). The selected pathogens include 8 types of bacteria resistant to at least one of the antibiotics described in Table 3. The quality controls for laboratory reporting AST results using CLSI standards were used across the sentinel hospitals (CLSI, 2017). Patients infected with the 8 pathogens found from blood (sepsis patients) were reported to the BoE at the early stage of the surveillance programme because bloodstream infection (BSI) could lead to higher unsuccessful treatment and fatality. However, the hospitals also voluntarily reported the patients infected with the resistant pathogens found from other specimen types such as urine, faeces, sputum, and pus. The hospitals assigned a responsible staff member who was either an infectious nurse or epidemiologist in the hospital to collect and report to the BoE monthly. The reported data was verified for duplication before sending to the BoE because two or more specimens might be collected at the same time on admission date. So, Chiang Mai province where there are 3 sentinel hospitals was selected as a study site and the surveillance data from the sentinel hospitals were made available for an epidemiological study to investigate factors associated with AMR.

Table 3.List of selected pathogens and antibiotic resistance under the AMR surveillance system in Thailand.

No.	Microorganism	Class of antibiotic	Antibiotics
1	*A. baumannii*	Carbapenem	meropenem, ertapenem
		Polypeptide antibiotic	colistin
2	*P. aeruginosa*	Carbapenem	meropenem, ertapenem
		Polypeptide antibiotic	colistin
		Antipseudomonal penicillin plus β-lactamase inhibitor	piperacillin-tazobactam
3	*K. pneumoniae*	Carbapenem	meropenem, ertapenem
		Polypeptide antibiotic	colistin
		Extended-spectrum cephalosporin	ceftriaxone, cefotaxime, ceftazidime
		Extended-spectrum cephalosporin plus β-lactamase inhibitor	cefoperazone-sulbactam
4	*Enterococcus* spp.	Polypeptide antibiotic	colistin
		Glycopeptide antibiotic	vancomycin
5	*S. aureus*	Penicillinase-resistant penicillin	Methicillin (oxacillin)
		Glycopeptide antibiotic	vancomycin
6	*Streptococcus pneumoniae (S. pneumoniae)*	Penicillin	penicillin
		Aminopenicillin	ampicillin
		Aminopenicillin plus β-lactamase inhibitor	amoxicillin-clavulanic acid
		Extended-spectrum cephalosporin	ceftriaxone, cefotaxime, ceftazidime
		Macrolide	erythromycin
		Fluoroquinolone	norfloxacin, ciprofloxacin
7	*E. coli*	Carbapenem	meropenem, ertapenem
		Polypeptide antibiotic	colistin
		Fluoroquinolone	norfloxacin, ciprofloxacin
		Extended-spectrum cephalosporin	ceftriaxone, cefotaxime, ceftazidime
		Extended-spectrum cephalosporin plus β-lactamase inhibitor	cefoperazone-sulbactam
8	*Salmonella* spp.	Polypeptide antibiotic	colistin
		Fluoroquinolone	norfloxacin, ciprofloxacin
		Extended-spectrum cephalosporin	ceftriaxone, cefotaxime, ceftazidime
		Extended-spectrum cephalosporin plus β-lactamase inhibitor	cefoperazone-sulbactam

6.2 Literature review

6.2.1 Antimicrobial resistance and sepsis

Antibiotics are mainly used to treat patients who were infected with bacteria by degrading or destroying the cell wall of bacteria (Harbottle et al., 2006). Sepsis is an important life-threatening condition, caused by bloodstream infection with bacteria leading to developing signs and symptoms of systemic inflammatory response syndrome in patients resulting in multiple-organ failure and death (Singer et al., 2016). Also, sepsis patients need some invasive treatments such as endotracheal tube intubation, intravenous catheterization, and urinary catheterization and need increased length of hospitalization. This might cause hospital-acquired infections during the hospitalization period. Appropriate treatment of definitive antibiotic is an essential part of sepsis management that could reduce the fatality of sepsis patients (Tancharoen, Pairattanakorn, Thamlikitkul, & Angkasekwinai, 2022). On the other hand, inappropriate use of antibiotics, for example, incomplete consumption of antibiotics course, use antibiotics without medical prescription could lead to AMR (WHO, 2021). Additionally, as more bacteria become resistant to antibiotics used to treat people with bacterial infection, more patients are at risk for developing sepsis due to the decreased efficacy of antibiotics (Shallcross & Davies, 2014). Balancing between antimicrobial stewardship and sepsis management in practice to reduce overtreatment of antibiotics is also important to save people's life from sepsis and decrease the problem of AMR, however, antimicrobial stewardship initiatives and sepsis management programme are sometimes implemented by different teams within public health sectors (Fitzpatrick et al., 2019).

6.2.2 Risk factors for getting infection with AMR bacteria

A systematic review on risk factors for developing AMR in China by Chen et al. (2021) suggests that there were four major risk factors for getting infection with AMR bacteria including sociodemographic factors, patient clinical information; admission to healthcare; and drug exposure. Sociodemographic factors include age, low income, migrant status. Specifically, older people aged equal to or more than 45 years was a risk factor for AMR infection. Similarly, a retrospective study in the US using a data from the National (Nationwide) Inpatient Sample – Healthcare Cost and Utilization Project (HCUP-NIS) found that older people had higher chance to get infection with AMR bacteria according to co-morbidities and physiological changes (Nguyen, Nguyen, Hughes, & O'Neill, 2019). Furthermore, older people were more susceptible to hospital-acquired infections combined with atypical symptoms leading to inappropriate use of antibiotics resulting in infection with AMR bacteria (Biedron & Chopra, 2013). However, infection with AMR bacteria could be found in new born especially in neonatal intensive care unit according to inadequately empirical antibiotic therapy (Ramirez & Cantey, 2019). For socioeconomic status related to infection with AMR bacteria, Allel et al. (2020) conducted research in Chilean hospitals found that there was an association between low-income and AMR of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* (p-value < 0.01). People with low economic status and migrants were vulnerable to AMR according to poor accessibility to healthcare provider which led them to the use of antibiotics without any medical prescription (Morgan, Okeke, Laxminarayan, Perencevich, & Weisenberg, 2011).

Patient clinical information risk factors include having underlying diseases and non-communicable diseases such as diabetes mellitus, chronic respiratory diseases, cardiovascular

diseases, chronic hepatic diseases, anaemia, and cancers. It could be explained that these co-morbidities related to immunocompromised status of patients led to an infection with AMR bacteria (WHO, 2021). A retrospective cohort study in Italy in nursing care setting suggests that co-morbidities were associated with infection with AMR pathogen (p-value < 0.05) (Laudisio et al., 2017). Similarly, elderly had a higher chance to get infection with AMR bacteria because they had history of having any underlying disease (Nguyen et al., 2019). However, a matched case-control study in France found that there was no an association between co-morbidities and AMR (Opatowski et al., 2021).

Admission in healthcare settings risk factors include increased length of hospitalization, surgery, invasive procedures such as endotracheal tube intubation, intravenous catheterization, and urinary catheterization. Increased length of hospitalization especially more than 7 days was a risk factor for hospital-acquired infection leading to infection with bacteria with AMR (Murni et al., 2022). Moreover, Manosuthi et al. (2017) conducted research in 50 selected hospitals in Thailand including government hospitals, university hospitals, and private hospitals found that invasive procedures including urinary catheterization, intravenous catheterization, respiratory ventilator, tracheostomy tube, and surgery were associated with HAIs on multivariate analysis with adjusted odds ratios ranged from 1.61 to 5.15 with 95% confidence intervals do not include 1. Similar to the systematic review on hand hygiene in healthcare workers by Mouajou, Adams, DeLisle, and Quach (2022), performing invasive procedures without hand hygiene practices related to HAIs. Bearman, Doll, Cooper, and Stevens (2019) suggested that strengthening infection prevention and control programme in hospitals could decrease the occurrence of HAIs up to 55% - 70%.

Drug exposure risk factors include history of prior and current antibiotic treatments. A meta-analysis on seasonal pattern of respiratory bacteria resistant to antibiotics by Martinez et al. (2019) showed that the higher use of antibiotic in winter was associated with the incidence of penicillin-resistant *S. pneumoniae* which was higher in winter as well. A case-control study in Denmark conducted by Jensen et al. (2022) revealed that the use of antibiotics prior to urinary tract infection episode ranged from 8 to 90 days was associated with trimethoprim, mecillinam, and nitrofurantoin resistant *E. coli*.

6.3 Objectives

The objectives of this study were:

1. To describe the epidemiological characteristics of sepsis patients infected with with AMR bacterial infection in 3 AMR surveillance sentinel hospitals in Chiang Mai, April 2017 – January 2018.
2. To examine differences between characteristics of patients by AMR status for all bacterial infections in Chomthong hospital, Chiang Mai.
3. To identify potential risk factors for AMR and for death during hospitalisation among patients with a bacterial infection in Chomthong hospital, Chiang Mai.

7. Chapter II: Methodology

7.1 Methods

7.1.1 Ethical considerations

The data were gathered as a part of the national AMR surveillance system in Thailand. The surveillance system was started in April 2017 by the BoE, MoPH, Thailand, which has direct authority to implement the surveillance system under the national strategic plan on AMR (2017-2021). The dataset was anonymised by excluding the name, surname, national identification number, hospital number of patients. The use of data was approved by the director of the BoE and the hospital directors. Prior to undertake this research, the project was assessed by peer review and judged to be low risk. Consequently, it has not been reviewed by one of the University's Human Ethics Committees. The project was recorded on the Low-Risk Database which is reported in the Annual Report of Massey University Human Ethics Committees.

7.1.2 Study population

The study population was drawn from three hospitals that are the sentinel sites of the AMR surveillance system and have laboratory capacity to test for AMR in bacterial organisms in Chiang Mai province (Nakornping, Chomthong, and Sanpatong hospitals). In 2017, there was a mid-year population of 1,610,419 registered in Chiang Mai (Chiang Mai Public Health Office, 2018). There are 25 districts and each district has at least one government hospital providing medical treatment to the people in the area. The list of districts of Chiang Mai and the mid-year population in each district are shown in Table 19. Nakornping hospital is the biggest governmental hospital in Chiang Mai which is under MoPH of Thailand. Nakornping hospital located in Mae Rim district is a tertiary care hospital in which there were 742 beds. Nakornping hospital does not serve only the people in the district but it does provide medical treatment to other people who were referred from other hospitals in Chiang Mai and neighbouring provinces. Chomthong hospital located in Chom Thong district is a secondary care hospital in which there were 210 beds. This hospital provides medical treatment to the people living in Chom Thong district and the patients who are referred to the hospital from smaller hospitals in neighbouring districts such as Mae Chaem, Hot, Doi Tao, and Omkoi districts. Sanpatong hospital located in San Pa Tong district is a primary care hospital in which there were 130 beds. The hospital mainly provides medical treatment to the people living in San Pa Tong district. If patients in Sanpatong hospital need higher level treatment or surgery, the hospital will refer the patients to Nakornping hospital. The map of Chiang Mai province by district is shown in Figure 5.

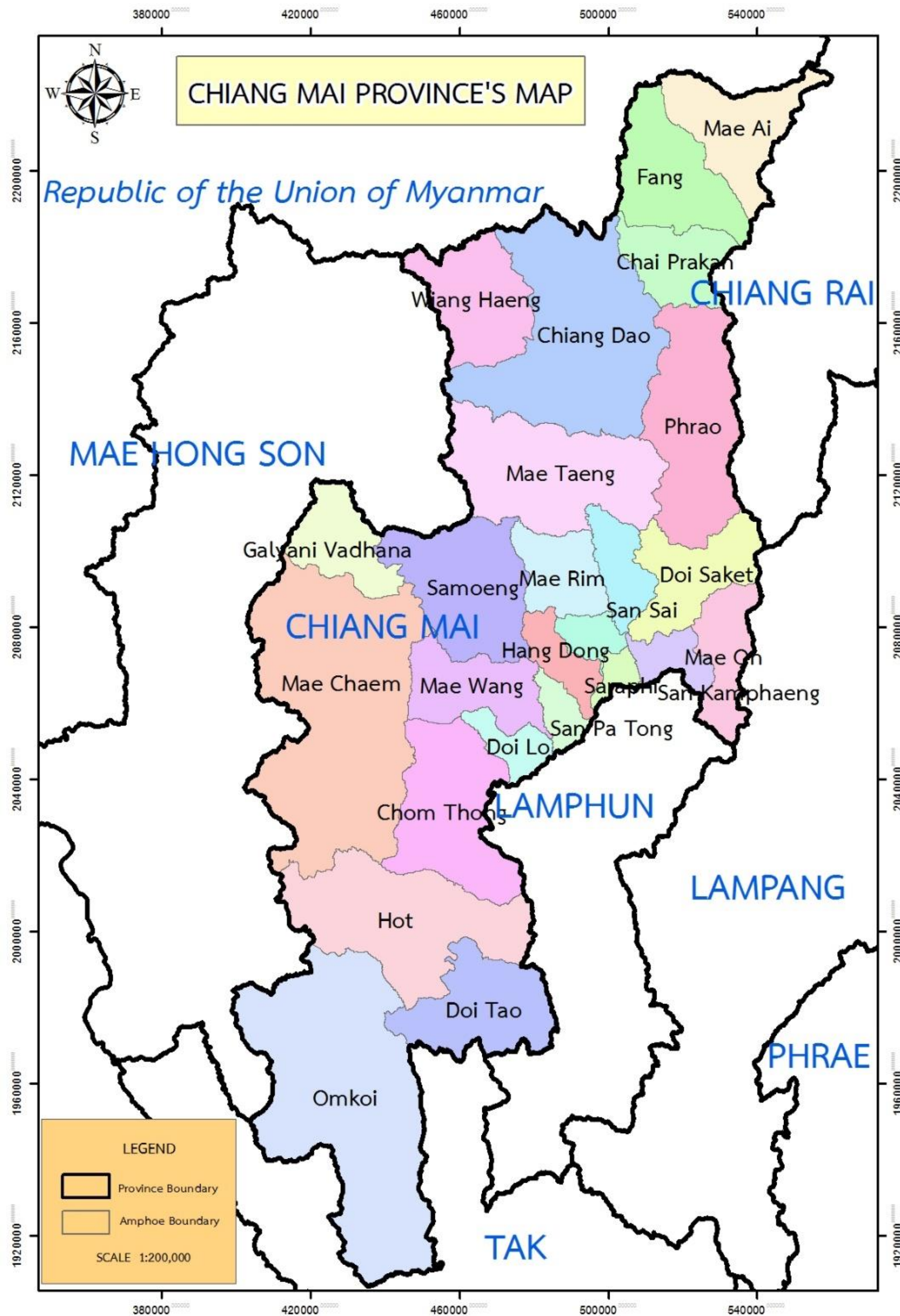

Figure 5. Map of Chiang Mai province, Thailand.

Source: http://www.chiangmai.go.th/english/index.php/welcome/information

7.1.3 Data source

The data used in the research excluded variables that could be used to trace back to patients such as Name, Surname, National ID, and Hospital number by a designated BOE's staff. The anonymised data in excel format from BoE was sent to a researcher. The period for which AMR sepsis cases were reported varied for each of the 3 hospitals as follows:

- Nakornping hospital provided the data of sepsis patients infected with a pathogen with AMR from 1 April 2017 to 31 January 2018.
- Sanpatong hospital provided the data of sepsis patients infected with a pathogen with AMR from 1 April 2017 to 31 July 2017.
- Chomthong hospital provided the data of both sepsis and non-sepsis patients for which a bacteria was cultured from the blood, including both resistant and non-resistant bacteria, from 1 April 2017 to 31 October 2017.

Table 4 illustrates the number of patients infected with AMR and non-AMR pathogens including sepsis and other infection sites from the 3 hospitals. Also, the table presents the total number of all patients admitted to an inpatient department (IPD) in each month.

Table 4. The number of patients reported to BoE from the 3 sentinel hospitals from April 2017 – January 2018.

Hospital	Apr 2017	May 2017	Jun 2017	Jul 2017	Aug 2017	Sep 2017	Oct 2017	Nov 2017	Dec 2017	Jan 2018	Total
Nakornping hospital											
- sepsis patients infected with a pathogen with AMR	1	1	16	12	19	16	10	8	11	12	106
- all IPD patients	3,748	4,234	4,316	4,070	4,423	4,183	4,500	4,448	4,230	4,328	42,480
Chomthong hospital											
- sepsis patients infected with a pathogen with AMR	11	3	6	2	5	6	3	-	-	-	36
- patients infected with AMR from other sites.	34	34	30	19	18	19	13	-	-	-	167
- patients infected with non-AMR	41	39	37	44	26	33	32	-	-	-	252
- all IPD patients	1,289	1,663	1,826	1,435	1,726	1,439	1,454	1,489	1,444	1,425	15,190
Sanpatong hospital											
- sepsis patients infected with a pathogen with AMR	2	1	2	1	-	-	-	-	-	-	6
- all IPD patients	964	1,027	1,065	1,036	1,145	1,200	1,077	996	1,043	1,038	10,591

" – " represents no data was sent to BoE during these months.

Variables in the spreadsheets from the 3 hospitals comprise gender, age, date of birth, race, occupation, physical address in province and district level, admission date, type of ward, type of admission, type of department, patient status, underlying disease status, initial diagnosis, specimen type, specimen collection date, type of organisms, and AMR status. The details of the variables are described in Table 5.

Table 5. Details of variables from the dataset of AMR surveillance in Chiang Mai.

Variable	Description	Values
ID	New unique identification number of the patients assigned specifically for the purposes of this study	1, 2, 3, …
Hospital	The hospital where the patients were admitted	Nakornping, Chomthong, and Sanpatong
Gender	Gender of the patients	Male, female
Age	Age of the patients	Age in years
Date of birth	The patients' date of birth	DD/MM/YYYY
Race	Race of the patients	Thai, Burmese, etc.
Occupation	Occupation of the patients	Housekeeper, agriculture, labourer/freelance, merchant/personal business, government officer, neonate/infant/pre-school age, student, unemployed/retired, unknown
District	The patients' physical address in district level in Chiang Mai	Mae Rim, Chomthong, Omkoi, Hot, San Pa Tong, etc.
Admission date	The patients' date of admission	DD/MM/YYYY
Type of department	Type of departments which the patients were admitted	Medicine, surgery, paediatric, etc.
Type of admission	The patients' type of admission	Outpatient department (OPD), inpatient department (IPD), intensive care unit (ICU)
Type of ward	Type of wards which the patients were admitted	Common, private
Patient status	The treatment outcome of the patients	Complete recovery, improved, not improved, dead
Underlying disease status	History of having any underlying disease	Yes, no
Underlying disease (specify)	The details of underlying disease	Hypertension, chronic kidney disease, diabetes mellitus, cancers, etc.
Initial diagnosis	The initial diagnosis of the patients given by physicians	Sepsis, pneumonia, UTI, etc.
Type of organisms	Name of organisms	*Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus* spp.*, Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, and Salmonella* spp.
AMR status	The resistant organisms which were resistant to any one of the antibiotics by Kirby-Bauer's method shown in Table 3	Yes (resistant), no (intermediate or susceptible)
Specimen type	The type of specimen collected from the patients at any site	Hemoculture, sputum culture, urine culture, pus culture, etc.
Specimen collection date	The date the specimens were collected	DD/MM/YYYY

7.1.4 Data management and analysis

The data received from the BoE were stored on a Massey OneDrive by password protection during analysis period. Microsoft Excel® was used to manage and clean the data used in the study. R programme version 4.1.2 was used to read in, and analyse the data for this study (R Core Team, 2021). The Excel spreadsheets from Nakornping, Chomthong, and Sanpatong hospitals were combined into a single spreadsheet. We used 3 variables including date of birth, admission date, and physical address for checking the duplication of the patients in the study. For Chomthong hospital that had the data of both sepsis and non-sepsis patients, if patients had results showing resistant organisms both from blood stream infection and other infection sites, the record of blood stream infection of the patients was selected for the analysis. Additionally, abbreviations and unclear values found in the spreadsheets were clarified by the staff of the hospitals who were responsible for recording the data. For this process, we only contacted staff in the BoE to get the information.

We defined new variables with recoded existing variables including:

- Age group – Age of the patients was classified into 5 age groups including: "0-20 years", "21-40 years", "41-60 years", "61-80 years", and "over 80 years".
- Hospital-acquired infection (HAI) – According to Horan and Gaynes (2004), an HAI was defined as an infection which occurred in a hospital 48 hours or more after the time of admission. So, we calculated the time difference between specimen collection date and admission date to categorise HAI status of the patients. In this study, we categorised patients whose specimen was collected 48 hours or more following admission as an HAI patient, assuming that the patients became infected 48 hours or more after the time of admission.
- Occupation related to agriculture – The occupation of patients into 2 groups including agriculture and non-agriculture groups.
- Race – The race of the patients was classified into 2 groups including Thai and non-Thai.
- Underlying disease – The underlying disease of the patients were categorised as "Yes" or "No" due to the data shown in variable "Underlying disease status". However, if the variable "Underlying disease status" was missing but there were the details of underlying disease in variable "Underlying disease (specify)" such as hypertension, cancers, the underlying disease would be categorised as "Yes".
- Dead status – The patients were classified as dead or alive. The value of patient status recorded as dead was categorised as "dead" and other values including complete recovery, improved, not improved were categorised as "alive".

7.2 Study I: Descriptive epidemiology of sepsis patients infected with AMR bacteria in 3 sentinel surveillance hospitals in Chiang Mai, Thailand, April 2017 – January 2018.

7.2.1 Case definition

A case was defined as either an outpatient or a patient admitted to a department in one of the three hospitals between 1st April 2017 and 31st January 2018 who were diagnosed with sepsis by physicians in the 3 sentinel hospitals including Nakornping, Chomthong, and Sanpatong hospitals and whose data was reported to BoE. For inclusion in this study sepsis cases were confirmed by bacterial hemoculture of at least one of the eight selected microorganisms and resistant to at least one of the antibiotics described in Table 3.

Diagnosis of sepsis might be made based on either the physicians' judgement or on the third international consensus definition for sepsis and septic shock (Singer et al., 2016). Specifically, a sepsis case means a patient with suspected infection who has Sequential Organ Failure Assessment (SOFA) (originally the Sepsis-related Organ Failure Assessment) score of 2 points or greater. The details of SOFA score are shown in Table 6.

Table 6 Sequential Organ Failure Assessment (SOFA) score adapted from Vincent et al. (1996).

System	Score				
	0	1	2	3	4
Respiratory system - PaO_2/FIO_2 (mmHg)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation - Platelet count ($\times 10^3$ /mm^3)	≥150	<150	<100	<50	<20
Liver - Bilirubin (mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12.0
Cardiovascular system - Hypotension	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine ≤5 or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system - Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Renal system - Creatinine (mg/dl) or urine output	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500 ml/day	≥5 or <200 ml/day

PaO_2, Partial pressure of oxygen; FIO_2, Fraction of inspired oxygen; MAP, Mean arterial pressure
Adrenergic agonists including dopamine, dobutamine, epinephrine, and norepinephrine are administered in µg/kg×min for at least 1 hr

7.2.2 Data extraction

A data frame used for the analyses in study I was extracted from the single combined spreadsheet. All records showing AMR status of "Yes" and specimen type of "Hemoculture" were selected into the data frame.

7.2.3 Data analysis

The overall prevalence of sepsis AMR in Chiang Mai was calculated by using the total number of sepsis AMR cases from the 3 sentinel hospitals divided by the number of mid-year populations in Chiang Mai in 2017. We also calculated the incidence of sepsis AMR cases in each hospital by using the number of sepsis AMR cases in each hospital divided by the total number of all IPD cases during the same period. We calculated proportions to describe the distribution of categorical variables including Gender, age group, race, occupation, underlying disease status, department of admission, department type, ward type, type of organism, and dead status amongst the AMR sepsis cases. The results were presented as numbers and percentages. Mean with standard deviation (SD) was computed to describe the normally distributed continuous variables such as age. Median with interquartile range (IQR) was calculated to summarise the non-normally distributed continuous variables. The number of AMR cases by week of blood specimen collection was plotted using "EpiCurve" package in R to describe the distribution of the cases by time. Age-adjusted morbidity rates with their 95% confidence interval (CI) at district level were calculated for each district to reduce the effect of age in different populations using "epiR" package in R programme. The rates were multiplied by 100,000 to describe as cases per 100,000 population. We used statistics of the mid-year population in Chiang Mai province and in each district in Chiang Mai in 2017 as the reference population of this study (Chiang Mai Public Health Office, 2018). A choropleth map done by package "maptools" was used to illustrate the distribution of sepsis patients infected with a pathogen with AMR and the location of the 3 sentinel hospitals in Chiang Mai.

7.3 Study II: Cross-sectional analytic study of risk factors for infection with an AMR-bacteria and death among patients infected with the eight selected bacterial pathogens in Chomthong hospital, Chiang Mai, Thailand, April – October 2017.

7.3.1 Case definition

An AMR case was defined as either an outpatient or a patient admitted to a department in Chomthong hospital between 1st April 2017 and 31st October 2017 who was diagnosed with an AMR bacterial infection of any site of the body by physicians in the hospital. The cases were confirmed by at least one positive culture of one of the eight selected bacterial pathogens resistant to at least one of the antibiotics. Resistance was defined as the results of antimicrobial susceptibility testing (AST) showing resistant to specific antibiotic described in Table 3.

A non-AMR case was defined as either an outpatient or a patient admitted to a department in Chomthong hospital between 1st April 2017 and 31st October 2017 who was diagnosed with a bacterial infection of any site of the body by physicians in the hospital. The non-cases were confirmed by at least one positive culture of one of the eight selected microorganisms for which there was no evidence of resistance to the antibiotics. Non-resistance was defined as the results of antimicrobial susceptibility testing (AST) showing non-resistance (susceptible or intermediate) to specific antibiotic described in Table 3.

For AMR cases and non-AMR cases only the first admission for the study period was included. However, to reduce misclassification bias, when a patient had one or more subsequent admissions, they were classified as an AMR case, when a resistant bacteria was cultured.

7.3.2 Data extraction

A data frame used for the analyses in the study II was also extracted from the single combined spreadsheet. All records from Chomthong hospital were selected into the data frame.

7.3.3 Data analysis

For the analysis of epidemiological characteristics of patients infected with one of the selected pathogens of study II, we calculated proportions to describe the distribution of categorical variables including gender, age group, race, occupation, underlying disease status, department of admission, department type, ward type, type of organism, and dead status in AMR and non-AMR cases. The results were presented as number and percentage. The proportion of resistance to antibiotics for each selected pathogen was also computed. Also, the percentage of multidrug-resistance to antibiotics for each selected pathogen was calculated. The definition of multidrug-resistance (MDR) was resistance to ≥ 1 antibiotic agent in ≥ 3 antibiotic classes which was described in the study of “Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance” by Magiorakos et al. (2012). Calculation of mean with standard deviation (SD) was performed to describe the continuous variable such as age. Median with interquartile range (IQR) was calculated to summarise the continuous variables which were skewed.

For the analysis of risk factors associated with AMR infection and death in study II, the outcome variables we used in our analyses were AMR status and dead status. Student’s t-test was

performed to determine the differences between the mean of variables. Levene's test was used to examine the homogeneity of the variances before the t-test was done. The threshold for statistical significance was a p-value < 0.05. Univariate odds ratios and 95%CIs were calculated to describe the measure of association between categorical variables. If there were over 20% of the cells which had an expected value less than or equal to 5, Fisher's exact test was used to determine 95%CIs. The 95% CIs of odds ratio which did not include 1 were considered to be statistically significant. Also, exposure variables showing p-value < 0.1 were considered to be fitted in logistic regression models. Backward stepwise algorithm, "step" function with backward direction in R, was carried out to select exposure variables for the final model. The likelihood ratio test (LRT) in "anova" function in R was done to compare the difference between fitted models before and after each backward step. If there was no difference (LRT's p-value > 0.05) between the models, the model after the backward step was chosen to be the final model. Coefficients of determination, and areas under ROC curve of the logistic regression models were also computed using "lrm" function of "rms" package in R. We excluded the cases for which the outcome was missing before model fitting.

8. Chapter III: Results

8.1 Study I: Descriptive epidemiology of sepsis patients infected with AMR bacteria in 3 sentinel surveillance hospitals in Chiang Mai, Thailand, April 2017 – January 2018.

Over the study period 148 unique sepsis patients infected with a pathogen with AMR from the 3 hospitals in Chiang Mai occurred and were reported to the BoE. The overall prevalence of sepsis with AMR in Chiang Mai province reported to BoE during April 2017 – January 2018 was 9.2 cases per 100,000 population (148/1,610,419). There were 106 sepsis patients infected with a pathogen with AMR reported from Nakornping hospital for 10 months which the incidence in the hospital was 2.5 cases per 1,000 patients (106/42,480). There were 36 sepsis patients infected with a pathogen with AMR reported from Chomthong for 7 months which the incidence in the hospital was 3.3 cases per 1,000 patients (36/10,832). Also, there were 6 sepsis patients infected with a pathogen with AMR reported from Sanpatong hospital for 4 months which the incidence in the hospital was 1.5 cases per 1,000 patients (6/4,092). Demographics of patients are shown in Table 7. The percentage of female patients overall was 51.3%. In Nakornping, Chomthong, and Sanpatong hospitals, there were 51.9%, 47%, and 67% females respectively. The median age of the patients in the three hospitals ranged from 64.0 to 68.0 years. The proportion of cases in the age group 61 – 80 years was the highest in Nakornping, Chomthong, and Sanpatong hospitals accounting for 49.1%, 36%, and 50% respectively. Over 95% of the patients were Thai. There were 87.7% (93/106) of the patients with sepsis AMR admitted to Nakornping hospital not living in the same district where the hospital is located whereas 56% (20/36) of the patients with sepsis AMR admitted to Chomthong hospital lived in the same district where the hospital is located and 100% (6/6) of the patients with sepsis AMR admitted to Sanpatong hospital lived in the same district where the hospital is located. For the occupation of the patients, the largest category was labourer/freelance – 25.5% of Nakornping and 28% of Chomthong. However, the occupation of many cases was unknown e.g 48.1% of the patients' occupations in Nakornping were unknown. More than half of the underlying disease status of the patients in Nakornping, Chomthong, and Sanpatong hospitals were missing accounting for 50% (53/106), 78% (28/36), and 50% (3/6) respectively. However, 84.9% (45/53) of the Nakornping hospital's patients whose underlying disease status was recorded had at least one underlying disease. There were 18.9% (10/53) of sepsis patients infected with a pathogen with AMR in Nakornping having chronic kidney disease followed by diabetes mellitus (17.0%) and cancers (15.1%).

Table 7. Demographic characteristics of sepsis patients infected with a pathogen with AMR in 3 sentinel hospitals in Chiang Mai, April 2017 – January 2018.

Variables	Nakornping (n=106)	Chomthong (n=36)	Sanpatong (n=6)
Gender			
Female	55 (51.9%)	17 (47%)	4 (67%)
Male	51 (48.1%)	19 (53%)	2 (33%)
Median of Age (IQR)	64.0 (54.3 – 76.6)	64.0 (53.3 – 79.3)	68 (60.0 – 77.5)
Age group			
0-20 years	6 (5.7%)	1 (3%)	0
21-40 years	3 (2.8%)	2 (6%)	1 (16.7%)
41-60 years	33 (31.1%)	12 (33%)	1 (16.7%)
61-80 years	52 (49.1%)	13 (36%)	3 (50.0%)
Over 80 years	12 (11.3%)	8 (22%)	1 (16.7%)
Race			
Thai	101 (95.3%)	36 (100%)	6 (100%)
Non-Thai	5 (4.7%)	0	0
Address (living in the same district where the hospital is located)			
Yes	13 (12.3%)	20 (56%)	6 (100%)
No	93 (87.7%)	16 (44%)	0
Occupation			
Housekeeper	3 (2.8%)	0	0
Agriculture	4 (3.8%)	9 (25%)	0
Labourer/freelance	27 (25.5%)	10 (28%)	2 (33%)
Merchant/personal business	3 (2.8%)	1 (3%)	0
Government officer	1 (0.9%)	1 (3%)	0
Neonate/infant/pre-school age	3 (2.8%)	1 (3%)	0
Student	2 (1.9%)	0	1 (17%)
Unemployed/retired	11 (10.4%)	10 (28%)	3 (50%)
Unknown	51 (48.1%)	4 (11%)	0
Other	1 (0.9%)	0	0
Underlying disease			
Cancer	8 (15.1%)	3 (33%)	0
CKD	10 (18.9%)	0	1 (33%)
COPD	5 (9.4%)	0	1 (33%)
Cirrhosis and liver failure	7 (13.2%)	0	0
Diabetes mellitus	9 (17.0%)	1 (11%)	0
Hypertension	7 (13.2%)	1 (11%)	0
Cardiovascular disease	1 (1.9%)	0	0
Cerebrovascular disease	2 (3.8%)	0	0
HIV infection	4 (7.5%)	0	1 (33%)
Other diseases	7 (13.2%)	1 (11%)	0
None	8 (15.1%)	3 (33%)	0

IQR, interquartile range; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus

Hospitalisation data of the sepsis patients infected with a pathogen with AMR is shown in Table 8. In Nakornping hospital, the median length of hospitalisation (LOH) was 11 days with interquartile range from 6 to 20 days. While the length of hospitalisation of the sepsis patients infected with a pathogen with AMR from Chomthong and Sanpatong hospital could not be calculated due to information on admission date was missing. Overall, most of the patients recorded in the dataset were admitted to the inpatient department (IPD) which accounted for 96.2%, 94%, and 67% in Nakornping, Chomthong, and Sanpatong hospitals respectively. The Medicine department was the most common department that the patients were admitted both in Nakornping, Chomthong, and Sanpatong hospitals accounting for 66.0%, 72%, and 100% respectively. There was only one case, from Sanpatong hospital, receiving treatment as an OPD patient. About 40% (41/106) of Nakornping hospital's sepsis patients showing AMR had hospital-acquired infections (i.e. detected with the AMR organisms more than 48 hours after admission). For Chomthong hospital, 50% (10/20) of the sepsis AMR infections were hospital acquired, however, 44% (16/36) of the data of HAI from Chomthong hospital could not be calculated due to missing data of admission date. Approximately one third of the Sanpatong's sepsis patients showing resistance had a hospital-acquired infection. The predominant organism cultured from AMR sepsis patients in Nakornping, Chomthong, and Sanpatong hospitals was *E. coli* accounting for 48.1%, 81%, and 67% respectively. Additionally, *K. pneumoniae* and *A. baumannii* were commonly found in Nakornping hospital accounting for 19.8% and 17.9% respectively. In the 3 study hospitals, there were 34 deaths. Overall case fatality rate (CFR) for sepsis patients infected with a pathogen with AMR was 23% (34/148). In Nakornping hospital, 27.4% of the sepsis patients showing AMR died during their hospitalisation period whereas 17% of Sanpatong hospital's sepsis patients infected with a pathogen with AMR died. For Chomthong hospital, of the 22/36 (61%) sepsis patients infected with a pathogen with AMR for which dead status was available, 4/22 (18%) died.

Table 8. Hospitalisation data of sepsis patients infected with a pathogen with AMR in 3 sentinel hospitals in Chiang Mai, April 2017 – January 2018.

Variables	Nakornping (n=106)	Chomthong (n=36)	Sanpatong (n=6)
Median of LOH (IQR)	11.0 (6.0 – 20.0)	-	-
Admission type			
OPD	0	0	1 (17%)
IPD	102 (96.2%)	34 (94%)	4 (67%)
ICU	4 (3.8%)	2 (6%)	1 (17%)
Department type			
Medicine	70 (66.0%)	26 (72%)	6 (100%)
Surgery	32 (30.2%)	7 (19%)	0
Paediatrics	4 (3.8%)	1 (3%)	0
Orthopaedics	0	2 (6%)	0
Hospital-acquired			
Yes	41 (38.7%)	10 (50%)	2 (33%)
No	65 (61.3%)	10 (50%)	4 (67%)
Organism			
S. pneumoniae	0	1 (3%)	0
S. aureus	6 (5.7%)	0	1 (17%)
P. aeruginosa	5 (4.7%)	2 (6%)	0
K. pneumoniae	21 (19.8%)	3 (8%)	0
E. coli	51 (48.1%)	29 (81%)	4 (67%)
Enterococcus spp.	4 (3.7%)	0	0
A. baumannii	19 (17.9%)	1 (3%)	1 (17%)
Dead status			
Yes	29 (27.4%)	4 (18%)	1 (17%)
No	77 (72.6%)	18 (82%)	5 (83%)

LOH, length of hospitalisation; IQR, interquartile range; OPD, outpatient department; IPD, inpatient department; ICU, intensive care unit

Figure 6 illustrates the percentages of the sepsis patients infected with a pathogen with AMR infection associated with each bacteria in the 3 sentinel hospitals in Chiang Mai. The highest percentage of the organisms was *E. coli* accounting for approximately 56.8% (84/148). The percentages of *K. pneumoniae* and *A. baumannii* found in the sepsis patients were 16.2% (24/148) and 14.2% (21/148) respectively.

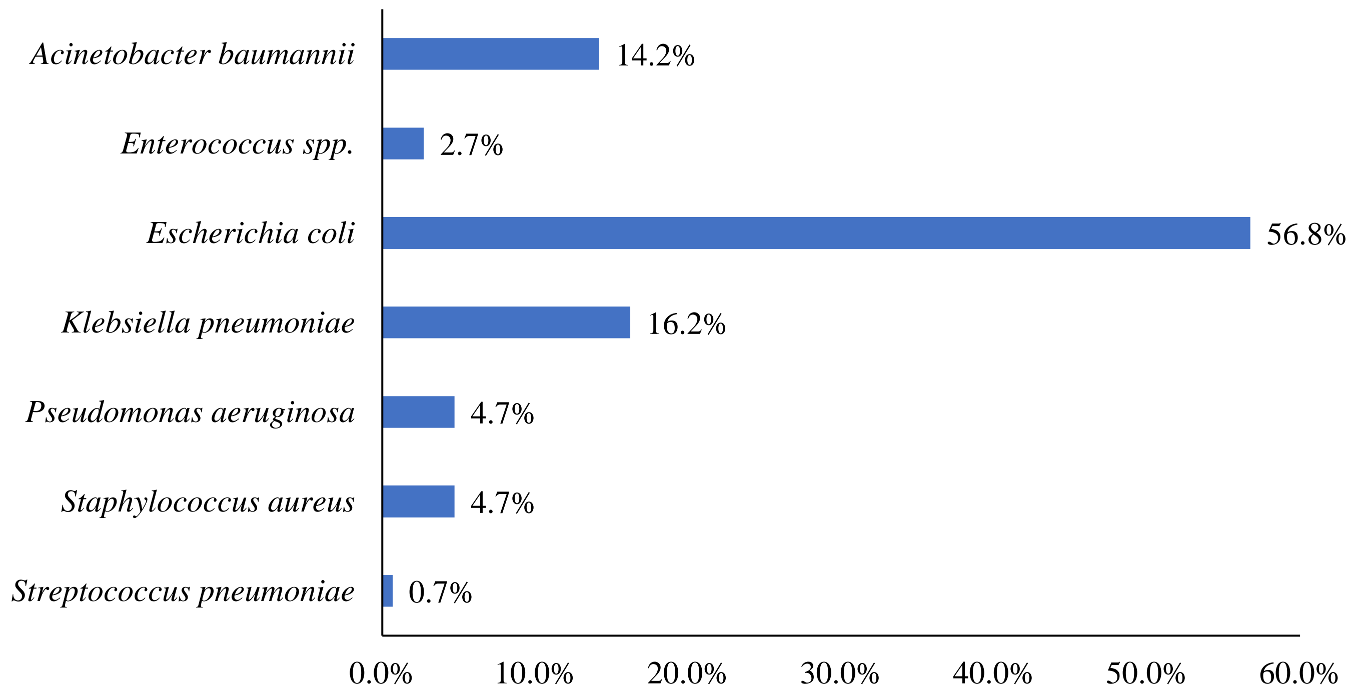

Figure 6. The percentages of sepsis patients infected with a pathogen with AMR by type of organism in 3 sentinel hospitals in Chiang Mai province, April 2017 – January 2018 (n = 148).

Figure 7 illustrates the percentages of the sepsis patients infected with a pathogen with AMR infection associated with each bacteria classified by HAI status in the 3 sentinel hospitals in Chiang Mai province. Among HAI group, the highest percentage of causative pathogent was *E. coli* accounting for 30% (16/53) following by *K. pneumoniae* and *A. baumannii* accounting for 26% and 23% respectively. On the other hand, *E. coli* was also the most common pathogen found in the non-HAI patients accounting for 67% (53/79) while the percentages of *K. pneumoniae* and *A. baumannii* were 13% and 11% respectively.

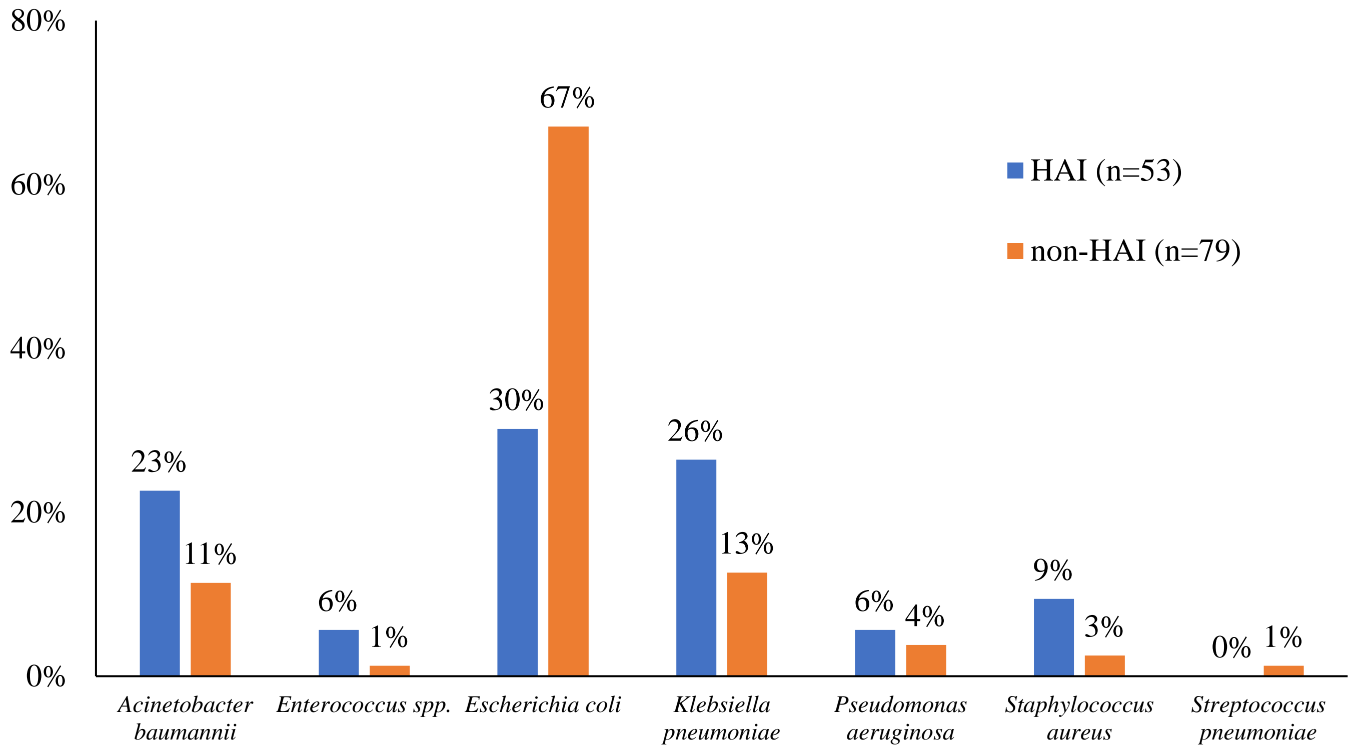

Figure 7. The percentages of sepsis patients infected with a pathogen with AMR by type of organisms and HAI status in 3 sentinel hospitals in Chiang Mai, April 2017 – January 2018.

Figure 8 shows a time series of the sepsis patients infected with a pathogen with AMR. The first case was reported to BOE through the AMR surveillance system in the 13th week of 2017 (April) from Chomthong hospital and the last case for this study was reported in the 4th week of 2018 (January) from Nakornping hospital. Approximately 33.8% (50/148) of the patients were reported from the 31st week (August) to the 40th week (September) of 2017. About 31% (11/36) of the Chomthong hospital's patients were reported in the first month of the study period and then there was about 1 patient per week reported to the BoE until the end of October 2017. For Nakornping hospital, 28.3% (30/106) of the patients were reported from the 31st week to the 36th week of 2017. Approximately 26.4% (28/106) of the Nakornping hospital's patients were found in the 22nd – 29th week of 2017 and 12.2% (13/106) of the patients were found in the 52nd week of 2017 – the 2nd week of 2018. For Sanpatong hospital, there were 6 patients reported to the BoE between the 15th week and the 28th week of 2017 (April – July).

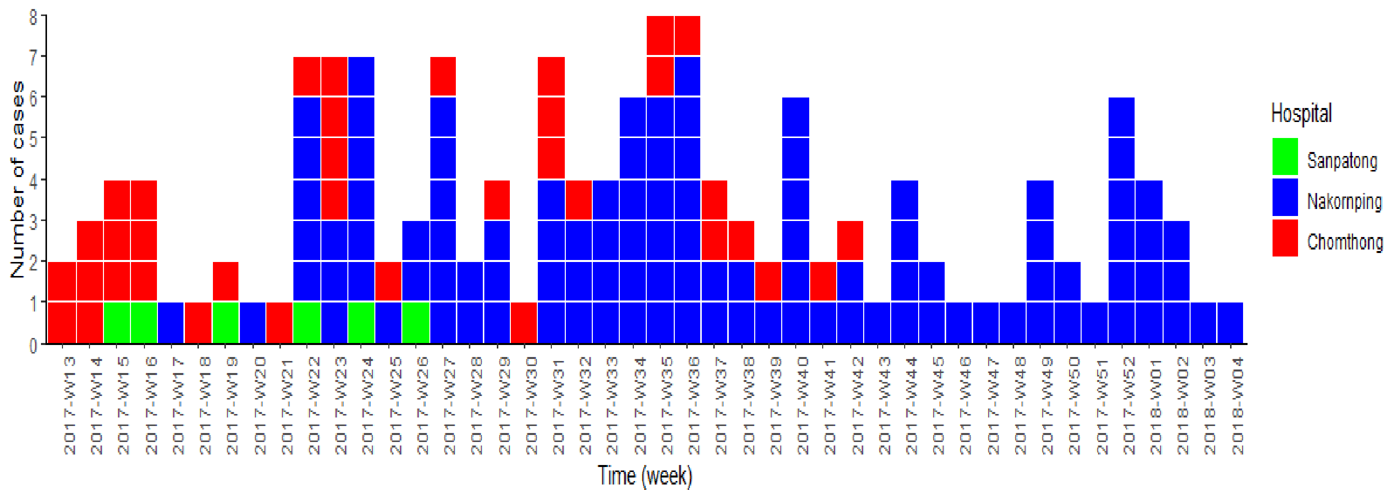

Figure 8. The number of sepsis patients infected with a pathogen with AMR by week of specimen collection in Chiang Mai, April 2017 – January 2018 (n = 148).

Figure 9 and Figure 10 illustrate the distribution of sepsis patients infected with a pathogen with AMR in Chiang Mai province by geographical area, across the 25 districts. It can be clearly seen that the 3 districts with the highest age-adjusted morbidity rates were Chomthong, Samoeng, and Mae Rim districts for which the age-adjusted morbidity rates were 28.4 (95%CI, 17.3 – 44.2), 21.7 (95%CI, 7.0 – 51.8), and 15.5 (95%CI, 8.3 – 26.6) cases per 100,000 population respectively. There was no sepsis AMR patient reported from Galyani Vadhana district. For other districts, the rates ranged from 2.2 to 10.2 cases per 100,000 population. There were 6 districts (24%) and 14 districts (56%) had the rates of 0.01 – 5.00 and 5.01 – 10.00 cases per 100,000 population respectively Only one district (4%), Chiang Dao, had the rate of 10.2 (95%CI, 3.7 – 23.1) cases per 100,000 population. For more detailed information on the age-adjusted rate and 95%CI in each district, the rates were shown in Table 20 in Appendix. Figure 2II3 also shows the location of Nakornping, Chomthong, and Sanpatong hospitals which were located in Mae Rim, Chom Thong, San Pa Tong districts respectively.

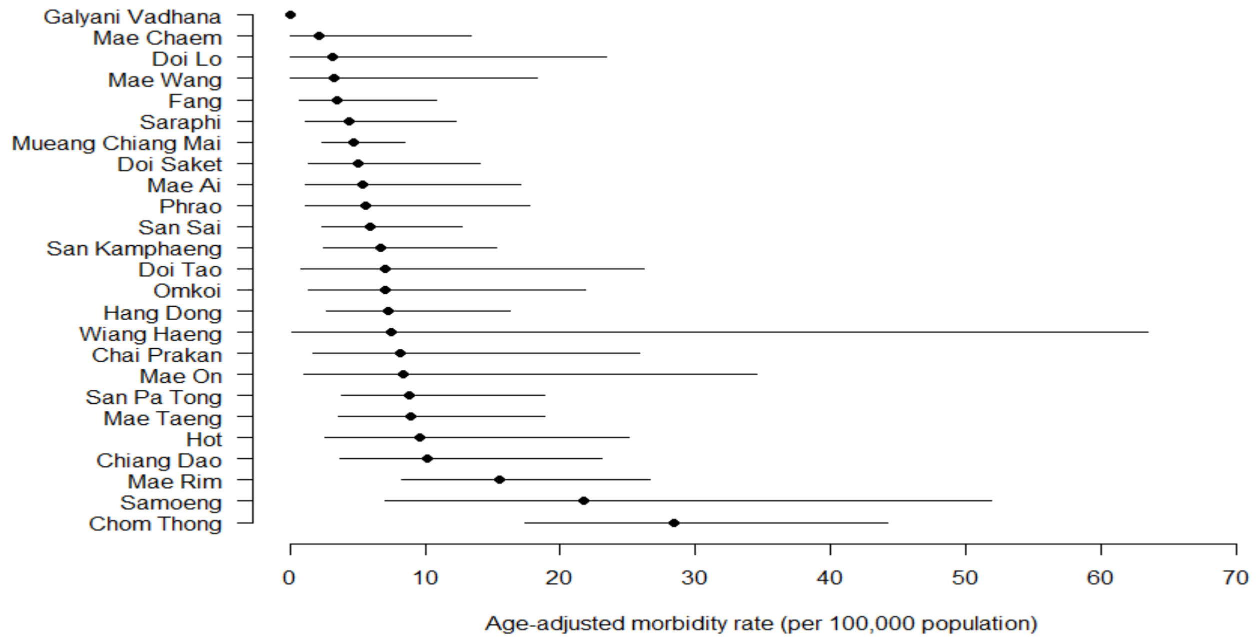

Figure 9. Age-adjusted morbidity rates and 95% confidence intervals of sepsis AMR by districts in Chiang Mai province (April 2017 – January 2018) for patients admitted to Nakornping, Chomthong, and Sanpatong hospitals.

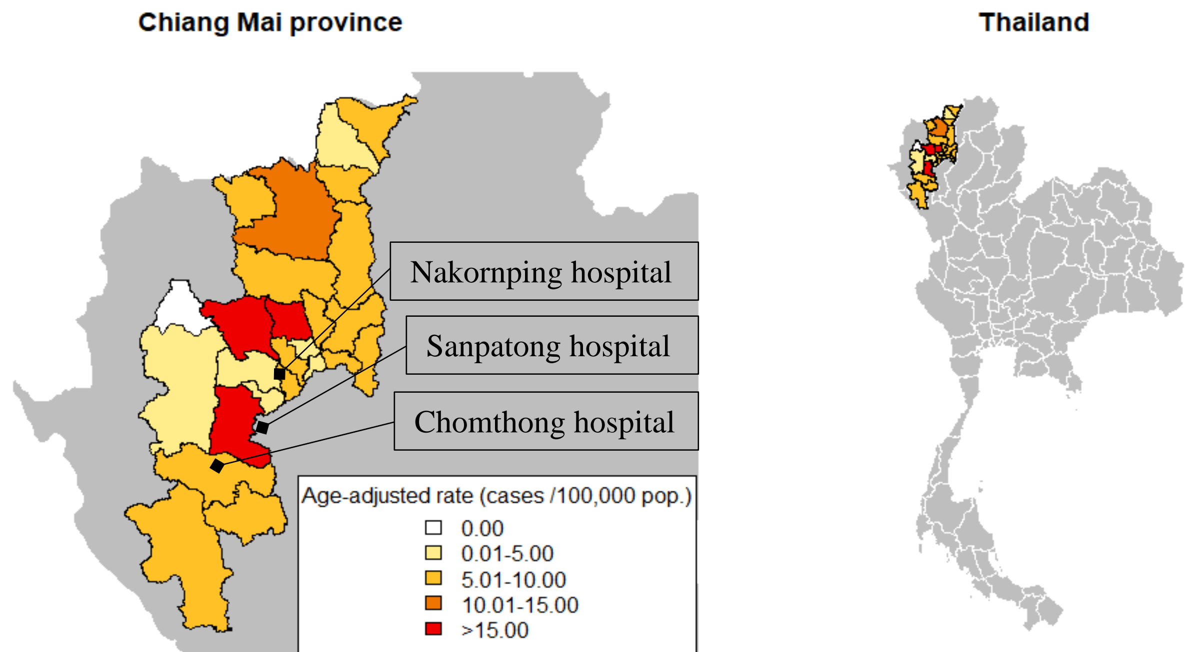

Figure 10. Geographical distribution of sepsis patients infected with a pathogen with AMR in Chiang Mai based on data from Nakornping, Chomthong, and Sanpatong hospitals, April 2017 – January 2018.

8.2 Study II: Cross-sectional analytic study of risk factors for infection with an AMR bacteria and death among infected patients with the eight selected pathogens in Chomthong hospital, Chiang Mai, Thailand, April – October 2017.

8.2.1 Analysis of epidemiological characteristics of patients infected with the eight selected pathogens

Table 9 reveals the demographics of the AMR cases and non-AMR cases reported from Chomthong hospital during the period April to October 2017. About 54.2% of the AMR cases and 51.6% of the non-AMR cases were male. The median age of the AMR cases (Median = 63.0, IQR 44.5 – 74.0 years) was higher than the median of age of the non-AMR cases (Median = 59.0, IQR 35.0 – 69.0 years). There were 42.4% of the cases and 37.3% of the non-cases aged 61-80 years. The vast majority of the AMR cases and non-AMR cases were Thai accounting for 98.5% and 98.4% respectively. Among the AMR cases, unemployed/retired status was the highest proportion (33.5%) of occupation following by labourer/freelance (24.6%) and agriculture (20.7%). Similarly, the occupational status with the highest proportion for the non-AMR cases was unemployed/retired (28.6%) following by labourer/freelance (25.4%) and agriculture (22.6%). About two-third of the AMR cases (65.5%) and non-AMR cases (64.7%) had no information on underlying disease recorded in the database of the surveillance programme. Approximately 58.6% (41/70) of the AMR cases and 44.9% (40/89) of the non-AMR cases had at least one underlying disease.

Table 9. Demographic data of patients infected with the eight selected pathogens* in Chomthong hospital, Chiang Mai, April – October 2017 (n=455).

Variables	AMR cases (n=203)	Non-AMR cases (n=252)
Gender		
Female	93 (45.8%)	122 (48.4%)
Male	110 (54.2%)	130 (51.6%)
Median of Age (IQR)	63.0 (44.5 – 74.0)	59.0 (35.0 – 69.0)
Age group		
0-20 years	26 (12.8%)	47 (18.7%)
21-40 years	21 (10.3%)	24 (9.5%)
41-60 years	43 (21.2%)	62 (24.6%)
61-80 years	86 (42.4%)	94 (37.3%)
Over 80 years	27 (13.3%)	25 (9.9%)
Race		
Thai	200 (98.5%)	248 (98.4%)
Non-Thai	3 (1.5%)	4 (1.6%)
Occupation		
Housekeeper	7 (3.4%)	3 (1.2%)
Agriculture	42 (20.7%)	57 (22.6%)
Labourer/freelance	50 (24.6%)	64 (25.4%)
Merchant/ personal business	5 (2.5%)	7 (2.8%)
Government officer	3 (1.5%)	3 (1.2%)
Neonate/infant/pre-school age	21 (10.3%)	33 (13.1%)
Student	3 (1.5%)	12 (4.8%)
Unemployed/retired	68 (33.5%)	72 (28.6%)
Unknown	4 (2.0%)	1 (0.4%)
Underlying disease		
Cancer	5 (7.1%)	2 (2.2%)
CKD	2 (2.9%)	2 (2.2%)
COPD	11 (15.7%)	10 (11.2%)
Cirrhosis and liver failure	0	0
Diabetes mellitus	7 (10.0%)	7 (7.9%)
Hypertension	5 (7.1%)	8 (9.0%)
Dyslipidemia	3 (4.3%)	5 (5.6%)
Cardiovascular disease and other heart diseases	6 (8.6%)	9 (10.1%)
HIV infection	1 (1.4%)	0
Other diseases	6 (8.6%)	2 (2.2%)
No	29 (41.4%)	49 (55.1%)

AMR, antimicrobial resistant; IQR, interquartile range; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

*Eight selected pathogens include *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus* spp., *Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, and Salmonella* spp.

Hospitalisation data of the AMR cases and non-AMR cases is shown in Table 10. About 63.5% (129/203) of the AMR cases and 60.7% (153/252) of the non-AMR cases were admitted to the Medicine department. Most of the AMR cases and non-AMR cases were IPD patients accounting for 90.6% and 92.0% respectively. Information on type of ward was missing for 26.1% (53/203) and 34.1% (86/252) of AMR cases and non-AMR cases respectively. About eighty-seven percent (130/150) of the AMR cases and 86.1% (143/166) of the non-AMR cases were admitted to common rooms. Information on admission date which was used for determining the status of hospital-acquired infection was missing for 26.6% (54/203) and 30.2% (76/252) of AMR cases and non-AMR cases respectively. There were 41.6% (62/149) of the AMR cases and 17.6% (31/176) of the non-AMR cases which met the criteria of hospital-acquired infection. Among the AMR cases, urinary tract was the most common site of infection (36.0%) following by respiratory tract (18.7%), wound/abscess (18.2%), and blood stream (17.7%). While, the most common site of infection among non-AMR cases was wound/abscess (29.4%) following by urinary tract (28.2%) and respiratory tract (22.6%). Approximately two-third (67.0%) of the organisms cultured from the AMR cases were *E. coli* but less than one-third (29.8%) of the organisms cultured from the non-AMR cases were *E. coli* and 28.6% of the organisms cultured from the non-AMR cases were *S. aureus*. There were 26.1% (53/203) of the AMR cases and 30.6% (77/252) of the non-AMR cases having missing data on dead status. Nine percent (14/150) of the AMR cases and 1.7% (3/175) of the non-AMR cases died during on their hospitalisation.

Table 10. Hospitalisation data of patients infected with the eight selected pathogens* in Chomthong hospital, Chiang Mai, April – October 2017 (n=455).

Variables	AMR cases (n=203)	Non-AMR cases (n=252)
Department type		
Medicine	129 (63.5%)	153 (60.7%)
Surgery	40 (19.7%)	44 (17.5%)
Paediatrics	23 (11.3%)	28 (11.1%)
Orthopaedics	7 (3.4%)	19 (7.5%)
OB-GYN	3 (1.5%)	2 (0.8%)
ENT	1 (0.5%)	5 (2.0%)
Psychiatry	0	1 (0.4%)
Admission type		
OPD	5 (2.5%)	10 (4.0%)
IPD	184 (90.6%)	232 (92.0%)
ICU	14 (6.9%)	10 (4.0%)
Ward type		
Common room	130 (86.7%)	143 (86.1%)
Private room	20 (13.3%)	23 (13.9%)
Hospital-acquired		
Yes	62 (41.6%)	31 (17.6%)
No	87 (58.4%)	145 (82.4%)
Site of infection		
Wound/abscess	37 (18.2%)	74 (29.4%)
Respiratory tract	38 (18.7%)	57 (22.6%)
Urinary tract	73 (36.0%)	71 (28.2%)
Gastrointestinal tract	14 (6.9%)	11 (4.4%)
Blood stream	36 (17.7%)	32 (12.7%)
Other	5 (2.5%)	7 (2.8%)
Organism		
S. pneumoniae	10 (4.9%)	1 (2.7%)
S. aureus	1 (0.5%)	72 (28.6%)
P. aeruginosa	14 (6.9%)	27 (10.7%)
K. pneuminiae	24 (11.8%)	43 (17.1%)
E. coli	136 (67.0%)	75 (29.8%)
Enterococcus spp.	3 (1.5%)	27 (10.7%)
A. baumannii	13 (6.4%)	8 (3.2%)
MDR organism		
Yes	130 (64.0%)	NA
No	73 (36.0%)	NA
Dead status		
Yes	14 (9.3%)	3 (1.7%)
No	136 (90.7%)	172 (98.3%)

AMR, antimicrobial resistant, OB-GYN, obstetrics and gynecology; ENT, ear nose and throat; OPD, outpatient department; IPD, inpatient department; ICU, intensive care unit; MDR, multidrug-resistance; NA, non-applicable.
*Eight selected pathogens include *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus* spp.*, Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, and Salmonella* spp.

Table 11 shows the percentages of isolates of the eight selected organisms resistant to antibiotics in Chomthong hospital. Over fifty percent of *A. baumannii* isolates were resistant to ceftazidime, ciprofloxacin, gentamycin, meropenem, norfloxacin, penicillin, cotrimoxazole, tetracycline, and piperacillin plus tazobactam. Penicillin was the antibiotic to which the most *A. baumannii* isolates were resistant (80%). Over fifty percent of *P. aeruginosa* isolates were resistant to norfloxacin, penicillin, and tetracycline. Norfloxacin was the antibiotic to which the most *P. aeruginosa* isolates were resistant (55%). Over fifty percent of *K. pneumoniae* isolates were resistant to penicillin (56%). Over fifty percent of *Enterococcus* spp. isolates were resistant to penicillin, cotrimoxazole, and tetracycline. Tetracycline was the antibiotic to which the most *Enterococcus* spp. isolates were resistant (73%). Over fifty percent of *S. aureus* isolates were resistant to penicillin (85%). Over fifty percent of *S. pneumoniae* isolates were resistant to norfloxacin (56%). Over fifty percent of *E. coli* isolates were resistant to penicillin and cotrimoxazole. Penicillin was the antibiotic to which the most *E. coli* isolates were resistant (61%). Both 2 *Salmonella* spp. isolates were resistant to ampicillin, gentamycin, norfloxacin, penicillin.

On the other hand, vancomycin was the only antibiotic that all the 8 selected organisms were susceptible to. Also, all *P. aeruginosa* isolates were susceptible to colistin, and ertapenem. All *Enterococcus* spp. isolates were susceptible to ertapenem. All *S. pneumoniae* isolates were susceptible to many antibiotics including amikacin, colistin, gentamycin, meropenem, cefoperazone plus sulbactam, piperacillin plus tazobactam, and ertapenem. In addition, all *E. coli* isolates were sensitive to meropenem, cefoperazone plus sulbactam, piperacillin plus tazobactam, and ertapenem. Also, *Salmonella* spp. isolates were susceptible to amikacin, amoxicillin plus clavulanic acid, ciprofloxacin, colistin, clindamycin, erythromycin, meropenem, cefoperazone plus sulbactam, cotrimoxazole, piperacillin plus tazobactam, and ertapenem.

Table 12 shows the percentages of isolates of the eight selected organisms resistant to antibiotic classes and the percentages of the organisms which were multidrug-resistant (MDR) in Chomthong hospital. Both 2 *Salmonella* spp. isolates were MDR. Approximately sixty-two percent (13/21) of *A. baumannii* isolates were MDR following by *E. coli*, *K. pneumoniae,* and *P. aeruginosa* accounting for 42.2% (89/211), 37% (25/67), and 32% (13/41) respectively. Whereas the percentage of *S. aureus* isolates which were MDR was 7% (5/73).

Table 11. Resistance prevalence to antibiotic agents of the eight selected pathogens in Chomthong hospital from all specimen types reported to BoE, April – October 2019.

Bacteria	% of isolates resistant to antibiotic agent										
	Amikacin	Amoxicillin plus Clavulanic acid	Ampicillin	Ceftazidime	Ciprofloxacin	Colistin	Ceftriaxone	Cefotaxime	Clindamycin	Erythromycin	Gentamycin
A. baumannii	47% (10/21)	19% (4/21)	32% (6/19)	57% (12/21)	52% (11/21)	5% (1/21)	43% (9/21)	48% (10/21)	15% (3/20)	15% (3/20)	52% (11/21)
P. aeruginosa	7% (3/41)	34% (14/41)	29% (10/35)	34% (14/41)	32% (13/41)	0% (0/41)	35% (14/40)	40% (16/40)	18% (7/40)	24% (10/41)	27% (11/41)
K. pneumoniae	4% (3/68)	21% (14/68)	33% (22/66)	24% (16/68)	12% (8/68)	2% (1/65)	32% (22/68)	32% (22/68)	8% (5/66)	18% (12/68)	10% (7/68)
***Enterococcus* spp.**	13% (4/30)	33% (10/30)	37% (11/30)	40% (12/30)	43% (13/30)	10% (3/30)	40% (12/30)	47% (14/30)	3% (1/30)	23% (7/30)	27% (8/30)
S. aureus	9% (6/70)	21% (15/73)	31% (21/67)	31% (22/70)	36% (25/70)	3% (2/67)	38% (28/73)	41% (30/73)	3% (2/73)	4% (3/73)	17% (12/70)
S. pneumoniae	0% (0/8)	33% (3/9)	44% (4/9)	25% (2/8)	33% (3/9)	0% (0/7)	44% (4/9)	50% (4/8)	25% (2/8)	30% (3/10)	0% (0/8)
E. coli	0.5% (1/211)	11.9% (25/211)	25.9% (50/193)	15.6% (33/211)	32.7% (69/211)	3.6% (7/194)	32.4% (68/210)	33.2% (70/211)	7.1% (14/196)	24.0% (49/204)	26.5% (56/211)
***Salmonella* spp.**	0% (0/1)	0% (0/2)	100% (1/1)	50% (1/2)	0% (0/2)	0% (0/2)	50% (1/2)	50% (1/2)	0% (0/2)	0% (0/2)	100% (1/1)

Table 11. Resistance prevalence to antibiotic agents of the eight selected pathogens in Chomthong hospital from all specimen type reported to BoE, April – October 2019 (cont.).

Bacteria	% of isolates resistant to antibiotic agent									
	Meropenem	Norfloxacin	Oxacillin	Penicillin	Cefoperazone plus Sulbactam	Cotrimoxazole	Tetracycline	Piperacillin plus Tazobactam	Vancomycin	Ertapenem
A. baumannii	57% (12/21)	52% (11/21)	25% (5/20)	80% (16/20)	48% (10/21)	62% (13/21)	60% (12/20)	57% (12/21)	0% (0/20)	10% (2/21)
P. aeruginosa	32% (13/41)	55% (21/38)	35% (14/40)	55% (22/40)	22% (9/41)	83% (34/41)	54% (22/41)	10% (4/41)	0% (0/41)	0% (0/40)
K. pneumoniae	6% (4/68)	42% (27/65)	17% (11/66)	56% (36/64)	2% (1/68)	38% (26/68)	40% (27/67)	7% (5/68)	0% (0/68)	3% (2/68)
***Enterococcus* spp.**	17% (5/30)	47% (14/30)	17% (5/30)	63% (17/27)	17% (5/30)	60% (18/30)	73% (22/30)	10% (3/30)	0% (0/30)	0% (0/30)
S. aureus	16% (11/70)	43% (31/72)	1% (1/73)	85% (62/73)	13% (9/70)	6% (4/73)	40% (29/73)	14% (10/70)	0% (0/73)	1% (1/71)
S. pneumoniae	0% (0/8)	56% (5/9)	13% (1/8)	20% (1/5)	0% (0/8)	30% (3/10)	20% (2/10)	0% (0/8)	0% (0/10)	0% (0/8)
E. coli	0% (0/211)	47.6% (97/204)	19.4% (38/196)	61.2% (115/188)	0% (0/211)	52.6% (111/211)	47.1% (96/204)	0% (0/211)	0% (0/204)	0% (0/211)
***Salmonella* spp.**	0% (0/2)	100% (2/2)	50% (1/2)	100% (2/2)	0% (0/2)	0% (0/2)	50% (1/2)	0% (0/2)	0% (0/2)	0% (0/2)

Table 12. Resistance prevalence to antibiotic classes and MDR of the eight selected pathogens in Chomthong hospital from all specimen type reported to BoE, April – October 2019.

Bacteria	% of isolates resistant to antibiotic class											
	Aminoglycosides	Antipseudomonal penicillins + β-lactamase inhibitors	Carbapenems	Extended-spectrum cepharosporins	Fluoroquinolones	Glycopeptides	Macrolides	Pennicillins	Pennicillins + β-lactamase inhibitors	Polymyxins	Tetracyclines	MDR†
A. baumannii	52% (11/21)	57% (12/21)	62% (13/21)	86% (18/21)	81% (17/21)	0% (0/20)	15% (3/20)	95% (20/21)	19% (4/21)	5% (1/21)	60% (12/20)	**62% (13/21)**
P. aeruginosa	27% (11/41)	10% (4/41)	32% (13/41)	59% (24/41)	63% (26/41)	0% (0/41)	24% (10/41)	76% (30/41)	34% (14/41)	0% (0/41)	54% (22/41)	**32% (13/41)**
K. pneumoniae	12 % (8/67)	8% (5/67)	6% (4/67)	34% (23/67)	45% (30/67)	0% (0/67)	15% (10/67)	76% (51/67)	21% (14/67)	2% (1/65)	40% (27/67)	**37% (25/67)**
Enterococcus spp.	33% (10/30)	10% (3/30)	17% (5/30)	63% (19/30)	47% (14/30)	0% (0/30)	17% (5/30)	83% (25/30)	33% (10/30)	10% (3/30)	73% (22/30)	**17% (5/30)**
S. aureus	19% (13/70)	14% (10/70)	15% (11/73)	52% (38/73)	56% (41/73)	0% (0/73)	3% (2/73)	90% (66/73)	21% (15/73)	3% (2/67)	40% (29/73)	**7% (5/73)**
S. pneumoniae	0% (0/8)	0% (0/8)	0% (0/8)	44% (4/9)	67% (6/9)	0% (0/10)	30% (3/10)	60% (6/10)	30% (3/10)	0% (0/7)	20% (2/10)	**20% (2/10)**
E. coli	26.5% (56/211)	0% (0/210)	0% (0/211)	33.2% (70/211)	54.5% (115/211)	0% (0/204)	23.4% (48/205)	71.6% (151/211)	11.8% (25/211)	3.6% (7/194)	47.1% (96/204)	**42.2% (89/211)**
Salmonella spp.	100% (1/1)	0% (0/2)	0% (0/2)	50% (1/2)	100% (2/2)	0% (0/2)	0% (0/2)	100% (2/2)	0% (0/2)	0% (0/2)	50% (1/2)	**100% (2/2)**

MDR, Multidrug-resistance.

†The definition of MDR according to Magiorakos et al. (2012) was applied for the study.

8.2.2 Analysis of risk factors associated with AMR infection

Table 13 reveals the results of univariate analysis between AMR status and potential risk factors such as gender, age, race, occupation, underlying disease, type of admission, type of ward, type of department, HAI, site of infection, and type of organism. The results suggest that HAI, site of infection, and organism (*E. coli*) were associated with infection with AMR bacteria with statistical significance (p-value < 0.05) Specifically, the odds of an AMR infection among the HAI cases was 3.22 times the odds of an AMR infection among the non-HAI cases (Crude OR 3.22, 95%CI 1.94 – 5.34). The crude OR of an AMR infection among the urinary tract infection, gastrointestinal tract infection, and blood stream infection groups were 2.06 (95%CI 1.23 – 3.43), 2.55 (95%CI 1.05 – 6.15), and 2.25 (95%CI 1.21 – 4.18) when compared with wound/abscess group respectively. Additionally, *E. coli* infections were associated with a higher risk of AMR when compared with other organisms including *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus* spp.*, Staphylococcus aureus, Streptococcus pneumoniae, and Salmonella* spp. (OR = 4.79, 95%CI 3.21 – 7.13).

The exposure variables with a p-value between 0.05 and 0.1 were considered to be fitted in the multivariate analysis as potential confounders, these included age in years and underlying disease. The mean of age with SD among the AMR cases (51.05 ± 25.18 years) was slightly lower than the mean of age with SD among the non-cases (55.73 ± 26.62 years) (p-value = 0.06). The odds of an AMR infection among the patients having any underlying disease was 1.73 times higher than those who did not have any underlying disease; however, it was not statistically significant (OR 1.73, 95%CI 0.92 – 3.26, p-value = 0.09). Other exposure variables including gender, race, occupation, department type, ward type, were not statistically significant in the univariate analysis.

Table 13. Univariate analysis showing the association between AMR status and potential risk factors.

Variables	AMR cases (n = 203)	Non-AMR cases (n = 252)	Crude OR (95% CI)	*p*-value
Gender				
Male	110/203 (54.2%)	130/252 (51.6%)	1.11 (0.77 – 1.61)	0.58
Female	93/203 (45.8%)	122/252 (48.4%)	Reference	
Age ± SD (years)	51.05 ± 25.18	55.73 ± 26.62	1.01 (1.00 – 1.01)[†]	0.06
Age group				
0 – 20 years	26/203 (12.8%)	47/252 (18.7%)	Reference	0.30
21 – 40 years	21/203 (10.3%)	24/252 (9.5%)	1.58 (0.69 – 3.60)	
41 – 60 years	43/203 (21.2%)	62/252 (24.6%)	1.25 (0.65 – 2.44)	
61 – 80 years	86/203 (42.4%)	94/252 (37.3%)	1.65 (0.91 – 3.03)	
Over 80 years	27/203 (13.3%)	25/252 (9.9%)	1.94 (0.89 – 4.29)	
Race				
Thai	200/203 (98.5%)	248/252 (98.4%)	1.08 (0.18 – 7.42)[‡]	0.93
Non-Thai	3/203 (1.5%)	4/252(1.6%)	Reference	
Occupation				
Agriculture	42/203 (20.7%)	57/252 (22.6%)	0.89 (0.57 – 1.40)	0.62
Others	161/203 (79.3%)	195/252 (77.4%)	Reference	
Underlying disease				
Yes	41/70 (58.6%)	40/89 (44.9%)	1.73 (0.92 – 3.26)	0.09
No	29/70 (41.4%)	49/89 (55.1%)	Reference	
Admission type				
IPD and ICU	198/203 (97.5%)	242/252 (96.0%)	1.63 (0.55 – 4.87)	0.37
OPD	5/203 (2.5%)	10/252 (4.0%)	Reference	
Private room				
Yes	20/150 (13.3%)	23/166 (13.9%)	0.96 (0.50 – 1.82)	0.89
No	130/150 (86.7%)	143/166 (86.1%)	Reference	
Department				
Medicine	129/203 (63.5%)	153/252 (60.7%)	Reference	0.24
Surgery	40/203 (19.7%)	44/252 (17.5%)	1.08 (0.64 – 1.81)	
Paediatric	23/203 (11.3%)	28/252 (11.1%)	0.97 (0.51 – 1.85)	
Other	11/203 (5.4%)	27/252 (10.7%)	0.48 (0.21 – 1.06)	
HAI				
Yes	62/152 (40.8%)	31/176 (17.6%)	3.22 (1.94 – 5.34)	<0.001
No	90/152 (59.2%)	145/176 (82.4%)	Reference	
Site of infection				
Wound/abscess	37/203 (18.2%)	74/252 (29.4%)	Reference	0.04
Respiratory tract	38/203 (18.7%)	57/252 (22.6%)	1.33 (0.75 – 2.36)	
Urinary tract	73/203 (36.0%)	71/252 (28.2%)	2.06 (1.23 – 3.43)	
GI tract	14/203 (6.9%)	11/252 (4.4%)	2.55 (1.05 – 6.15)	
Blood stream	36/203 (17.7%)	32/252 (12.7%)	2.25 (1.21 – 4.18)	
Other	5/203 (2.5%)	7/252 (2.8%)	1.43 (0.42 – 4.81)	
Organism				
E. coli	136/203 (67.0%)	75/252 (29.8%)	4.79 (3.21 – 7.13)	<0.001
Other organisms[§]	67/203 (33.0%)	177/252 (70.2%)	Reference	

OR, odds ratio; CI, confidence interval; SD, standard deviation; ICU, intensive care unit; HAI, hospital-acquired infection; GI, gastrointestinal.
[†]Logistic regression model was used to determine OR of Age in years
[‡]Fisher's exact tests were performed to determine 95%CI
[§]Other organisms include *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus* spp., *Staphylococcus aureus, Streptococcus pneumoniae, and Salmonella* spp.

Table 14 demonstrates coefficients of determination (r^2), and areas under ROC curve of the logistic regression models. In this multivariate analysis, the model no.1 included exposure variables with *p*-value less than 0.1 including age, underlying disease, hospital-acquired infection, site of infection, and *E. coli* infection. Coefficients of determination (r^2) of the model no.1 was 0.380 meaning 38% of the variability observed in the outcome variable was explained by the model no.1 and areas under ROC curve of model no.1 was 0.812 meaning the model no.1 had good measure of separability with 81.2%. The model no.2 composed of exposure variables suggested from backward stepwise algorithm including underlying disease, hospital-acquired infection, and *E. coli* infection. Coefficients of determination (r^2) of the model no.2 was 0.362 meaning 36.2% of the variability observed in the outcome variable was explained by the model no.2 and areas under ROC curve of model no.2 was 0.797 meaning the model no.2 had good measure of separability with 79.7%. There was no difference between model no.1 and model no.2 according to likelihood ratio test's *p*-value = 0.8231. Thus, the model after backward step, which was the model no.2, was chosen to be a final model for multivariate analysis.

Table 14. Comparison of logistic regression models which AMR status as the outcome.

No.	Model	r^2	Area under ROC curve	*p*-value*
1	$AMR = \beta_0 + \beta_1 Age + \beta_2 UD + \beta_3 HAI + \beta_4 SoI + \beta_5 Ecoli$	0.380	0.812	0.8231
2	$AMR = \beta_0 + \beta_1 UD + \beta_2 HAI + \beta_3 Ecoli$	0.362	0.797	

r^2, coefficient of determination; ROC, Receiver operating characteristic; AMR, antimicrobial resistance; UD, underlying disease; HAI, hospital-acquired infection; SoI, site of infection; Ecoli, *E. coli* infection.
*Likelihood ratio test's *p*-value

Table 15 shows the results of multivariate analysis which AMR status was a dependent variable. Underlying disease, HAI, and *E. coli* infection were statistically significant risk factors for having AMR infection when adjusted with gender, age, occupation, and type of department. The adjusted odds of having AMR among the patients having underlying disease was 2.66 times higher than the odds of getting AMR among the patients having underlying disease after adjusted with HAI, and *E. coli* infection (adjusted OR 2.66, 95%CI 1.13 – 6.25). The odds of getting AMR among the HAI patients was 4.39 times higher than the odds of getting AMR among the non-HAI patients after adjusted with underlying disease, and *E. coli* infection (adjusted OR 4.39, 95%CI 1.84 – 10.48). The odds of getting AMR among patients with an *E. coli* infection was 10.69 times higher than the odds of getting AMR among patients infected with other organisms including *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus* spp., *Staphylococcus aureus, Streptococcus pneumoniae, and Salmonella* spp. after adjusted with underlying disease, and HAI (adjusted OR 10.69, 95%CI 4.47 – 25.55).

Table 15. Multivariate analysis showing the association between AMR status and potential risk factors.

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)
Underlying disease – Yes	1.73 (0.92 – 3.26)	2.66 (1.13 – 6.25)
HAI – Yes	3.22 (1.94 – 5.34)	4.39 (1.84 – 10.48)
E. coli infection – Yes	4.79 (3.21 – 7.13)	10.69 (4.47 – 25.55)

HAI, hospital-acquired infection; OR, odds ratio; CI, confidence interval.

8.2.3 Analysis of risk factors associated with death

Table 16 reveals the results of univariate analysis between dead status and potential risk factors such as AMR infection, HAI, gender, age, race, occupation, underlying disease, type of admission, type of ward, type of department, and *E. coli* infection. Hospital-acquired infection, sepsis, AMR infection and MDR infection were associated with dead status of the patients. Specifically, the odds of death among patients with a HAI was statistically significant 5.90 times higher than the odds of death among patients who did not get HAI (Crude OR 3.87, 95%CI 1.43 – 10.51). The odds of death among sepsis patients was 4.25 times higher than the odds of death among non-sepsis patients (Crude OR 4.25, 95%CI 1.48 – 12.22). The odds of death among patients with an AMR infection was 5.90 times higher than the odds of death among patients who had an infection with non-resistant bacteria (Crude OR 5.90, 95%CI 1.66 – 20.95). Also, the odds of death among patients with an MDR infection was 4.38 times higher than the odds of death among patients who had an infection with non-MDR bacteria (Crude OR 4.38, 95%CI 1.50 – 12.76). Whereas gender, age, race, occupation, underlying disease, type of admission, type of ward, type of department, and *E. coli* infection were not statistically associated with dead status of the patient (p-value > 0.05).

Table 16.Univariate analysis showing the association between dead status and potential risk factors.

Variables	Dead (n = 17)	Alive (n = 308)	Crude OR (95% CI)	*p*-value
Gender				
Male	10/17 (59%)	167/308 (54.2%)	1.21 (0.45 – 3.25)	0.71
Female	7/17 (41%)	141/308 (45.8%)	Reference	
Age ± SD (years)	58.59 ± 21.35	49.44 ± 27.78	1.01 (0.99 – 1.04)†	0.19
Age group				
0 – 20 years	1/17 (6%)	65/308 (21.1%)	Reference	0.49
21 – 40 years	3/17 (18%)	34/308 (11.0%)	5.64 (0.43 – 305.05) ‡	
41 – 60 years	3/17 (18%)	60/308 (19.5%)	3.22 (0.25 – 173.03) ‡	
61 – 80 years	9/17 (53%)	121/308 (39.3%)	4.81 (0.64 – 214.92)‡	
Over 80 years	1/17 (6%)	28/308 (9.1%)	2.30 (0.03 – 184.69)‡	
Race				
Thai	16/17 (94%)	304/308 (98.7%)	0.21 (0.02 – 11.01)‡	0.14
Non-Thai	1/17 (6%)	4/308 (1.3%)	Reference	
Occupation				
Agriculture	1/17 (6%)	69/308 (22.4%)	0.22 (0.01 – 1.45)‡	0.11
Others	16/17 (94%)	239/308 (77.6%)	Reference	
Underlying disease				
Yes	6/8 (75%)	75/151 (49.7%)	3.04 (0.52 – 31.52)‡	0.16
No	2/8 (25%)	76/151 (50.3%)	Reference	
Admission type				
IPD and ICU	17/17 (100%)	295/308 (95.8%)	∞ (0.16 – ∞)‡	0.39
OPD	0/17 (0%)	13/308 (4.2%)	Reference	
Private room				
Yes	1/17 (6%)	42/295 (14.2%)	0.38 (0.01 – 2.56)‡	0.33
No	16/17 (94%)	253/295 (85.8%)	Reference	
Department				
Medicine	12/17 (71%)	149/308 (48.4%)	Reference	0.21
Surgery	4/17 (24%)	77/308 (25.0%)	0.65 (0.15 – 2.22)‡	
Paediatric	1/17 (6%)	46/308 (14.9%)	0.27 (0.01 – 1.93)‡	
Other	0/17 (0%)	36/308 (11.7%)	0 (0 – 1.58)‡	
HAI				
Yes	10/17 (59%)	83/308 (27.0%)	3.87 (1.43 – 10.51)	0.004
No	7/17 (41%)	225/308 (73.0%)	Reference	
Sepsis				
Yes	6/17 (35%)	35/308 (11.4%)	4.25 (1.48 – 12.22)	0.01
No	11/17 (65%)	273/308 (88.6%)	Reference	
Organism				
E. coli	6/17 (35%)	126/308 (40.9%)	0.79 (0.28 – 2.19)	0.65
Other organisms§	11/17 (65%)	182/308 (59.1%)	Reference	
AMR infection				
Yes	14/17 (82%)	136/308 (44.2%)	5.90 (1.66 – 20.95)	0.002
No	3/17 (18%)	172/308 (55.8%)	Reference	
MDR organism				
Yes	12/17 (71%)	109/308 (35.4%)	4.38 (1.50 – 12.76)	0.007
No	5/17 (29%)	199/308 (64.6%)	Reference	

AMR, antimicrobial resistance; HAI, hospital-acquired infection; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; MDR, multidrug-resistance.

† Logistic regression model was used to determine OR of Age in years

‡Fisher's exact tests were performed to determine 95%CI

§Other organisms include *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus* spp., *Staphylococcus aureus, Streptococcus pneumoniae, and Salmonella* spp.

For multivariate analysis which dead status was an outcome, the model no.1 included exposure variables w *p*-value less than 0.1 including AMR infection, HAI, sepsis, and infection with MDR organism. Coefficients of determination (r^2) of the model no.1 was 0.185 meaning 18.5% of the variability observed in the outcome variable was explained by the model no.1 and areas under ROC curve of model no.1 was 0.780 meaning the model no.1 had good measure of separability with 78%. The model no.2 composed of exposure variables suggested from backward stepwise algorithm including HAI, sepsis, and infection with MDR organism. Coefficients of determination (r^2) of the model no.2 was 0.174 meaning 17.4% of the variability observed in the outcome variable was explained by the model no.2 and areas under ROC curve of model no.2 was 0.761 meaning the model no.2 had good measure of separability with 76.1%. There was no difference between model no.1 and model no.2 according to likelihood ratio test's *p*-value = 0.2511. Thus, the model after backward step, which was the model no.2, was chosen to be a final model for multivariate analysis.

Table 17.Comparison of logistic regression models for factors associated with dead status of patients.

No.	Models	r^2	Area under ROC curve	*p*-value*
1	Dead = $\beta_0 + \beta_1$HAI + β_2Sepsis + β_3AMR + β_4MDR	0.185	0.780	0.2511
2	Dead = $\beta_0 + \beta_1$HAI + β_2Sepsis + β_3MDR	0.174	0.761	

r^2, coefficient of determination; ROC, Receiver operating characteristic; HAI, hospital-acquired infection; AMR, antimicrobial resistance; MDR, multidrug-resistance.
*Likelihood ratio test's *p*-value.

Table 18 shows the results of multivariate analysis which dead status was a dependent variable. Hospital-acquired infection, sepsis, and infection with MDR organism were statistically significant risk factor for death of the patients. Specifically, having HAI was a risk factor for death when adjusted with sepsis, and infection with MDR organism (adjusted OR 4.58, 95%CI 1.25 – 16.78). The odds of death among the sepsis patients was 4.62 times higher than the odds of death among the non-sepsis after adjusting for HAI, and infection with an MDR organism (adjusted OR 4.62, 95%CI 1.51 – 14.11). The odds of death among the patients infected with an MDR organism was 3.95 times higher than the odds of death among the patients infected with non-MDR organism after adjusted with HAI, and sepsis (adjusted OR 3.95, 95%CI 1.30 – 12.00).

Table 18. Multivariate analysis showing the association between dead status and potential risk factors.

Variables	Crude OR (95% CI)	Adjusted OR (95%CI)
HAI – Yes	3.87 (1.43 – 10.51)	3.05 (1.08 – 8.65)
Sepsis – Yes	4.25 (1.48 – 12.22)	4.62 (1.51 – 14.11)
MDR – Yes	4.38 (1.50 – 12.76)	3.95 (1.30 – 12.00)

AMR, antimicrobial resistance; MDR, multidrug-resistance; OR, odds ratio; CI, confidence interval.

9. Chapter IV: Discussion and conclusions

9.1 Discussion

Our study revealed the overall prevalence of sepsis patients infected with a pathogen with AMR in Chiang Mai province through the presence of the cases in 3 government hospitals during April 2017 – January 2018 was 9.2 cases per 100,000 population. This prevalence is highly likely to underrepresent all sepsis AMR cases in Chiang Mai because the surveillance system did not cover some hospitals that were able to perform AMR testing, for example, there were a university hospital and private hospitals in Chiang Mai which were not contributing data to the surveillance system. Another reason could be an impact of low hemoculture utilisation because the study of Lim et al. (2021) found that if a hospital improves utilisation rate of hemoculture from 26% to 82%, the overall incidence rate of patients with third-generation cephalosporin resistant *E. coli* infection will markedly increase from 2.4 to 9.5 cases per 100,000 population per year. Although we could not calculate the hemoculture utilisation rate, which was defined as the ratio of the number of hemocultures per 1,000 patient-days, in each hospital in this study, the hemoculture utilisation rates are expected to be low. In similar setting in northeastern Thailand in 2015, the hemoculture utilization rate in a referral hospital was only 20.5% (Teerawattanasook et al., 2017). However, the prevalence of sepsis AMR in our study is higher than the result of a study in Thailand collecting data of hospital-acquired infections caused by 5 pathogens including *E. coli*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *S. aureus* from 1,023 hospitals including government, university, and private hospitals in 2010 (Pumart et al., 2012). The study found that there were 3,407 AMR bloodstream infections in Thailand which there were about 64.4 million population in 2010 (5.29 infections per 100,000 population). The study also revealed that there were 0.5 bloodstream infections with AMR pathogens per 1,000 hospitalisations while the incidence of sepsis with AMR in Nakornping, Chomthong, and Sanpatong hospitals was 2.5, 3.3, and 1.5 cases per 1,000 IPD patients respectively.

In our study also showed that there were 34 deaths (2.1 deaths per 100,000 population) associated with sepsis with AMR. This mortality rate is likely to be underestimated according to the coverage of the surveillance system in the province resulting in underreported deaths associated with AMR and the impact of low hemoculture utilisation rate in hospitals. Although the study of Pumart et al. (2012) did not show the mortality rate of sepsis with AMR, the results suggested that there were 38,481 deaths related to AMR organism infections from any site (59.7 death per 100,000 population). Lim and colleagues (2016) used the data from Pumart et al. (2012) and estimated that there were around 19,122 deaths annually caused by MDR organism infections in Thailand. In a systematic review using a predictive statistical model in 2019 estimated that there were 389,000 deaths in south Asia accounting for 21.5 deaths per 100,000 population associated with bacterial AMR, there were 254,000 deaths in southeast Asia, east Asia, and Oceania 11.7 deaths per 100,000 population attributable to bacterial AMR, and there were 255,000 deaths in sub-Saharan Africa accounting for 23.7 deaths per 100,000 population attributable to bacterial AMR (Murray et al., 2022). The reasons why our study showed lower prevalence and death rate than the systematic review might be because our study I focused on sepsis patients infected with

8 AMR pathogens whereas the systematic review covered both sepsis and non-sepsis patients infected with AMR including 22 pathogens.

The proportion of HAI among the sepsis patients infected with a pathogen with AMR in Nakornping, Chomthong, and Sanpatong were 38.7%, 50%, and 33% respectively. An article by Bearman et al. (2019) suggests that around 55% to 70% of hospital-acquired infections are preventable. The occurrence of sepsis patients infected with a pathogen with AMR in the hospital could be reduced if we can prevent the risk factors for HAI. One of the risk factors for HAI is increased length of hospital stay more than 7 days (Murni et al., 2022). Our study found that the median of length of hospital stay in Nakornping hospital was 11 days with interquartile range from 6 to 20 days. Other risk factors for HAI include inadequate hand hygiene practices and invasive procedure, for example, urethral catheterization, venous catheterization, and endotracheal tube intubation (Manosuthi et al., 2017; Mouajou et al., 2022). Although our study did not have the data on these factors, a national point prevalence survey conducted in 2018 revealed that the tertiary and secondary government hospitals were associated with HAI (Moolasart et al., 2019). This might be because the tertiary and secondary hospitals performed invasive procedures more than primary hospital.

The most common resistant organism found in our study was *E. coli* both in sepsis and non-sepsis patients (Figure 6 and Table 10) accounting for 56.8% and 46.8% respectively. Also, there was a significantly strong association between *E. coli* infection and AMR. For the dead patients, there were 6 deaths (35.3%) associated with *E. coli* infection. Similarly, Murray et al. (2022) found that *E. coli* was the leading pathogen for death associated with resistance. However, in our study *E. coli* infection was not significantly associated with the outcome of death. In our study, *E. coli* is the most common pathogen found both in HAI and non-HAI (30.2% and 67.1% respectively). *K. pneumoniae* and *A. baumannii* are likely to be commonly associated with HAI (26.4% and 22.6% respectively) more than community infection (12.7% and 11.4% respectively). Similar to the national survey of HAI in Thailand in 2018, the most common pathogens were gram-negative bacteria including *K. pneumoniae* and *A. baumannii* accounting for 18.5% and 17.8% respectively (Moolasart et al., 2019). However, in northeast of Thailand, 14.7% (252/1,717) of MDR *E. coli* bacteraemia, 58.1% (301/518) of MDR *K. pneumoniae* bacteraemia, and 67.1% (374/557) of MDR *A. baumannii* bacteraemia were hospital-acquired.

Our epidemic curve could not present the seasonal pattern of sepsis AMR obviously across the 3 sentinel hospitals because there was only 1 year of data which varies by hospital. Moreover, our study did not focus on a specific pathogen that might happen seasonally. For example, the morbidity rate of penicillin-resistant *S. pneumoniae* was higher in winter because the seasonal pattern of AMR rate of *S. pneumoniae* was related to seasonality of respiratory tract infection such as pneumonia and the use of antibiotics during winter (Martinez et al., 2019). However, we observed that about one-third of sepsis patients infected with a pathogen with AMR in Nakornping occurred from July to August (rainy season in Thailand). This might be because the common pathogens in Nakornping hospital were *E. coli* and *K. pneumoniae*. Specifically, a study in nursing home setting in the US found that the peaks in the incidence of antimicrobial-resistant *K.*

pneumoniae and ciprofloxacin-resistant *E. coli* occurred in summer (June – September) (Cassone et al., 2021).

Chomthong hospital reported AMR sepsis cases for 3 months fewer than Nakornping hospital and Sanpatong hospital reported AMR sepsis cases for 6 months fewer than Nakornping hospital (Table 4). This might be because of lack of staff responsible for AMR surveillance in the hospital especially infection control nurses and public health officers. The nurses might be needed for the purpose of providing care and treatment and the public health officers might be needed for the purpose of routine surveillance reporting and conducting field outbreak investigation. So, the surveillance might increase the workload of the staff and have insufficient time for reporting the AMR surveillance data resulting in loss of AMR cases reporting. The lack of staff is more likely in the smaller hospital especially, Sanpatong hospital. Another reason might be lack of clinical microbiologists and equipment for hemoculture testing and performing AST in the hospitals.

For the geographical distribution of the patients, it could be seen that the 3 highest age-adjusted morbidity rates were in Chomthong 28.44 (95%CI 17.34 – 44.18) cases per 100,000 population, Samoeng 21.73 (95%CI 7.04 – 51.82) cases per 100,000 population, and Mae Rim 15.51 (95%CI 8.25 – 26.57) cases per 100,000 population. Two out of three sentinel hospitals are located in the districts with high age-adjusted morbidity rate. Nakornping hospital is located in Mae Rim district and Samoeng is a district neighbouring Mae Rim. Chomthong hospital is located in Chom Thong district. It might be explained that people living in the districts and neighbouring districts that the 2 hospitals located may be easier to access to the sentinel hospitals and diagnose with AMR infection than those who live in other districts. Although the hospitals located in the other districts were not able to perform antimicrobial susceptibility test, the hospitals might refer sepsis patients with suspected AMR infection to Nakornping or Chomthong hospitals if their clinical symptoms were not responded from antibiotics treatment. It can be seen from our results that 87.7% of the patients with sepsis AMR admitted to Nakornping hospital and 55.6% of the patients with sepsis AMR admitted to Chomthong hospital did not live in the same district where the hospitals are located. However, AMR data is only available for patients from these districts that attended Nakornping or Chomthong hospitals. So, there might be more cases in the other districts left that were not been identified due to the capacity of laboratory testing in each district. Another reason why Nakornping which is a tertiary hospital and Chomthong is a secondary hospital had higher morbidity rates might be AMR infection was associated with HAI (adjusted OR 4.39, 95%CI 1.84 – 10.48) and Manosuthi et al. (2017) found that in Thailand, the rate of HAI in tertiary hospitals (5.0% 95%CI 4.6% – 5.4%) higher than secondary hospitals (3.9% 95%CI 3.4% – 4.6%) and higher than primary hospital (2.0% 95%CI 1.3% – 2.7%). The study also found that HAI rate in university hospitals was the highest (7.3% 95%CI 4.6% – 9.3%), however, the age-adjusted morbidity rate in Mueang Chiang Mai district where a university hospital located was not the highest (4.65 cases per 100,000 population 95%CI 2.32 – 8.47) because the people living in Mueang Chiang Mai district may find it easier to access to the university hospital and private hospitals which were not include in our study.

The highest proportion of MDR pathogen in Chomthong hospital was *Salmonella* spp. accounting for 100% but there were only 2 isolates tested for antimicrobial susceptibility.

Similarly, the study of MDR *Salmonella* spp. prevalence in pigs and human in Thailand and Laos found that 92% (23/25) of *Salmonella* isolates from human in Thailand and 100% (16/16) of *Salmonella* isolates from human in Laos were MDR (Sinwat et al., 2016). Our study revealed that 62% (13/21) of *A. baumannii* isolates, 42.2% (89/211) of *E. coli* isolates, and 37% (25/67) of *K. pneumoniae* isolates in Chomthong hospital were MDR. According to the data collected from patients with bacteremia in 9 provinces in northeast of Thailand, the study showed that 52.3% (557/1065) of *Acinetobacter* spp. isolates, 40.1% (1717/4279) of *E. coli* isolates, and 31.1% (518/1661) of *K. pneumoniae* isolates were MDR (Lim et al., 2016).

In our study, we found that underlying disease, HAI, and *E. coli* infection were significantly associated with AMR infection of any site which the adjusted ORs were 2.66, 4.39, and 10.69 respectively. It could be explained that having an underlying disease resulting in immunocompromised status of patients led to easier getting an infection with AMR pathogen (WHO, 2021). The National Steering Committee on Antimicrobial Resistance of Thailand (2020) found that the incidence proportion and incidence rate of AMR in patients with HAI were 0.5% of total discharged patients and 1.4 per 1,000 patient-days respectively in Bamrasnaradura Infectious Disease Institute. World Health Organization [WHO] (2018) also reveals that the percent of *E. coli* resistant to ciprofloxacin varied from 8.4% to 92.9% in countries reporting to GLASS. Ciprofloxacin is commonly used to treat urinary tract infections which correspond to the results of the Table 11 that the 32.7% and 54.5% of *E. coli* isolates were resistant to ciprofloxacin and fluoroquinolones respectively. However, there might be other potential risk factors, for instance, socioeconomic factors, history of getting invasive procedure during hospitalization, and history of antibiotics use because in our study, we did not collect data to examine an association between those factors and infection with AMR bacteria. A systematic review on risk factors for AMR in China found that there were 4 major factors related to AMR which were first, sociodemographic factors including low income, urban residence, and migrant status; second, patient clinical information; third, admission to healthcare settings including invasive procedures performed length of hospitalization; and fourth, drug exposure including previous and current antibiotics use (Chen et al., 2021).

There was a reasonable level of sepsis patients with resistant pathogen infections in the surgical department especially in Nakornping hospital (Table 8). Indeed, 30.2% (32/106) of sepsis patients infected with AMR pathogen admitted to surgical department. Forty-seven percent (15/32) of the sepsis patients infected with AMR pathogen and admitted to surgical department were HAI. This might be because there were a lot of invasive procedure performed to the patients in surgical departments leading to HAIs (Moolasart et al., 2019; Mouajou et al., 2022). Forty-four percent (14/32) of the sepsis patients admitted to surgical department were infected with antimicrobial resistant *E. coli*. In surgical wards at a national referral hospital in Uganda, there was a statistically significant increased trend in resistance of gram-negative bacteria including *E. coli*, *K. pneumoniae* to third-generation cephalosporins from 2014 to 2018 (Mboowa et al., 2021). The study also found that 20.6% of HAIs in the hospital were bloodstream infections. Additionally, a study in Benin showed that the most common pathogen of HAIs in patients with gastrointestinal surgery was *E. coli* accounting for 38% (31/84) and 69.4% of *E. coli* isolates were ESBL-producing (Yehouenou et al., 2020).

After univariate and multivariate analyses were performed, HAI, MDR infection, and sepsis were significantly associated with death during hospitalisation period which the adjusted ORs were 3.05, 3.95, 4.62. On the other hand, AMR seems to be a confounding factor. This could be explained that AMR was associated with MDR infection but the virulence of MDR pathogen is higher than AMR pathogen leading to the outcome of death because the MDR organisms cause more failure of treatment resulting in worsening of signs and symptoms (Pop-Vicas & Opal, 2014). Also, by the definitions of AMR and MDR, there was a collinearity between AMR and MDR. Infection prevention and control is the most important factor for controlling HAI. Up to seventy percent of HAIs are preventable by infection prevention and control programme with engagement of senior leaders in the hospitals (Bearman et al., 2019). Similarly, sixty-five to seventy percent of catheter-associated bloodstream infections and catheter-associated urinary tract infections could be preventable due to comprehensive implementation of infection prevention and control programme (Umscheid et al., 2011). Sepsis is the strongest significant association with the outcome death during the patient's admission. This might be explained that sepsis is a life-threatening condition worsening tissue perfusion to vital organs and resulting in disseminated intravascular coagulopathy which cause multiple organ failure (Vincent, 2016).

9.2 Limitations

There were some limitations in our study. First, the patchiness of reported data and the lack of the data from other 22 district hospitals which did not perform AST and missing data from the university and private hospitals resulting in the accuracy of the results. Second, our data could not identify whether seasonality of the AMR exist because we collected data for 10 months (April 2017 – January 2018). Third, the completeness of some variables in the data might not be adequate because there were a lot of missing data of some important variables, for example, underlying disease, dead status. This could result in the non-differential misclassification bias of the results as well. In addition, some variables that might related to AMR were not planned to be collected at the beginning such as education, income, length of hospitalisation, history of antibiotics use both in hospital and community, the details of occupation if related to antibiotics use in animals.

9.3 Recommendations

For the local level including Chiang Mai provincial health office and the hospitals, we recommend that the AMR issue should be considered as an important issue in the local level to increase resource needed to the surveillance system. Specifically, identifying issues related to reporting system and areas of improvement should be carried out in each hospital due to the hospitals having different context, for example, limited resources, awareness of health care workers and executives to AMR issue. Moreover, the number of staff who are responsible for AMR surveillance should be increased and the system of extraction and submission of surveillance data in each hospital should be developed to strengthen the quality of data collection, analysis, interpretation and timely dissemination to key persons. The use of the surveillance data within the hospitals and province such as identifying population at risk, risk factors for having infection with AMR pathogen should be done to determine and address AMR issues in the area. Additional information should be collected to the surveillance system and used for further analysis, for example, the number of hemocultures tested in the hospital, the number of parenteral antibiotic records, invasive procedures done in the patients.

Additionally, hospital-acquired infection precaution in all hospitals should be strengthened to reduce the occurrence of AMR infection because the results suggest that there was a significant association between HAI and AMR infection. The bacteria associated with HAI should be monitored in the hospital as well. According to the study results, HAI prevention and control practices in the hospitals could also reduce the death of the inpatients. Sepsis management including definitive antibiotic therapy, maintaining organ and tissue perfusion using intravascular fluid therapy, and close monitoring of the shock status of the patients should be strengthened in the hospitals as well to decrease the occurrence of death. Further research in the hospitals may be required to identify risk factors for getting AMR in order to prevent the cases in the future.

For the central level including Department of Disease Control (DDC) and Ministry of Public Health (MoPH). We recommend that the reasons for the variable reporting rate from the sentinel hospitals should be investigated to understand whether this reflects the real situation or there are other factors contributing to the situation. This is important for interpreting the current and any future surveillance data. There may be interventions that could improve the reporting of surveillance data. Also, interventions that may improve the hemoculture utilization rate in the hospitals. The quality of the laboratory performance should be monitored to understand the reliability of their results. The surveillance system should be expanded in terms of the number of hospitals, provinces, time period, site of infection, and type of organisms. This will assist the DDC and MoPH to see the whole picture and understand more the epidemiological knowledge of AMR in the country. Also, increase a collaboration with other hospitals which are not under MoPH, for instance, university hospitals, local administration organisation's hospitals, military hospitals to cover more AMR cases that directly visit non-MoPH hospitals. The central level should provide information and technology system supporting the local level such as an online report system or a mobile application for reporting AMR cases. This could help to reduce the workload of the staff in the local level and increase the quality of the data to be real-time. Furthermore, the central level should increase budget for laboratory testing or increase capacity of the laboratory in each government hospital to be able to test the resistance of antibiotics. Further studies with the collaboration with other organisations such as Department of Livestock Development, universities should be conducted to understand the AMR situation in Thailand in the concept of "One Health".

9.4 Conclusions

Our study concludes that the overall prevalence of sepsis patients infected with a pathogen with AMR and AMR mortality rate in Chiang Mai province may be higher than 9.2 cases per 100,000 population and CFR for sepsis patients infected with a pathogen with AMR was 23% (34/148). The percentage of female patients overall was 51.3%. The median of age of the patients in the three hospitals ranged from 64.0 to 68.0 years. The highest percentage of the organisms was *E. coli* accounting for approximately 56.8 percent (84/148). About forty percent (53/132) of sepsis patients infected with a pathogen with AMR were HAI. Seasonality of sepsis with AMR was not presented but about one-third of sepsis patients infected with a pathogen with AMR in Nakornping occurred in rainy season in Thailand. People living in Mae Rim and Chom Thong districts that Nakornping and Chomthong hospitals located respectively may be easier to diagnose with AMR infection than those who live in other districts. In Chomthong hospital, 61.9% of *A. baumannii* isolates were MDR following by *E. coli* isolates (42.2%), *K. pneumoniae* isolates (37.3%), and *P. aeruginosa* isolates (31.7%). Underlying disease, HAI, and *E. coli* infection were risk factors for

AMR infection which the adjusted OR were 2.66 (95%CI 1.13 – 6.25), 4.39 (95%CI 1.84 – 10.48), and 10.69 (95%CI 4.47 – 25.55) respectively. HAI, MDR infection, and sepsis were risk factors for death during hospitalisation period which the adjusted ORs were 3.05 (95%CI 1.08 – 8.65), 3.95 (95%CI 1.30 – 12.00), and 4.62 (95%CI 1.51 – 14.11) respectively. Both local and central levels of public health sectors should take an AMR to be an important issue in order to increase resources including workforce, budget, infrastructure and information technology support to the surveillance system. Strengthening HAI prevention and control could reduce the occurrence of AMR and death during the patients' hospitalisation.

10. Appendix

10.1 Figures and tables related to analysis of Study I

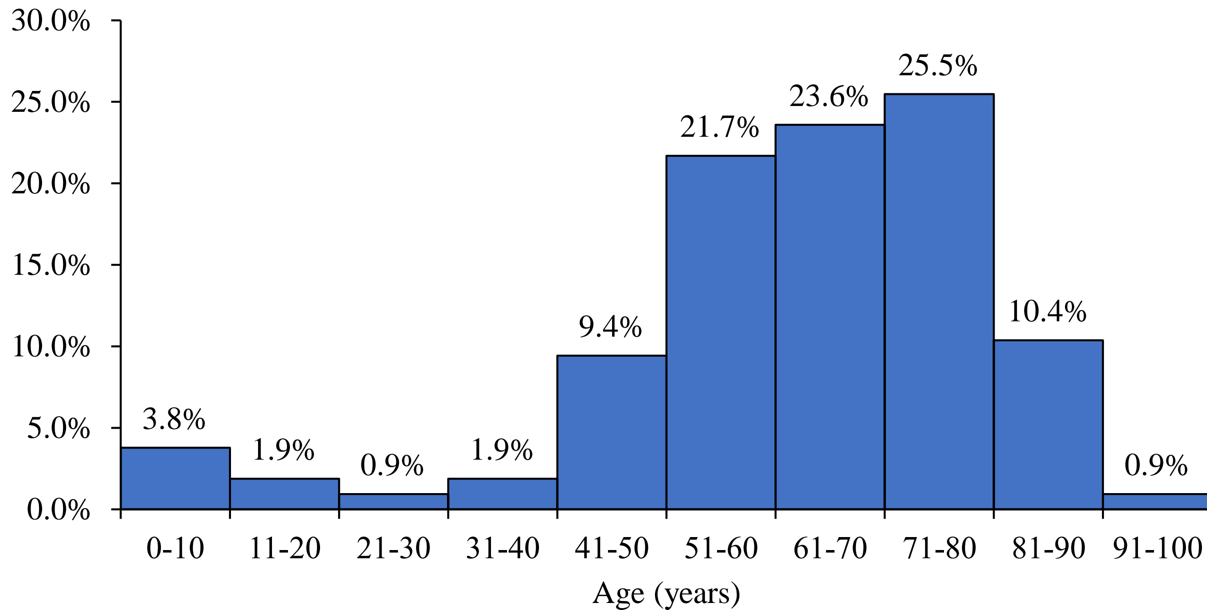

Figure 11. Percentage of sepsis cases with AMR by age in Nakornping hospital (n = 106).

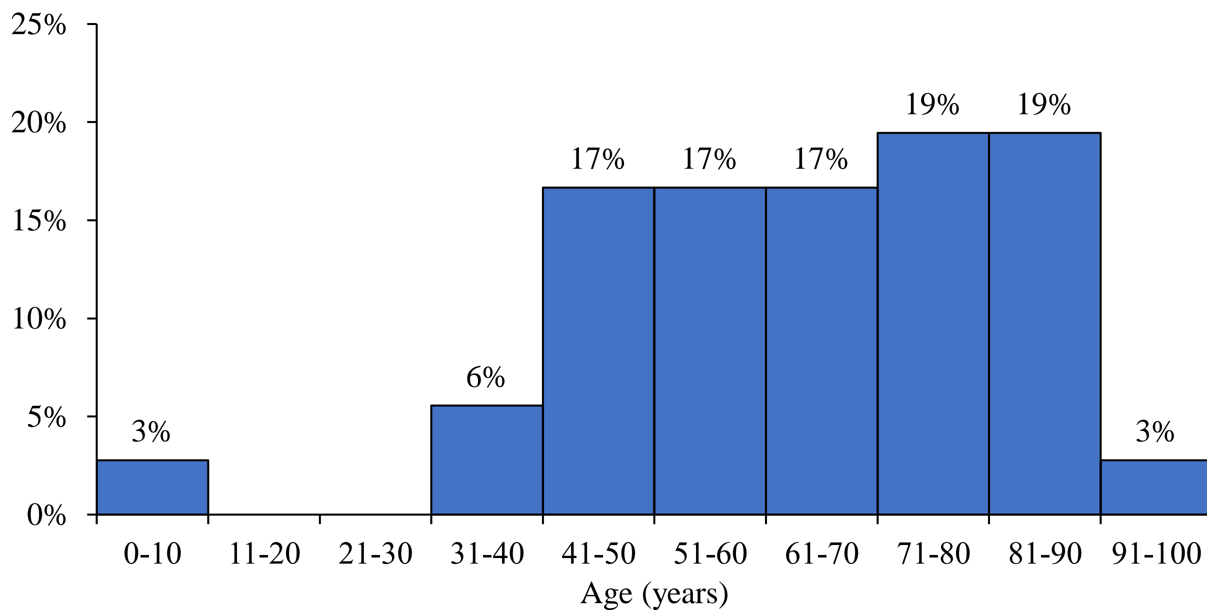

Figure 12. Percentage of sepsis cases with AMR by age in Chomthong hospital (n = 36).

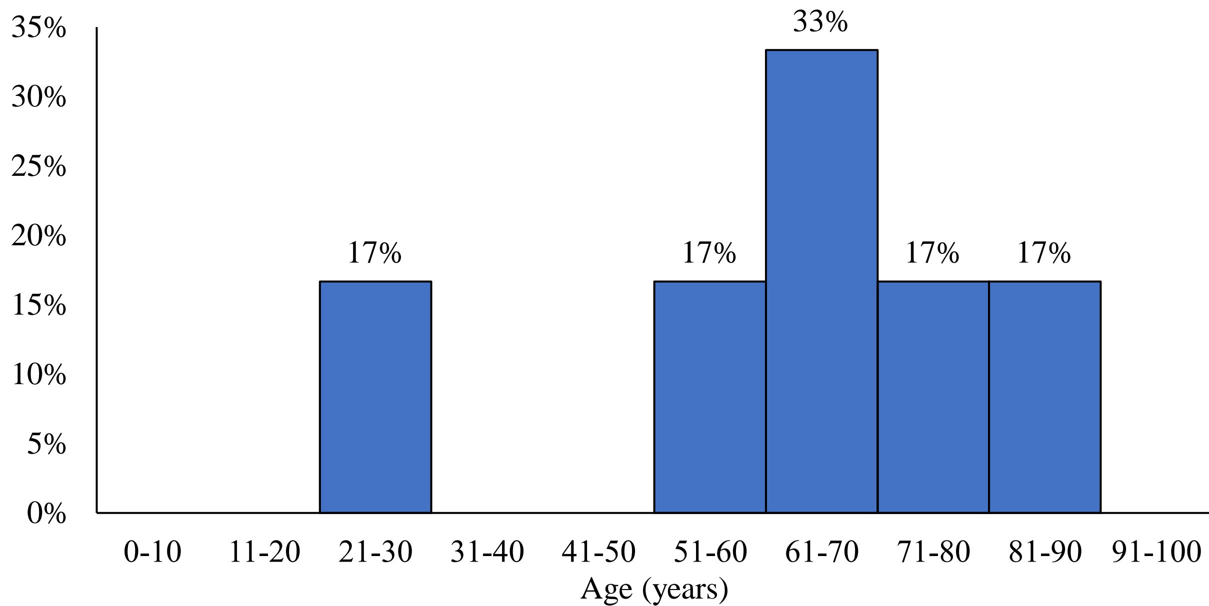

Figure 13. Percentage of sepsis cases with AMR by age in Sanpatong hospital (n = 6).

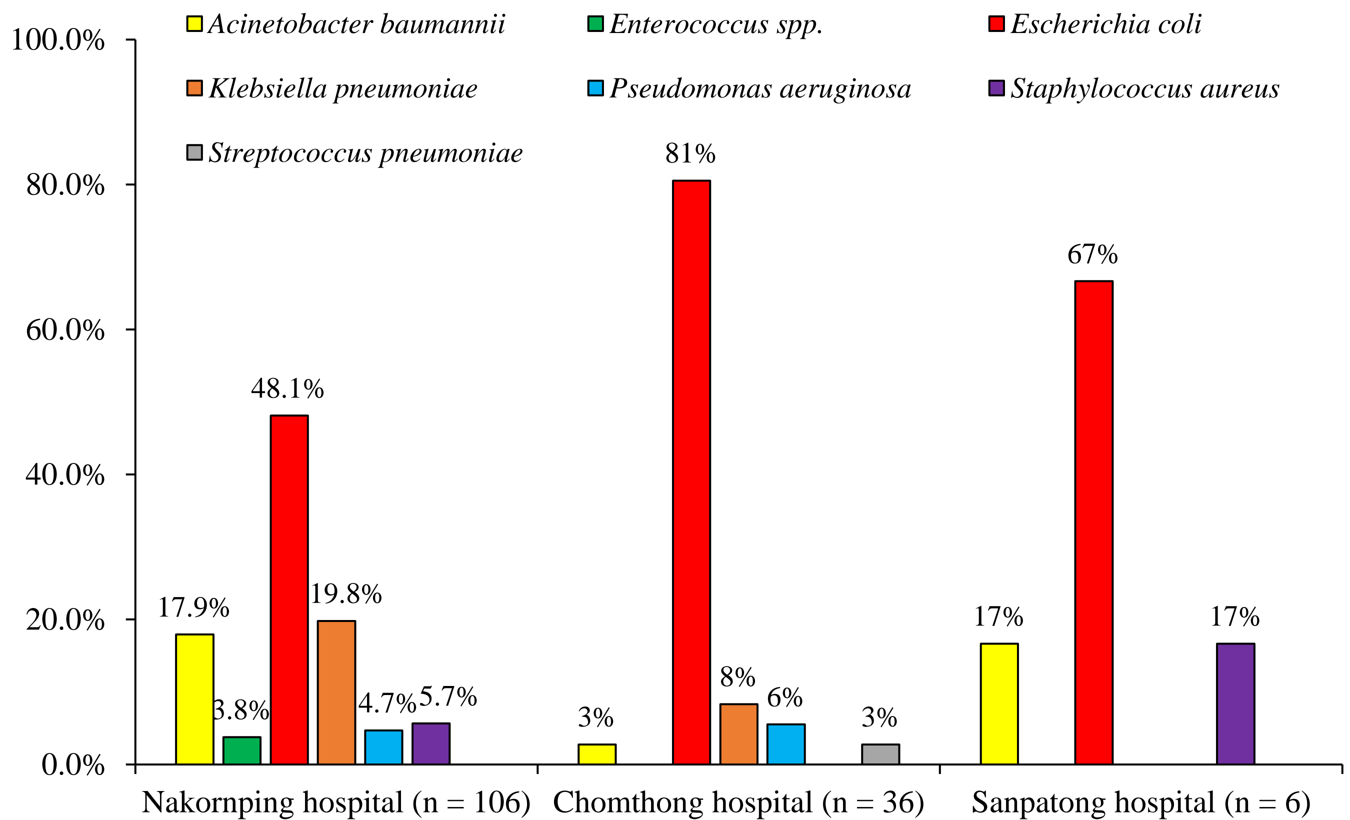

Figure 14.Percentage of bacteria by species for resistant bacteria isolated from sepsis cases in the 3 sentinel hospitals in Chiang Mai

Table 19. Mid-year population classified by age group in each district in Chiang Mai, 2017.

District	Age group (years)	Mid-year population
Chai Prakan	0 – 20	9,577
	21 – 40	10,977
	41 – 60	11,471
	61 – 80	5,214
	Over 80	722
	Total	37,961
Chiang Dao	0 – 20	21,536
	21 – 40	21,670
	41 – 60	18215
	61 – 80	8,033
	Over 80	1,244
	Total	70,698
Chom Thong	0 – 20	15,324
	21 – 40	19,328
	41 – 60	19,436
	61 – 80	10,363
	Over 80	2,040
	Total	66,491
Doi Lo	0 – 20	4,514
	21 – 40	7,044
	41 – 60	8,849
	61 – 80	4,614
	Over 80	811
	Total	25,832
Doi Saket	0 – 20	13,407
	21 – 40	21,069
	41 – 60	23,662
	61 – 80	11,412
	Over 80	1,863
	Total	71,413
Doi Tao	0 – 20	6,229
	21 – 40	7,779
	41 – 60	8,432
	61 – 80	4,191
	Over 80	733
	Total	27,364
Fang	0 – 20	21,259
	21 – 40	25,049
	41 – 60	26,923
	61 – 80	12,372
	Over 80	1,774
	Total	87,377

Table 19. Mid-year population classified by age group in each district in Chiang Mai, 2017(cont.).

District	Age group (years)	Mid-year population
Hang Dong	0 – 20	16,819
	21 – 40	25,484
	41 – 60	28,814
	61 – 80	12,023
	Over 80	1,821
	Total	84,961
Hot	0 – 20	11,506
	21 – 40	13,009
	41 – 60	12,405
	61 – 80	5,567
	Over 80	1,165
	Total	43,652
Mae Ai	0 – 20	19,008
	21 – 40	18,543
	41 – 60	18,375
	61 – 80	8,144
	Over 80	1,076
	Total	65,146
Mae Chaem	0 – 20	19,136
	21 – 40	19,157
	41 – 60	14,119
	61 – 80	5,515
	Over 80	1,399
	Total	59,326
Mae On	0 – 20	3,954
	21 – 40	5,829
	41 – 60	7,448
	61 – 80	3,362
	Over 80	593
	Total	21,186
Mae Rim	0 – 20	18,685
	21 – 40	25,965
	41 – 60	25,533
	61 – 80	12,198
	Over 80	2,112
	Total	84,493
Mae Taeng	0 – 20	14,903
	21 – 40	20,476
	41 – 60	23,002
	61 – 80	11,469
	Over 80	1,710
	Total	71,560

Table 19. Mid-year population classified by age group in each district in Chiang Mai, 2017(cont.).

District	Age group (years)	Mid-year population
Mae Wang	0 – 20	7,299
	21 – 40	9,444
	41 – 60	9,292
	61 – 80	4,411
	Over 80	976
	Total	31,422
Mueang Chiang Mai	0 – 20	45,610
	21 – 40	69,124
	41 – 60	69,507
	61 – 80	36,750
	Over 80	7,027
	Total	8,018
Omkoi	0 – 20	24,619
	21 – 40	18,740
	41 – 60	11,042
	61 – 80	6,028
	Over 80	1,860
	Total	62,289
Phrao	0 – 20	9,441
	21 – 40	12,966
	41 – 60	16,653
	61 – 80	8,230
	Over 80	1,282
	Total	48,572
Samoeng	0 – 20	5,965
	21 – 40	6,843
	41 – 60	6,777
	61 – 80	2,967
	Over 80	613
	Total	23,165
Saraphi	0 – 20	14,658
	21 – 40	23,762
	41 – 60	27,388
	61 – 80	13,209
	Over 80	2,281
	Total	81,298
San Kamphaeng	0 – 20	15,582
	21 – 40	25,025
	41 – 60	28,281
	61 – 80	12,869
	Over 80	2,245
	Total	84,002

Table 19. Mid-year population classified by age group in each district in Chiang Mai, 2017(cont.).

District	Age group (years)	Mid-year population
San Pa Tong	0 – 20	12,939
	21 – 40	20,152
	41 – 60	24,691
	61 – 80	14,127
	Over 80	3,060
	Total	74,969
San Sai	0 – 20	26,995
	21 – 40	40,884
	41 – 60	41,000
	61 – 80	18,007
	Over 80	2,450
	Total	129,336
Wiang Haeng	0 – 20	6,840
	21 – 40	5,344
	41 – 60	4,040
	61 – 80	1,338
	Over 80	177
	Total	17,739
Galyani Vadhana	0 – 20	4,070
	21 – 40	4,511
	41 – 60	2,459
	61 – 80	941
	Over 80	168
	Total	12,149

Table 20. Age-adjusted morbidity rates of AMR by district in Chiang Mai, April 2017 – January 2018.

District	Age-adjusted morbidity rate (per 100,000 population)	95%Confidence interval
Chai Prakan	8.20	1.69 – 25.86
Chiang Dao	10.20	3.67 – 23.05
Chom Thong	28.44	17.34 – 44.18
Doi Lo	3.15	0.08 – 23.43
Doi Saket	5.09	1.39 – 14.00
Doi Tao	7.05	0.85 – 26.18
Fang	3.48	0.72 – 10.83
Hang Dong	7.28	2.65 – 16.27
Hot	9.60	2.60 – 25.04
Mae Ai	5.34	1.10 – 17.01
Mae Chaem	2.15	0.05 – 13.35
Mae On	8.38	1.01 – 34.47
Mae Rim	15.51	8.25 – 26.57
Mae Taeng	8.90	3.58 – 18.84
Mae Wang	3.28	0.08 – 18.30
Mueang Chiang Mai	4.65	2.32 – 8.47
Omkoi	7.07	1.37 – 21.79
Phrao	5.63	1.16 – 17.77
Samoeng	21.73	7.04 – 51.82
Saraphi	4.39	1.20 – 12.29
San Kamphaeng	6.70	2.46 – 15.30
San Pa Tong	8.87	3.78 – 18.87
San Sai	5.98	2.38 – 12.73
Wiang Haeng	7.50	0.19 – 63.43
Galyani Vadhana	0.00	-

10.2 Figures related to analysis of Study II

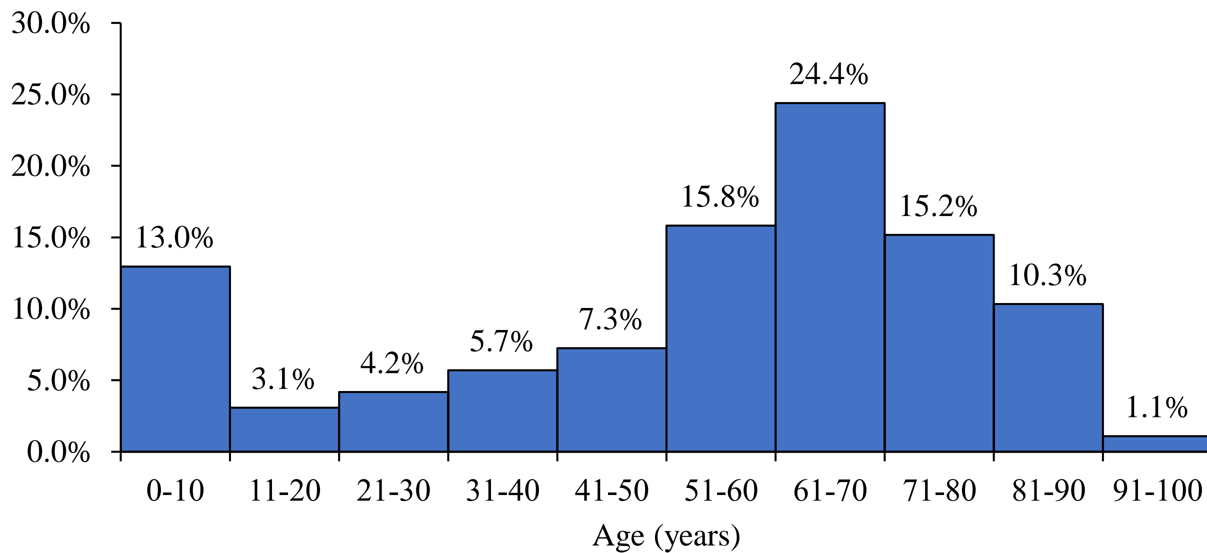

Figure 15. Percentage of the patients infected with 8 selected pathogens in Chomthong hospital, April – October 2017 (n = 455).

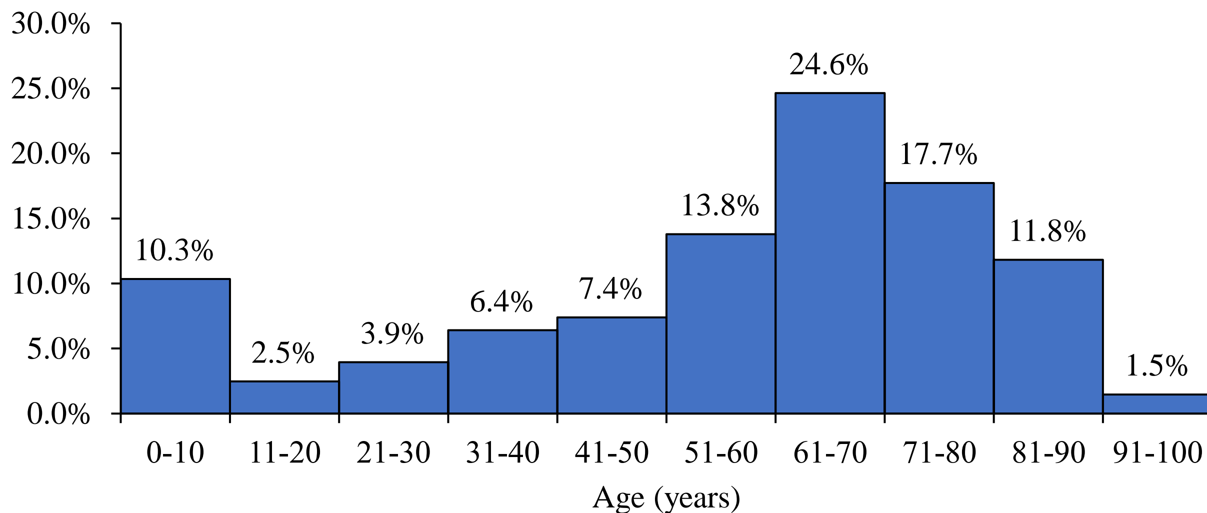

Figure 16. Figure 16. Percentage of the patients infected with AMR pathogens in Chomthong hospital, April – October 2017 (n = 203).

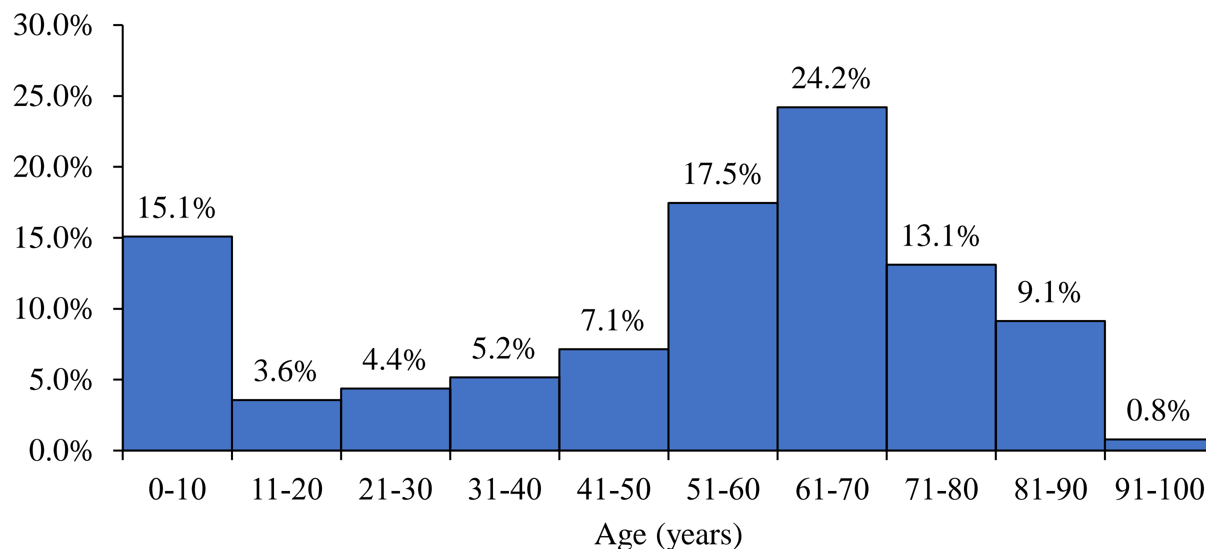

Figure 17. Percentage of the patients infected with non-AMR pathogens in Chomthong hospital, April – October 2017 (n = 252).

11. References

Allel, K., García, P., Labarca, J., Munita, J. M., Rendic, M., & Undurraga, E. A. (2020). Socioeconomic factors associated with antimicrobial resistance of Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli in Chilean hospitals (2008-2017). *Rev Panam Salud Publica, 44*, e30. doi:10.26633/rpsp.2020.30

Alnemri, A. R., Almaghrabi, R. H., Alonazi, N., & Alfrayh, A. R. (2016). Misuse of antibiotic: A systemic review of Saudi published studies. *Current Pediatric Research, 20*(2), 169-173.

Bearman, G., Doll, M., Cooper, K., & Stevens, M. P. (2019). Hospital infection prevention: How much can we prevent and how hard should we try? *Current Infectious Disease Reports, 21*(1), 2. doi:10.1007/s11908-019-0660-2

Biedron, C., & Chopra, T. (2013). Issues surrounding antibiotic use in older adults. *Current Translational Geriatrics and Experimental Gerontology Reports, 2*(3), 151-158. doi:10.1007/s13670-013-0050-9

Cantón, R., González-Alba, J. M., & Galán, J. C. (2012). CTX-M enzymes: Origin and diffusion. *Frontiers in Microbiology, 3*, 110. doi:10.3389/fmicb.2012.00110

Cassone, M., Mantey, J., Gontjes, K. J., Lansing, B. J., Gibson, K. E., Wang, J., & Mody, L. (2021). Seasonal patterns in incidence and antimicrobial resistance of common bacterial pathogens in nursing home patients and their rooms. *Frontiers in Public Health, 9*. doi:10.3389/fpubh.2021.671428

Centers for Disease Control and Prevention [CDC]. (2019). *Antibiotic resistance threats in the United States 2019.* Atlanta, GA: U.S. Department of Health and Human Services, CDC.

Chen, Q., Li, D., Beiersmann, C., Neuhann, F., Moazen, B., Lu, G., & Müller, O. (2021). Risk factors for antibiotic resistance development in healthcare settings in China: a systematic review. *Epidemiology and Infection, 149*, e141. doi:10.1017/S0950268821001254

Chiang Mai Public Health Office. (2018). *The data of mid-year population in Chiang Mai between 2003 and 2017*. Retrieved from http://www.chiangmaihealth.go.th/cmpho_web/detail_article2.php?info_id=670

Clinical and Laboratory Standards Institute [CLSI]. (2017). *M100 performance standards for antimicrobial susceptability testing* (27th ed.). Pennsylvania: CLSI.

Cosgrove, S. E., & Carmeli, Y. (2003). The impact of antimicrobial resistance on health and economic outcomes. *Clinical Infectious Diseases, 36*(11), 1433-1437. doi:10.1086/375081

Department of Medical Sciences [DMSc]. (2017). *Medical and public health microbiology laboratory standards guide*. Bangkok: Text and Journal Publication Co., Ltd.

Erku, D. A., Mekuria, A. B., & Belachew, S. A. (2017). Inappropriate use of antibiotics among communities of Gondar town, Ethiopia: a threat to the development of antimicrobial resistance. *Antimicrobial Resistance and Infection Control, 6*, 112. doi:10.1186/s13756-017-0272-2

Essack, S. Y., Desta, A. T., Abotsi, R. E., & Agoba, E. E. (2017). Antimicrobial resistance in the WHO African region: current status and roadmap for action. *Journal of Public Health, 39*(1), 8-13. doi:10.1093/pubmed/fdw015

Farra, A., Frank, T., Tondeur, L., Bata, P., Gody, J. C., Onambele, M., . . . Breurec, S. (2016). High rate of faecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae in healthy children in Bangui, Central African Republic. *Clinical Microbiology and Infection, 22*(10), 891.e891-891.e894. doi:10.1016/j.cmi.2016.07.001

Fitzpatrick, F., Tarrant, C., Hamilton, V., Kiernan, F. M., Jenkins, D., & Krockow, E. M. (2019). Sepsis and antimicrobial stewardship: two sides of the same coin. *BMJ Qual Saf, 28*(9), 758-761. doi:10.1136/bmjqs-2019-009445

Fleming-Dutra, K. E., Hersh, A. L., Shapiro, D. J., & et al. (2016). Prevalence of inappropriate antibiotic prescriptions among us ambulatory care visits, 2010-2011. *JAMA, 315*(17), 1864-1873. doi:10.1001/jama.2016.4151

Gold, H. S. (2001). Vancomycin-resistant enterococci: Mechanisms and clinical observations. *Clinical Infectious Diseases, 33*(2), 210-219. doi:10.1086/321815

Harbottle, H., Thakur, S., Zhao, S., & White, D. G. (2006). Genetics of antimicrobial resistance. *Animal Biotechnology, 17*(2), 111-124. doi:10.1080/10495390600957092

Horan, T. C., & Gaynes, R. P. (2004). Surveillance of nosocomial infections. In C. G. Mayhall (Ed.), *Hospital epidemiology and infection control* (pp. 1659-1702). Philadelphia: Lippincott Williams and Wilkins.

Ibrahim, E. H., Sherman, G., Ward, S., Fraser, V. J., & Kollef, M. H. (2000). The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU Setting. *Chest, 118*(1), 146-155. doi:10.1378/chest.118.1.146

Jensen, M. L. V., Siersma, V., Søes, L. M., Nicolaisdottir, D., Bjerrum, L., & Holzknecht, B. J. (2022). Prior antibiotic use increases risk of urinary tract infections caused by resistant *Escherichia coli* among elderly in primary care: A case-control study. *Antibiotics, 11*(10). Retrieved from doi:10.3390/antibiotics11101382

Kazaryan, I., Sevikyan, A., Vardanyan, L., Amirkhanyan, A., & Melikyan, M. (2021). Dispensing antibiotics without prescription at pharmacies: barriers and strategies for improvement. *European Journal of Public Health, 31*(Supplement_3), ckab165.366. doi:10.1093/eurpub/ckab165.366

Kotwani, A., Joshi, J., Lamkang, A. S., Sharma, A., & Kaloni, D. (2021). Knowledge and behavior of consumers towards the non-prescription purchase of antibiotics: An insight from a qualitative study from New Delhi, India. *Pharm Pract (Granada), 19*(1), 2206. doi:10.18549/PharmPract.2021.1.2206

Laudisio, A., Marinosci, F., Gemma, A., Bartoli, I. R., Montenegro, N., & Incalzi, R. A. (2017). The burden of comorbidity is associated with antibiotic resistance among institutionalized elderly with urinary infection: A retrospective cohort study in a single Italian nursing home between 2009 and 2014. *Microb Drug Resist, 23*(4), 500-506. doi:10.1089/mdr.2016.0016

Lautenbach, E., Patel, J. B., Bilker, W. B., Edelstein, P. H., & Fishman, N. O. (2001). Extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: Risk factors for infection and impact of resistance on outcomes. *Clinical Infectious Diseases, 32*(8), 1162-1171. doi:10.1086/319757

Lim, C., Hantrakun, V., Teerawattanasook, N., Srisamang, P., Teparrukkul, P., Sumpradit, N., . . . Limmathurotsakul, D. (2021). Impact of low blood culture usage on rates of antimicrobial resistance. *Journal of Infection, 82*(3), 355-362. doi:10.1016/j.jinf.2020.10.040

Lim, C., Takahashi, E., Hongsuwan, M., Wuthiekanun, V., Thamlikitkul, V., Hinjoy, S., . . . Limmathurotsakul, D. (2016). Epidemiology and burden of multidrug-resistant bacterial infection in a developing country. *eLife, 5*, e18082. doi:10.7554/eLife.18082

Machowska, A., & Lundborg, C. S. (2019). Drivers of Irrational Use of Antibiotics in Europe. *Int J Environ Res Public Health, 16*(1), 27. doi:10.3390/ijerph16010027

Magiorakos, A. P., Srinivasan, A., Carey, R. B., Carmeli, Y., Falagas, M. E., Giske, C. G., . . . Monnet, D. L. (2012). Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clinical Microbiology and Infection, 18*(3), 268-281. doi:10.1111/j.1469-0691.2011.03570.x

Manosuthi, W., Thientong, V., Moolasart, V., Rongrungrueng, Y., Sangsajja, C., & Danchaivijitr, S. (2017). Healthcare-associated infections at selected hospitals in Thailand. *Southeast Asian J Trop Med Public Health, 48*(1), 204-212.

Martinez, E. P., Cepeda, M., Jovanoska, M., Bramer, W. M., Schoufour, J., Glisic, M., . . . Franco, O. H. (2019). Seasonality of antimicrobial resistance rates in respiratory bacteria: A systematic review and meta-analysis. *PLoS ONE, 14*(8), e0221133. doi:10.1371/journal.pone.0221133

Mboowa, G., Aruhomukama, D., Sserwadda, I., Kitutu, F. E., Davtyan, H., Owiti, P., . . . Kajumbula, H. (2021). Increasing antimicrobial resistance in surgical wards at Mulago

National Referral Hospital, Uganda, from 2014 to 2018-Cause for concern? *Trop Med Infect Dis, 6*(2). doi:10.3390/tropicalmed6020082

Moffatt, J. H., Harper, M., Harrison, P., Hale, J. D. F., Vinogradov, E., Seemann, T., . . . Boyce, J. D. (2010). Colistin resistance in *Acinetobacter baumannii* is mediated by complete loss of lipopolysaccharide production. *Antimicrobial Agents And Chemotherapy, 54*(12), 4971-4977. doi:10.1128/AAC.00834-10

Moolasart, V., Manosuthi, W., Thienthong, V., Vachiraphan, A., Judaeng, T., Rongrungrueng, Y., . . . Danchaivijitr, S. (2019). Prevalence and risk factors of healthcare-associated Infections in Thailand 2018: A point-prevalence survey. *J Med Assoc Thai, 102*(12), 1309-1316.

Morgan, D. J., Okeke, I. N., Laxminarayan, R., Perencevich, E. N., & Weisenberg, S. (2011). Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet Infectious Diseases, 11*(9), 692-701. doi:10.1016/S1473-3099(11)70054-8

Mouajou, V., Adams, K., DeLisle, G., & Quach, C. (2022). Hand hygiene compliance in the prevention of hospital-acquired infections: a systematic review. *J Hosp Infect, 119*, 33-48. doi:10.1016/j.jhin.2021.09.016

Munita, J. M., & Arias, C. A. (2016). Mechanisms of antibiotic resistance. *Microbiology spectrum, 4*(2), 10.1128/microbiolspec.VMBF-0016-2015. doi:10.1128/microbiolspec.VMBF-0016-2015

Murni, I. K., Duke, T., Kinney, S., Daley, A. J., Wirawan, M. T., & Soenarto, Y. (2022). Risk factors for healthcare-associated infection among children in a low-and middle-income country. *BMC Infectious Diseases, 22*(1), 406. doi:10.1186/s12879-022-07387-2

Murray, C. J. L., Ikuta, K. S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., . . . Naghavi, M. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet, 399*(10325), 629-655. doi:10.1016/S0140-6736(21)02724-0

National Steering Committee on Antimicrobial Resistance of Thailand. (2020). *Thailand’s one health report on antimicrobial consumption and antimicrobial resistance in 2018.* Nonthaburi: International Health Policy Program, Ministry of Public Health, Thailand.

Nguyen, H. Q., Nguyen, N. T. Q., Hughes, C. M., & O’Neill, C. (2019). Trends and impact of antimicrobial resistance on older inpatients with urinary tract infections (UTIs): A national retrospective observational study. *PLoS ONE, 14*(10), e0223409. doi:10.1371/journal.pone.0223409

O'Neill, J. (2014). *Antimicrobial resistance: Tackling a crisis for the health and wealth of nations*. Retrieved from https://amr-

review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf

Opatowski, M., Brun-Buisson, C., Touat, M., Salomon, J., Guillemot, D., Tuppin, P., & Watier, L. (2021). Antibiotic prescriptions and risk factors for antimicrobial resistance in patients hospitalized with urinary tract infection: a matched case-control study using the French health insurance database (SNDS). *BMC Infectious Diseases, 21*(1), 571. doi:10.1186/s12879-021-06287-1

Pop-Vicas, A., & Opal, S. M. (2014). The clinical impact of multidrug-resistant gram-negative bacilli in the management of septic shock. *Virulence, 5*(1), 206-212. doi:10.4161/viru.26210

Pouwels, K. B., Dolk, F. C. K., Smith, D. R. M., Robotham, J. V., & Smieszek, T. (2018). Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. *Journal of Antimicrobial Chemotherapy, 73*(suppl_2), 19-26. doi:10.1093/jac/dkx502

Pumart, P., Phodha, T., Thamlikitkul, V., Riewpaiboon, A., Prakongsai, P., & Limwattananon, S. (2012). Health and economic impacts of antimicrobial resistance in Thailand. *Journal Health Services Research Policy, 9*, 352–360.

R Core Team. (2021). R: A language and environment for statistical computing (Version 4.1.2). Vienna, Austria: R Foundation for Statistical Computing. Retrieved from https://www.R-project.org/

Ramirez, C. B., & Cantey, J. B. (2019). Antibiotic resistance in the neonatal intensive care unit. *Neoreviews, 20*(3), e135-e144. doi:10.1542/neo.20-3-e135

Rodríguez-Martínez, J.-M., Poirel, L., & Nordmann, P. (2009). Molecular epidemiology and mechanisms of carbapenem resistance in *Pseudomonas aeruginosa*. *Antimicrobial Agents And Chemotherapy, 53*(11), 4783-4788. doi:10.1128/AAC.00574-09

Shallcross, L. J., & Davies, D. S. C. (2014). Antibiotic overuse: a key driver of antimicrobial resistance. *The British Journal of General Practice, 64*(629), 604-605. doi:10.3399/bjgp14X682561

Shet, A., Sundaresan, S., & Forsberg, B. C. (2015). Pharmacy-based dispensing of antimicrobial agents without prescription in India: appropriateness and cost burden in the private sector. *Antimicrobial Resistance and Infection Control, 4*, 55. doi:10.1186/s13756-015-0098-8

Shrestha, P., Cooper, B. S., Coast, J., Oppong, R., Do Thi Thuy, N., Phodha, T., . . . Lubell, Y. (2018). Enumerating the economic cost of antimicrobial resistance per antibiotic

consumed to inform the evaluation of interventions affecting their use. *Antimicrobial Resistance & Infection Control, 7*(1), 98. doi:10.1186/s13756-018-0384-3

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., . . . Angus, D. C. (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA, 315*(8), 801-810. doi:10.1001/jama.2016.0287

Sinwat, N., Angkittitrakul, S., Coulson, K. F., Pilapil, F., Meunsene, D., & Chuanchuen, R. (2016). High prevalence and molecular characteristics of multidrug-resistant Salmonella in pigs, pork and humans in Thailand and Laos provinces. *J Med Microbiol, 65*(10), 1182-1193. doi:10.1099/jmm.0.000339

Stapleton, P. D., & Taylor, P. W. (2002). Methicillin resistance in *Staphylococcus aureus*: mechanisms and modulation. *Science progress, 85*(Pt 1), 57-72.

Sumpradit, N., Poonpolsup, S., Wongkongkathep, S., Janejai, N., Paveenkittiporn, W., Boonyarit, P., . . . Tangcharoensathien, V. (2017). New chapter in tackling antimicrobial resistance in Thailand. *BMJ, 358*(Suppl1), 20-24. doi:10.1136/bmj.j2423

Tadesse, B. T., Ashley, E. A., Ongarello, S., Havumaki, J., Wijegoonewardena, M., González, I. J., & Dittrich, S. (2017). Antimicrobial resistance in Africa: a systematic review. *BMC Infectious Diseases, 17*, 616. doi:10.1186/s12879-017-2713-1

Tancharoen, L., Pairattanakorn, P., Thamlikitkul, V., & Angkasekwinai, N. (2022). Epidemiology and burden of sepsis at Thailand's largest university-based national tertiary referral center during 2019. *Antibiotics (Basel), 11*(7). doi:10.3390/antibiotics11070899

Tangcharoensathien, V., Sattayawutthipong, W., Kanjanapimai, S., Kanpravidth, W., Brown, R., & Sommanustweechai, A. (2017). Antimicrobial resistance: from global agenda to national strategic plan, Thailand. *Bulletin of the World Health Organization, 95*(8), 599-603. doi:10.2471/BLT.16.179648

Teerawattanasook, N., Tauran, P. M., Teparrukkul, P., Wuthiekanun, V., Dance, D. A. B., Arif, M., & Limmathurotsakul, D. (2017). Capacity and utilization of blood culture in two referral hospitals in Indonesia and Thailand. *Am J Trop Med Hyg, 97*(4), 1257-1261. doi:10.4269/ajtmh.17-0193

Umscheid, C. A., Mitchell, M. D., Doshi, J. A., Agarwal, R., Williams, K., & Brennan, P. J. (2011). Estimating the Proportion of Healthcare-Associated Infections That Are Reasonably Preventable and the Related Mortality and Costs. *Infection Control & Hospital Epidemiology, 32*(2), 101-114. doi:10.1086/657912

Van Boeckel, T. P., Gandra, S., Ashok, A., Caudron, Q., Grenfell, B. T., Levin, S. A., & Laxminarayan, R. (2014). Global antibiotic consumption 2000 to 2010: an analysis of

national pharmaceutical sales data. *The Lancet Infectious Diseases, 14*(8), 742-750. doi:10.1016/S1473-3099(14)70780-7

Vincent, J. L. (2016). The clinical challenge of sepsis identification and monitoring. *PLoS Med, 13*(5), e1002022. doi:10.1371/journal.pmed.1002022

Vincent, J. L., Moreno, R., Takala, J., Willatts, S., De Mendonça, A., Bruining, H., . . . Thijs, L. G. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine, 22*(7), 707-710. doi:10.1007/BF01709751

WHO regional office for Europe, & European Centre for Disease Prevention and Control [ECDC]. (2022). *Antimimrobial resistance surveillance in Europe 2022 - 2020 data.* Stockholm, Sweden: ECDC.

World Health Organization [WHO]. (2015a). *Global action plan on antimicrobial resistance*. Geneva, Switzerland: World Health Organization.

World Health Organization [WHO]. (2015b). *Global Antimicrobial Resistance Surveillance System: Manual for early implementation*. Geneva, Switzerland: World Health Organization.

World Health Organization [WHO]. (2017). *Critically important antimicrobials for human medicine – 5th rev.* Geneva, Switzerland: World Health Organization.

World Health Organization [WHO]. (2018). *Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2017-2018*. Geneva, Switzerland: World Health Organization.

World Health Organization [WHO]. (2021). *Antimicrobial resistance*. Retrieved from https://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance

Yam, E. L. Y., Hsu, L. Y., Yap, E. P.-H., Yeo, T. W., Lee, V., Schlundt, J., . . . Wilder-Smith, A. (2019). Antimicrobial resistance in the Asia Pacific region: a meeting report. *Antimicrobial Resistance & Infection Control, 8*(1), 202. doi:10.1186/s13756-019-0654-8

Yehouenou, C. L., Kpangon, A. A., Affolabi, D., Rodriguez-Villalobos, H., Van Bambeke, F., Dalleur, O., & Simon, A. (2020). Antimicrobial resistance in hospitalized surgical patients: a silently emerging public health concern in Benin. *Annals of Clinical Microbiology and Antimicrobials, 19*(1), 54. doi:10.1186/s12941-020-00398-4