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Physicians-Pharmacists Team Intervention in Antimicrobial Stewardship in Hospitals: A Systematic Review and Meta-Analysis

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Abstract
World Health Organization (WHO) stated that one of the ten threats to global health in the year 2019 is antimicrobial resistance (AMR) or antibiotic resistance. The AMR happens when microorganisms, such as bacteria and fungi, develop the ability to stop an antimicrobial, or multiple antimicrobials, from working against it. Its emergence is creating "superbugs" that make treating basic infections difficult and surgery risky. The purpose of this study was to summarize multiple interventional studies into a single report to validate if these interventions would establish a statistically significant difference in antibiotic resistance reduction between patients managed by a Physicians – Pharmacists Team intervention in antimicrobial stewardship programs and those regular patients who were given only the usual medical treatment. The researcher performed a systematic search of Biomed Central, NCBI, Proquest, Elsevier, Google Scholar, Cochrane electronic databases, and EBSCOhost(UIC-Lrsc) from 2000- 2019. Studies were included if they are RCTs or have the quasi-experimental design. Initial studies reviewed were 351, and only 12 studies met the inclusion criteria and selected for systematic review and meta-analysis. The researcher identified five intervention types: Audit and Feedback (6), Point of Care (3), Automatic Stop Order (1), ASP intervention on SAB therapy (1), and Post Prescription Review and Authorization done by a trained pharmacist (1). Physicians – Pharmacists Team interventions were associated with reductions in DDD of surgical antibiotic prophylaxis in antibiotic utilization (control: 16.6 vs. exptl: 12.8, p=0.000), total number of antibiotic days per patient (control: 7.6 vs.vi exptl: 6.6, p=0.006), bacteremia > 7 days (control: 4 days vs. exptl: 3 days, p=0.024), length of stay (control: 7.2 vs. exptl: 6.5, p=0.004), infection-related mortality no. (control: 16 vs. exptl: 8, p=0.047) , overall time to first antibiotic (control: 9:09 vs. exptl: 1:23, p<0.001), antibiotic consumption (control 33% vs. exptl: 3% , p=0.003), median duration of IV antimicrobial treatment (control: 71.7 hours vs. exptl: 55.5 hours, p=0.017), length of antimicrobial therapy (control: 11 days vs. exptl: 10 days, p=0.000), length of IV therapy (control: 10 days vs. exptl: 8 days, p>0.001), total # of DDD of the targeted antibiotics (control: 10 vs. exptl: 8, p=0.040) and total # of days receiving the targeted antibiotics per patient (control: 6 vs. exptl: 4, p=0.002). In conclusion, the results emphasized that the Physicians – Pharmacists Team interventions in antimicrobial stewardship such as Audit and Feedback, Point of Care, Automatic Stop Order, and ASP intervention on SAB therapy are more effective than the conventional methods. Thus, these interventions in antimicrobial stewardship will significantly reduce, lessen, slow down, or prevent the emergence of antimicrobial resistance. Furthermore, among the various interventions, the prospective audit and feedback strategy will have a greater chance to be widely applied because of its clear advantages.

Chapter 1
INTRODUCTION
Background of the Study

World Health Organization (WHO) stated that one of the ten threats to global health in the year 2019 is antimicrobial resistance or antibiotic resistance. The World Health Assembly‘s endorsement of the Global Action Plan on Antimicrobial Resistance (AMR) in May 2015, and the Political Declaration of the High-Level Meeting of the General Assembly on AMR in September 2017, both recognize AMR as a global threat to public health. These policy initiatives acknowledge the overuse and misuse of antimicrobials as a main driver for the development of resistance, as well as a need to optimize the use of antimicrobials. As to support countries in implementing the Global Action Plan to optimize the use of antimicrobial medicines, antimicrobial stewardship (AMS) programmes with practical guidance on how to implement it was provided in the human health sector at the national and healthcare facility level in low- and middle-income countries.

Antibiotic is considered in the past as a phenomenal drug treating many bacterial infections and medicine's most significant success (Sampson, 2018). Since their discovery, antibiotics have served as the cornerstone of modern medicine. This time, however, its success is running out of time. The persistent overuse and misuse of antibiotics in human and animal health have encouraged the emergence and spread of antibiotic resistance, which happens when microorganisms, such as bacteria and fungi, develop the ability to stop an antimicrobial or multiple antimicrobials, from working against it. This scenario threatens to send us back to a time when we were unable to quickly treat infections such as pneumonia, tuberculosis, gonorrhea, and salmonellosis. The inability to prevent infections could seriously compromise surgery and procedures such as chemotherapy.

The emergence of antimicrobial resistance (AMR) is creating "superbugs" that make treating basic infections difficult and surgery risky. It is now one of the biggest public health challenges of our time. Each year in the US, at least 2.8 million people get an antibiotic-resistant infection, and more than 35,000 people die. Projections suggest that by 2050, more people will die of bacterial infections than cancer. If not adequately addressed, the number could grow to 10 million per year by 2050 (United States Pharmacopeia (USP), 2019). Becoming a significant health threat, the United Nation's General Assembly includes AMR as a priority health issue. Fighting this threat is a public health priority that requires a collaborative global approach across sectors. Centers for Disease Control and Prevention (CDC, 2019) is working to combat this threat. WHO also has been leading multiple initiatives to address antimicrobial resistance. A global action plan on antimicrobial resistance, including antibiotic resistance, was endorsed at the World Health Assembly in May 2015. The global action plan aims to ensure the prevention and treatment of infectious diseases with safe and effective medicines (WHO, 2015).

In our country, the Antimicrobial Resistance Surveillance Program (ARSP) found alarming rates of resistance among pathogens (Ong et al., 2016). One is the steady increase of Methicillin-Resistant Staphylococcus aureus (MRSA) –an important cause of hospital and community-acquired pneumonia. Another is a high resistance rate of Neiserria gonorrhea to ciprofloxacin(70%), oflaxacin (70%), and tetracycline (55%) (Ababa, 2018). The Department of Health (DOH) intensifies its campaign to increase public awareness on antimicrobial resistance (AMR), which is now becoming a serious health concern among Filipinos, especially for those being treated with infectious diseases (Montemayor, 2018). According to our secretary of health (Ubial, 2016), the Philippines is committed to lead the fight against

AMR in the region globally recognizing that AMR is a national priority. He encouraged every Filipino to work together for a better healthcare system for our countrymen.

Antimicrobial has been associated with increased mortality, treatment failure, and healthcare costs. To help combat this, antimicrobial stewardship programmes, have been implemented in many countries. These stewardship programmes can help reduce inappropriate prescription and broad-spectrum use of antimicrobials, improve clinical outcomes for the population as a whole, slow down the emergence of antimicrobial resistance, and conserve healthcare resources. Antimicrobial stewardship programmes optimize the use of antimicrobials, improve patient outcomes, reduce AMR and health-care-associated infections, and save healthcare costs, amongst others. Physician – Pharmacists Team is an integral part of the stewardship team and has an essential role in tackling antimicrobial resistance. The term antimicrobial stewardship emerged relatively recently and is being applied in an increasingly diverse range of contexts. In the context of inpatient hospital care, it is frequently coordinated by a multidisciplinary team who lead an antimicrobial stewardship programme that selects from a menu of potential interventions that are adaptable and customizable concepts (Septimus & Owens, 2011), designed to fit the institutional infrastructure: how an antimicrobial stewardship team is embedded in the hospital infrastructure, who is on the team, who is supporting the team, what clinical data are available to the team, and to what extent the stewardship team can directly influence prescribers. Moreover, pharmacists dedicate a large portion of their time to delivering antimicrobial stewardship strategies, including, but not limited to, optimizing prescribing behavior, monitoring antimicrobial use, infection prevention and education, training and public engagement (Garau & Bassetti, 2018).

Furthermore, a vast set of published literature regarding antimicrobial stewardship of Physicians - Pharmacists Team has assessed favorable results, a systematic review and a meta-analysis are the best methods to be used to identify a single result for this exponentially-growing number of interventional studies. Systematic reviews are usually performed to gather the available evidence and develop guidelines for professional practice. To ensure robust evidence, the quality of systematic reviews is required to be thoroughly evaluated. (Rotta et al., 2015). Additionally, the findings of SRs and meta-analyses (MAs) are used for clinical decision making and are integral in developing sound clinical practice guidelines and recommendations (Knoll et al., 2016).

There is no official available study on Physicians – Pharmacists Team intervention in antimicrobial stewardship to prevent antimicrobial resistance in the hospital setting using systematic reviews and meta-analysis. It is for this reason that the researcher, who is a clinical pharmacist, will conduct a systematic review and meta-analysis on the different interventions initiated by Physicians –Pharmacists Team in the prevention of antimicrobial resistance between 2000 to 2019. The systematic review on the prevention of antimicrobial resistance through these various interventions will address the role of Physician – Pharmacist Team within an antimicrobial stewardship programmes and the opportunities for pharmacist importance and strategies in the hospital setting. Generally, the findings of this systematic review can be useful for clinical decision making and in developing sound clinical practice guidelines and recommendations on antibiotic resistance prevention in delivering utmost therapy for our patients in the different hospitals and addressing our country's call regarding AMR prevention.

The researcher had also seen multiple systematic reviews and meta-analyses in the effectiveness of antimicrobial stewardship programs in the hospitals and the impact of pharmacist's role in antimicrobial stewardship programs and strategies in the prevention of antimicrobial resistance. These studies are, ―*Impact of antimicrobial stewardship in critical care: a systematic review*‖ by Kaki et al. (2011);

"*Antimicrobial Stewardship Programs in Inpatient Hospital Settings: A Systematic Review"* by Wagner et al. (2014); *"Systematic Review and Meta-analysis of Clinical and Economic Outcomes from the* 6 *Implementation of Hospital-Based Antimicrobial Stewardship Programs*‖ authored by Karanika et al. (2016); *"Antimicrobial Stewardship in Inpatient Settings in Asia) Pacific Region: A Systematic Review and Meta-analysis*‖ by Honda et al. (2017); *"Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review*‖ written by Nathwani et al. (2019). The results gave a unanimous vote that antimicrobial stewardship programs have a vital impact in the prevention of antimicrobial resistance and that pharmacist has a crucial role within that program, but these studies do not indicate different pharmacist intervention utilized in their systematic reviews and meta-analyses. On the other hand, this study dealt with looking for studies that employed Physicians – Pharmacists Team intervention in antimicrobial stewardship programs to prevent antimicrobial resistance.

Synonyms of antimicrobial resistance (AMR) were used in this systematic review and meta-analysis, such as antibiotic resistance, antimicrobial stewardship program as AMS program or ASP; Collaborative Pharmacist intervention in AMS program or Stewardship interventions.

The purpose of this study was to summarize multiple interventional studies into a single report to show if these interventions give a statistically significant difference in antibiotic resistance reduction between groups of patients managed by a Physicians – Pharmacists Team intervention in antimicrobial stewardship and those patients not enlisted as part of the intervention.

In addition, the disclosure and dissemination of the study findings to the stakeholders of the study were one of the utmost priorities of the researcher. The study results may best serve the pharmacy program, school administrators, and the entire pharmacy profession in the healthcare system. Likewise, the results of this study would be presented to faculty, academic coordinators, school administrators, technical and ethical research committees, other researchers, and scholars during conferences and research forums.

Review Question

Is there a significant difference in the prevention of antimicrobial resistance between patients in hospitals with and without Physicians – Pharmacists Team intervention from the various interventional studies investigated?

Interventional studies, as used in this investigation, pertain to randomized controlled studies (RCTs) or quasi-experimental studies that involve pre-test and post-intervention to control and experimental groups to prevent AMR.

This study is a systematic review and meta-analysis of several similar studies involving Physicians – Pharmacists Team intervention in antimicrobial stewardship conducted to patients admitted in the hospital to prevent AMR.

Review of the Related Literature

This section states several ideas and notions of multiple researchers that are suitable for this study. In this review of related literature, WHO programs on AMR, the meaning of antimicrobial resistance, antimicrobial stewardship, Physicians – Pharmacists Team intervention in antimicrobial stewardship, systematic review, and meta-analysis, and other related terms of this topic were explored.

WHO on AMR and AMS Programs. For decades microbes, in particular, bacteria, have become increasingly resistant to various antimicrobials. The World Health Assembly's endorsement of the Global Action Plan on Antimicrobial Resistance (AMR) in May 2015, and the Political Declaration of the High-Level Meeting of the General Assembly on AMR in September 2017, both recognize AMR as a global threat to public health. These policy initiatives acknowledge the overuse and misuse of antimicrobials as a main driver for the development of resistance, as well as a need to optimize the use of antimicrobials. The Global Action Plan on AMR sets out five strategic objectives as a blueprint for countries in developing national action plans (NAPs) on AMR: Objective 1: Improve awareness and understanding of AMR through effective communication, education, and training. Objective 2: Strengthen the knowledge and evidence base through surveillance and research. Objective 3: Reduce the incidence of infection through adequate sanitation, hygiene, and infection prevention measures. Objective 4: Optimize the use of antimicrobial medicines in human and animal health. Objective 5: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines, and other interventions. WHO created a toolkit that aims to support countries in implementing Objective 4 of the Global Action Plan – ‗optimize the use of antimicrobial medicines‖ – by providing practical guidance on how to implement antimicrobial stewardship (AMS) programmes in the human health sector at the national and healthcare facility level in low- and middle-income countries (LMICs). Antimicrobial stewardship programmes optimize the use of antimicrobials, improve patient outcomes, reduce AMR and health-care-associated infections, and save healthcare costs, amongst others. An AMS programme aims to optimize the use of antibiotics; to promote behavior change in antibiotic prescribing and dispensing practices; to improve quality of care and patient outcomes; to save on unnecessary healthcare costs; to reduce further emergence, selection and spread of AMR; to prolong the lifespan of existing antibiotics; to limit the adverse economic impact of AMR, and to build the best-practices capacity of healthcare professionals regarding the rational use of antibiotics (WHO, 2019).

Antimicrobial Resistance (AMR). It is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antivirals, and antimalarials) from working against it (WHO, 2017). Antimicrobial resistance happens when microorganisms (such as bacteria, fungi, viruses, and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics). Microorganisms that develop antimicrobial resistance are sometimes referred to as "superbugs." As a result, the medicines become ineffective, and infections persist in the body, increasing the risk of spread to others. Penicillin, the first commercialized antibiotic, was discovered in 1928 by Alexander Fleming. Ever since there has been discovery and acknowledgment of resistance alongside the development of new antibiotics. Germs will always look for ways to survive and resist new drugs. More and more, germs are sharing their resistance, making it harder for us to keep up. (CDC, 2019).

Antibiotic-resistant infections are already widespread in the US and across the globe (Golkar et al., 2014). Many public health organizations have described the rapid emergence of resistant bacteria as a ―crisis‖ or ―nightmare scenario‖ that could have ―catastrophic consequences.‖ The CDC declared in 2013 that the human race is now in the "post-antibiotic era." In 2014, the World Health Organization (WHO) warned that the antibiotic resistance crisis is becoming terrible.

Among gram-positive pathogens, a global pandemic of resistant S. aureus and Enterococcus species currently poses the biggest threat. MRSA kills more Americans each year than HIV/AIDS, Parkinson‘s disease, emphysema, and homicide combined. Vancomycin-resistant enterococci (VRE) and a growing number of additional pathogens are developing resistance to many common antibiotics. The global spread of drug resistance among common respiratory pathogens, including Streptococcus pneumonia and Mycobacterium tuberculosis, is epidemic. (Rossolini et al., 2014). Gram-negative pathogens are particularly worrisome because they are becoming resistant to nearly all the antibiotic drug options available, creating situations reminiscent of the pre-antibiotic era. The emergence of Multi-Drug Resistant

(MDR) gram-negative bacilli has affected practice in every field of medicine. The most serious gram-negative infections occur in health care settings and are most commonly caused by Enterobacteriaceae (mostly Klebsiella pneumoniae), Pseudomonas aeruginosa, and Acinetobacter. MDR gram-negative pathogens are also becoming increasingly prevalent in the community. These include extended-spectrum beta-lactamase-producing Escherichia coli and Neisseria gonorrhoeae. (CDC, 2013)

Antibiotic Resistome. This study was anchored to the theory of antibiotic resistome. Resistome means a group of all existing resistance genes(known or unknown) in the world. Antibiotic resistome is dynamic and ever-expanding, yet its foundations were laid long before the introduction of antibiotics into clinical practice.

Awareness of the problem of antimicrobial resistance has risen in both academic and public circles since the Center for Disease Control, and Prevention (CDC) issued a threat report in September 2013, naming infections with Clostridium difficile, Carbapenem-resistant Enterobacteriaceae (CRE), and drug-resistant Neisseria gonorrhoeaeas among the most urgent problems facing clinicians today. While pathogens have become multidrug or extensively drug-resistant, drug companies are drastically reducing their drug discovery programs, leaving a treatment gap that has grave public health consequences. The same CDC report identified four core actions that will help to stop the emergence of additional resistance in pathogens, including preventing the spread of resistance and developing new diagnostic tests for resistant bacteria. Combating the problem requires an understanding of the biological principles and factors that lead to the evolution, divergence, and spread of antibiotic resistance genes. In 2006, the concept of an antibiotic resistome was advanced as a framework to understand and study the origins, evolution, and emergence of resistance. The resistome includes not only the genes that confer resistance to pathogens in the clinic but also to the non-pathogenic species that dominate the environment. Our initial 'resistome' concept also included protoresistance genes, which are precursor genes that are the grist for the evolutionary mill that serves as the source of resistance elements. We now include 'silent'resistance genes in the resistome's evolutionary toolbox, which, like protoresistance genes, do not cause phenotypic resistance until their expression changes through mobilization or mutation to associated regulatory elements. (Perry et al., 2014)

Antimicrobial Stewardship. In its broadest sense, antimicrobial stewardship encompasses any activity that promotes the judicious use of antimicrobial agents in human medicine, veterinary medicine, and animal agriculture around the globe to help combat antimicrobial resistance and preserve drug effectiveness.

In clinical practice, stewardship focuses on coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the timely selection of the optimal antimicrobial regimen of dose, duration of therapy, and route of administration. The primary goals of antimicrobial stewardship are to Slow the spread of antimicrobial-resistant organisms. Extend the lifespan of existing antimicrobial agents and protect the effectiveness of new ones. Improve the quality of patient care and minimize adverse effects of antimicrobial therapy, such as toxicity, allergic reactions, and increased risk of Clostridium difficile infection. Enhance capabilities to identify resistant organisms and monitor the prevalence of resistant infections in people and animals. While the terms **―antimicrobial stewardship" and "antibiotic stewardship"** are often used interchangeably, antimicrobial stewardship promotes the appropriate use of all antimicrobials, including antibiotics, antivirals, antiprotozoals, and antifungals. Antibiotic stewardship is a subset of antimicrobial stewardship. It comprises interventions to prevent drug-resistant bacterial infections, select antibiotic therapy targeted toward susceptible or resistant bacteria, and reduce unnecessary or inappropriate antibiotic administration and use (Center for Infectious Disease Research and Policy (CIDRAP, 2020).

Physicians – Pharmacists Team Interventions in Antimicrobial Stewardship. The term antimicrobial stewardship emerged relatively recently, and is being applied in an increasingly diverse range of contexts; many current definitions of antimicrobial stewardship are technical and focus on prescriptions. Actions that attempt to influence the behavior of prescribers, patients directly, vets and farmers are often clearly aiming to either enable responsible antimicrobial use (e.g., decision support tools, audit, and feedback) or to restrict inappropriate or unnecessary antimicrobial use (e.g., selective reporting of susceptibility testing, formulary restrictions) (Davey et al., 2017). These actions may be correctly termed 'stewardship interventions' in the context of inpatient hospital care. They are frequently coordinated by a multidisciplinary team who lead an antimicrobial stewardship programme that selects from a menu of potential interventions that are adaptable and customizable concepts (Septimus & Owens, 2011), designed to fit the institutional infrastructure: how an antimicrobial stewardship team is embedded in the hospital infrastructure, who is on the team, who is supporting the team, what clinical data are available to the team, and to what extent the stewardship team can directly influence prescribers. As stewardship teams are usually directly responsible for implementing antimicrobial stewardship interventions, hospital quality officers or advisors can support their work with knowledge of effective implementation methodology and involving implementation specialists. Historically, ‗antimicrobial stewardship‘ was mostly used in the narrow context of programmes within individual hospitals. During the 1990s and 2000s, programmes were developed and implemented in many countries, often led by pharmacists in the USA, and in Europe by specialists in infectious diseases or clinical microbiology, often together with a pharmacist. (Kazanjian, 2016). Pharmacists can reduce inappropriate antimicrobial regimens through various Antimicrobial Stewardship strategies, including, but not limited to, optimizing prescribing behavior, monitoring antimicrobial use, infection prevention and education, training, and public engagement. (Garau & Bassetti, 2018). Pharmacists dedicate a large proportion of their time to optimizing prescribing behavior and monitoring antibiotic use. Antimicrobial prescription surveillance systems that monitor the clinical information of a patient and verify that the on-going treatment remains appropriate can have a significant positive financial and clinical impact on the hospital. Pharmacists are central to the delivery of education on stewardship to healthcare professionals, patients, and members of the public.

Indicators Measuring Antibiotic Resistance. A set of outcome indicators has been developed to help monitor the progress in combatting antimicrobial resistance. The indicators, which are the result of a collaboration between the European Food Safety Authority, European Medicines Agency, and European Centre for Disease Prevention and Control, cover antibiotic consumption and resistance for both humans and animals. The indicators are divided into primary and secondary categories. Primary indicators broadly reflect the situation around antimicrobial use and resistance, and secondary indicators have been designed to provide information on more specific issues.

For human antibiotic use, the primary recommended indicator is the total consumption of antibacterial medicines for systemic use — in hospitals — measured by defined daily doses per 1,000 inhabitants and per day.

The first secondary indicator is the ratio of broad-spectrum penicillins, cephalosporins, macrolides, and fluoroquinolones to the use of narrow-spectrum penicillins, cephalosporins, and erythromycin. The second is the proportion of total hospital consumption of glycopeptides, third and fourth generation cephalosporins, monobactams, carbapenems, fluoroquinolones, polymyxins, piperacillin and enzyme inhibitor, linezolid, tedizolid, and daptomycin.

For monitoring antibiotic resistance, the joint scientific opinion recommends the primary indicator to be the proportion of methicillin-resistant Staphylococcus aureus (MRSA) and third-generation cephalosporin-resistant Escherichia coli — both pathogens are described as being of 'major public health importance.'

Without these indicators, we would not be able to assess our progress in tackling the serious health threat posed by antimicrobial resistance (Wilkinson, 2017).

DOH Antimicrobial Stewardship Program in the Hospital. The advent of high resistant pathogens calls our nation to get involved in global efforts to fight AMR. The Philippine Action Plan to Combat AMR: One Health Approach launched in 2015 and the National Policy on Infection Prevention and Control in 2016, are the two of the government's responses to the anticipated perils AMR Program in health facilities ensuring rational prescribing, dispensing and use of antimicrobials to optimize the treatment for infectious diseases towards improving patient outcomes, preventing further impoverishment due to healthcare costs and, and protecting the welfare of the public at large. The National Antimicrobial Stewardship (AMS) Program is the concerted implementation of systematic, multidisciplinary, multi-pronged interventions in both public and private hospitals in the Philippines to improve the appropriate use of antimicrobials, which is essential for preventing the emergence and spread of AMR. Ultimately, the establishment and strengthening of the AMS program in hospitals are critical to achieving the national goal of reducing the morbidity and mortality due to AMR. The Manual of Procedures (MOP) was developed to assist and align the efforts in implementing AMS programs in all hospitals across the country. The National AMS Program is based on six core elements, namely Leadership; Policies, Guidelines, and Policies; Surveillance AMU and AMR; Action; Education; and Performance Evaluation. Clinical pharmacist or pharmacist takes a role in core element 4: Action. In this action, the AMS Program employs a coordinated, multi-prolonged, multidisciplinary approach to safeguard and optimize the use of all antimicrobials used in hospitals. Persuasive interventional strategies aim to persuade healthcare professionals to prescribe antimicrobials appropriately by addressing underlying knowledge, attitudes, or behaviors through active interaction and discussion. Audit and Feedback and Point-of-Care interventions are two strategies under this type. Restrictive intervention strategies control the use of antimicrobials by instituting "barriers" to prescribing and administering certain antimicrobials or after the duration of time. The AMS Program employs Antimicrobial Restriction and Pre-authorization and 7th-day Automatic Stop Order. All AMS strategies and interventions implemented shall be monitored individually and as a whole to measure their effectiveness and to identify areas for further improvement. Performance indicators comprise of quality, quantity, process, and outcome indicators. Examples of outcome indicators are DDD/1000 patient-days of all restricted and monitored antimicrobials (AM); DDD/1000 patient-days of all IV and PO formulations of AM subjected to IV-to-PO switch intervention, and median and range of total AM days of each case admission. (Ong et al., 2016)

Outcome Indicators. According to WHO, the aim of an Antimicrobial stewardship programme is often achieved by reducing overall Antimicrobial consumption and perhaps reducing the overall use of specific (broad-spectrum) antibiotics. However, it is equally important to document that this reduction is not associated with unintended negative patient outcomes. Furthermore, AMS aims to prevent negative patient outcomes and improve patient outcomes, providing further arguments for assessing outcome measures. In healthcare settings without established surveillance programmes for AMR and healthcare-associated infections or electronic health records, it may be challenging to obtain reliable data about clinical outcomes. Given the sound evidence for the safety and effectiveness of AMS programmes, it may be justifiable as a first step to focus on outcome measures related to antimicrobial use. (WHO, 2019)

Moreover, according to Wathne et al. (2019), antimicrobial outcomes can be categorized as primary and secondary outcomes based on The National Guidelines for Antibiotic Use in Hospitals in Norway. Primary outcomes are based on antibiotic consumption and utilization. The primary outcome of the study was the antibiotic consumption of the targeted antibiotics, measured by the DDDs per patient, and duration of treatment in days per patient. Secondary outcome measures were the length of stay, 30-day readmission, and mortality (all-cause in-house and 30-day mortality). Patient secondary outcomes are to be measured to ensure that the interventions did not have any negative consequences for patient treatment. The same outcome measures were used by a study authored by Masia et al. (2008).

Feasibility of Systematic Review and Meta-analysis for RCTs and Quasi-Experimental Studies AMR Prevention. There are several systematic reviews available online to retrieve from different databases for Randomized controlled trials or quasi-experimental studies tackling the prevention of AMR. One study is written by (Divala et al., 2018) entitled "*Effect of the duration of antimicrobial exposure on the development of antimicrobial resistance (AMR) for macrolide antibiotics: protocol for a systematic review with a network meta-analysis."* The study conducted a systematic review, selecting studies if they are published randomized controlled trials (RCTs) which report the relationship between taking a macrolide for any indication and incidence of resistant Streptococcus pneumonia in patients of any age group and used a predefined search strategy to identify studies meeting these eligibility criteria in MEDLINE, Embase, Global Health and the Cochrane Central Register of RCTs.

Systematic Review and Meta-analysis. A systematic review collects all possible studies related to a given topic and design, and reviews and analyzes their results. The quality of studies is evaluated during the systematic review process, and a statistical meta-analysis of the study results is conducted based on their quality. A meta-analysis is a valid, objective, and scientific method of analyzing and combining different results. Usually, to obtain more reliable results, a meta-analysis is mainly conducted on randomized controlled trials (RCTs), which have a high level of evidence. (Ahn & Kang, 2018). Systematic reviews and meta-analyses are common in the medical literature, routinely appearing in specialist and general medical journals, and forming the cornerstone of Cochrane. The majority of systematic reviews focus on summarising the benefit of one or more therapeutic interventions for a particular condition.

Forest Plot. Effect Sizes. Meta-analysis starts with a summary of the data form each study and use it to compute an effect size for the study. An effect size is a number that reflects the magnitude of the relationship between two variables. Meta-analysis in medicine often refers to the effect size as the treatment effect. The term effect size is appropriate when the index is used to quantify the relationship between any two variables or a difference between any two groups. By contrast, the term treatment effect is appropriate only for an index used to quantify the impact of deliberate intervention. The forest plot of meta-analysis is used to assess the impact of an intervention. In the plot, each study is represented by a square, bounded on either side by a confidence interval. The location of each square on the horizontal axis represents the effect size for that study. The confidence interval represents the precision with which the effect size has been estimated. The size of each square is proportional to the weight that will be assigned to the study when computing the combined effect. The effect size could represent the impact of the intervention. For measures of effect size based on ratios, a ratio of 1.0 represents no difference between groups. For measures of groups based on differences (such as mean difference), a difference of 0.00 represents no difference between groups (Borenstein et al., 2011).

Q Test. The standard chi-squared test (Cochran Q test) for statistical heterogeneity tests the statistical hypothesis that the true treatment effects (the effect size parameters) are the same in all the primary studies included in the meta-analysis (Sutton et al., 2000). This statistical test uses a test statistic Q that has a chi-squared distribution on k-1 degrees of freedom (k represents the number of studies) under the statistical hypothesis; the corresponding p-value for the test statistic is examined (Sutton et al., 2000). The statistical power of the test is, in most cases, very low due to the small number of studies; heterogeneity may be present even if the Q statistic is not statistically significant at conventional levels of significance, such as 0.05. A cut-off significance level of 0.10 rather than the usual 0.05 has been advocated (Sutton et al., 2000). If results of the test are statistically significant ($p<0.05$) the statistical hypothesis that the true treatments effects (the effect size parameters) are the same in all the primary studies included in the meta-analysis (the hypothesis of homogeneity) is rejected, therefore, it is considered that there is statistical heterogeneity.

I2. The goal of a meta-analysis is not merely to report the mean effect size but also to indicate how the effect sizes in the various studies are dispersed about the mean. We need to know also if the impact is consistent, varies moderately, or varies widely from study to study. Researchers often use the I**2** statistic to quantify the amount of dispersion (Higgins & Thompson, 2002). I**2** is an intuitive statistic for many reasons. It ranges from 0% to 100%, so we have a clear sense of where the heterogeneity in any given meta-analysis falls relative to this range. The range is independent of the specific effect size. It so has the same meaning for a meta-analysis of odds ratios as it does for a meta-analysis of mean differences. I**2** is mainly unaffected by the number of studies in the meta-analysis, and so allows us to compare the I**2** for different analyses even if the number of studies differs.

Additionally, there are widely used benchmarks for I**2**. For example, I**2** values of 25%, 50%, and 75% have been interpreted as representing small, moderate, and high levels of heterogeneity. These are seen to provide a convenient context for discussing the results of any analysis. (Borenstein et al., 2017)

Tau2. In random-effects meta-analysis, the extent of variation among the effects observed in different studies (between-study variance) is referred to as tau-squared, τ**2**, or Tau**2** (Deeks et al., 2008). τ**2** is the variance of the effect size parameters across the population of studies, reflecting the variance of the true effect sizes. The square root of this number is referred to as tau (T). T**2**and Tau reflects the amount of true heterogeneity. T**2** represents the absolute value of the true variance (heterogeneity). T**2** is the variance of the true effects, while tau (T) is the estimated standard deviation of underlying true effects across studies (Deeks et al., 2008). The summary meta-analysis effect and T as the standard deviation may be reported in random-effects meta-analysis to describe the distribution of true effects (Borenstein et al., 2011).

Related Study. *Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis* a study authored by Schuts et al. (2016) when they did a systematic review and meta-analysis to assess whether antimicrobial stewardship objectives had any effects in hospitals and long-term care facilities on four predefined patients' outcomes: clinical outcomes, adverse events, costs, and bacterial resistance rates. They identified 14 stewardship objectives and did a separate systematic search for articles relating to each one in Embase, Ovid MEDLINE, and PubMed. Overall, the quality of evidence was generally low, and heterogeneity between studies was mostly moderate to high. For the objectives of empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation, the overall evidence showed significant benefits for one or more of the four outcomes. Evidence of effects was less clear for adjusting therapy according to renal function, discontinuing therapy based on lack of clinical or microbiological evidence of infection, and having a local antibiotic guide. Their findings of beneficial effects on outcomes with nine antimicrobial stewardship objectives suggest they can guide stewardship teams to improve the quality of antibiotic use in hospitals.

Conceptual Framework

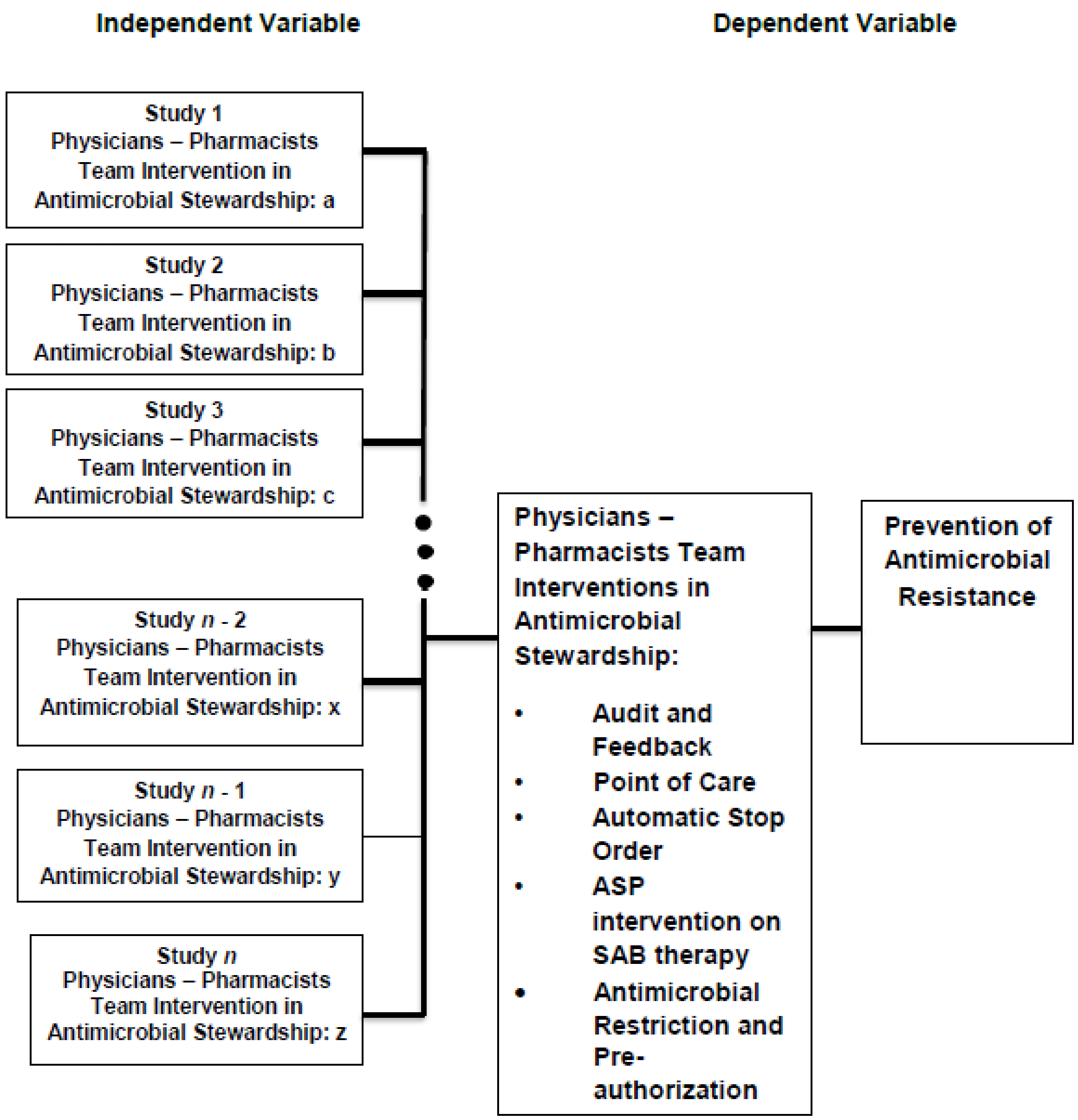

Figure 1. The Conceptual Framework of this Study Showing the Relationship of the Variables.

As shown in figure 1, the independent variables in the studies reviewed, and meta-analyzed were the various interventions to prevent antimicrobial resistance embodied in the studies that employed Physicians – Pharmacists Team interventions in antimicrobial stewardship. Independent variables are types of variables that produce effects or results on dependent variables in causal hypotheses (Neuman, 2014). Physicians – Pharmacists Team interventions in antimicrobial stewardship are core elements needed to optimize antimicrobial use through Physicians – Pharmacists Team's initiatives and strategies. (Garau & Bassetti, 2018). The study categorized the Physicians – Pharmacists Team interventions into five taxonomy. These are Audit and Feedback, Point of Care, Automatic Stop Order, ASP intervention on SAB therapy and Antimicrobial Restriction, and Pre-authorization. The reviewed literature and studies are associated with these five interventions.

The dependent variable in the studies to be reviewed and meta-analyzed is the prevention of antimicrobial resistance, specifically the various outcomes that indicate or describe the extent of antimicrobial resistance prevention. Dependent variables are the effect or result variables that are caused by independent variables in causal hypotheses (Neuman, 2014). Antimicrobial Resistance occurs when bacteria and other microbes adapt and become less susceptible to medical treatment, according to United States Pharmacopeia. 26

Chapter 2
METHODS

This chapter provides the research design, place of study, data sources and selection, criteria for inclusion, quality assessment, data synthesis and analysis, and the ethical considerations.

Research Design

This study employed a systematic review and a meta-analysis to verify from a carefully selected number of primary studies the effectiveness of physicians–pharmacists team intervention through an antimicrobial stewardship in preventing antimicrobial resistance among the patients. A systematic review is an initiation of whether research findings are constant and can be generalized across populations, settings, and treatment variations, or whether results vary remarkably by specific subsets (Mulrow, 1994). The systematic review gives the best proof of the effectiveness of multiple perspectives for assisting behavioral change (Bero et al., 1998).

On the other hand, meta-analysis is the statistical technique that integrates or merges the results of multiple independent experiments that the researcher deems combinable (Huque, 1988). Meta-analysis of observational studies show specific problems because of innate biases and differences in study designs. Still, they may give an instrument for aiding to perceive and quantify sources of discrepancy in results between the studies (Stroup et al., 2000). With these methods, this study was able to answer the review question. These methods form a single interpretation from the results of multiple related studies.

Place of Study

The study was conducted at the University of the Immaculate Conception, Bonifacio Street, Davao City, Philippines, as a partial requirement for the degree of Master of Science in Pharmacy. The University of the Immaculate Conception was founded in 1905 and had been generating numerous Master graduates in different fields and courses that it offers. This university has a good track record for research and publication and a well-articulated mechanism for its quality assurance as evidenced by national and international accreditation certifications.

The researcher also made use of the conducive areas that are wifi accessible such as the libraries and internet cafes.

Data Sources and Selection

The online research websites from the World Wide Web, which the researchers had utilized to gather the specific studies containing required data were Biomed Central, Cochrane Library, Elsevier, Science Direct, ProQuest, Google Scholar, and EBSCOhost (UIC –Lrsc). Initially, 351 numbers of articles were targeted to be included in this study.

The quasi-experimental and randomized controlled trial studies gathered in this systematic review were those focused on the different Physicians –Pharmacists Team intervention in antimicrobial stewardship. These were accessed adequately from online journals and critically analyzed by the researcher. The studies from various websites were found using the following keywords: Physicians – Pharmacists Team intervention in antimicrobial stewardship (AMS), antimicrobial stewardship program, antimicrobial resistance, antibiotic resistance, and stewardship interventions.

The researcher evaluated the studies found by looking if the titles, abstracts, and methods used were relevant to the systematic review. The critical viewpoints that the researcher considered for a study that was effectively put in to use were: the study deals on Physicians – Pharmacists Team intervention in antimicrobial stewardship conducted to patients admitted in the hospital; the study is available for public utility for strategic antimicrobial resistance preventions; and lastly, the institutions supporting directly and indirectly the studies havee high credibility and standards. The criteria mentioned were set by the researcher to have a fair and eligible review on each of the studies. The studies utilized met the required specifications.

Criteria for Inclusion

This section provides the set of criteria for the researches used for the review. The researcher gathered studies that met the following criteria: topic is regarding Physicians – Pharmacists Team interventions in AMR prevention, the design is RCT or quasi-experimental with pre-test and post-test, the year of publication is between 2000-2019, the study was conducted at the hospital, it is written in English, and the study has a statistical validity with respect to sample size, level of significance and sample size.

The criteria used to exclude the studies for the systematic review and meta-analysis were the following: irrelevant studies because they were identified as purely observational studies or experimental studies without interventions, settings were in the community or outpatient or after hospital discharge, systematic reviews, not a Physicians – Pharmacists Team intervention and research that do not reveal relevant information fit for the study; were identified to be a duplicated study in terms of publication status; cohort studies where observations were made without interventions; studies that have abstracts only or no full text of article were available; and the sample size of the experimental and control group was less than 50. Hence, this particular systematic review and meta-analytical study focused on two-groups, with pre-test and post-test quasi-experimental studies, that measured the prevention of antimicrobial resistance in the hospital setting to eliminate biases and heterogeneity between the collected studies that might result into the interpretation of the analysis as void.

Data Extraction

Studies used for systematic review and meta-analysis are Physicians – Pharmacists Team intervention in antimicrobial stewardship programs conducted to patients admitted in the hospital to prevent antimicrobial resistance. The general features of primary studies considered for preliminary screening were authors, the number of authors, year study was published, the name of hospital or country the research was conducted, language used, design, control group mean, treatment or experimental group mean, experimental or treatment group sample size, control group sample size, p-value, F or T-Test value, total population, patient, and the website. The data extracted of the included studies were its title, author, year published and place of the study conducted, publisher and link, design, the sample size of treatment and control groups, outcome indicators of Physicians – Pharmacists Team interventions, the mean of scores of two groups, the standard mean difference, and the p-value.

Quality Assessment

There was no single precise, systematic method to assess the quality of studies that took part in this systematic review. The assessments made were based on factual means with specifications to the credibility of the researcher as a clinical pharmacist herself, the authenticity of the studies, the connection of variables between studies, the validity of the research method used that follows quasi-experimental and RCTs uniformity and the integrity of the institutions or organizations supporting the studies. Furthermore, studies classified to be significant contained highly constructed focus questions that primarily concerned the Physicians – Pharmacists Team intervention in AMS to prevent AMR.

The consideration in including the studies to this systematic review was made to ensure that the studies follow the same quality standards regarding the bases mentioned. The studies were considered highly commendable because each of the interventions grasps the prevention of antibiotic resistance among patients admitted to the hospital.

The following are the criteria that met the quality assessment: (1) the chosen studies are authored by a reputable pharmacist or any practicing healthcare professionals, (2) the articles are recently published in the online journal, (3) the chosen studies are conducted in at least 100-bed capacity hospitals, (4) the study's intervention is clearly defined as Physicians – Pharmacists Team intervention (5) the outcome measures of the chosen studies are clearly defined as to prevent antimicrobial resistance, (6) the selected studies have quantifiable and traceable statistical parameters, (7) the chosen studies are either RCTs or quasi-experimental with two groups and assignments as pre-test and post-test.

Data Synthesis and Analysis

Thematic Analysis. The study utilized the Participants, Interventions, Comparison, and Outcomes (PICO) Analysis. Initially, the studies were tabulated to see if they have a valid electronic source. Then, they were inspected to fit the inclusion criteria that were devised by the researchers. A flow diagram was created to show the process of selecting and excluding studies until all criteria were inspected. Then, the remaining studies were tabulated again. This time, the data that were tabulated were the data from the data extraction section as included in the second table.

The narrative synthesis followed after. The narrative synthesis was broken down into two sections. The first section was the organization of the description of the studies into logical categories, such as, where the research was conducted, the gender of the samples, the method of evaluation, and moderator variables, if any. The second section was the synthesis of the findings across all included studies. The studies were listed and summarized, those whose results came out for the hypothesis being tested, and those that were against (Pettigrew & Roberts, 2006).

Meta-analysis. In a meta-analysis, the effect size standardized findings across studies such that they can be directly compared (Lipsey & Wilson, 2001). For quasi-experimental and RCT studies, the standardized mean difference was to get the effect size of a specific study with respect to all the remaining studies. The standardized mean difference was defined as the magnitude of the difference between the means of two groups as a function of the groups' standard deviations (Card, 2015). The data used in these computations came from the data extracted, as described in the data extraction section of this chapter. The index of standardized mean difference used in this meta-analysis is Cohen's *d*.

The inverse variance weight then is computed as studies generally vary in size. This statistical tool makes sure that the larger studies should carry more weight in the analysis than smaller studies (Lipsey & Wilson,

2001).
The standard error was included in computation as it is a direct index of the effect size. It was used to create confidence intervals. Lipsey & Wilson (2001) also contends that the smaller the standard error, the more precise the effect size.
Finally, the weighted mean effect size was computed. It is the effect size of all the remaining studies. This value determines the closeness of the results of every study using various statistical tools. For this study, Cohen's rule-of-thumb was used to assess the closeness of every study's findings. Cohen's rule-of-thumb describes the range of variability of the results of the studies (Lipsey & Wilson, 2001). If the weighted mean effect size is from 0 to 0.20, there is a small variability between the results; 0.21-0.79, a medium variability; and 0.80-1, a large variability.
The standard error for the weighted mean effect size was computed to gather the amount of precision across studies and estimate the precision of the mean effect size.
After computing the standard error for the weighted mean effect size, the value made for statistical inferences calculated the confidence intervals. To evaluate statistical significance, a Wald test (Z) was used. The standard error of the mean effect size was also used to compute confidence intervals.
Heterogeneity and Publication Bias. In heterogeneity of the studies, looking for study heterogeneity will not be done anymore as the inclusion criteria were already specific and precise (Pettigrew & Roberts, 2006). Therefore, only the statistical heterogeneity was computed. Statistical heterogeneity, as explained by Card (2015), is when the deviation among studies exceed the amount of expectable deviation. The Q statistic and I2 were used to identify statistical heterogeneity. These statistical tools find the impact of heterogeneity on meta-analyses. The Q statistic was a measure of weighted squared deviations, and I2 was the ratio of true heterogeneity to the total observed variation.
Higgins (2004) suggests that while I2 may never reach 100%, values in excess of 70% should invite caution and may mean a heterogeneous group of studies. If it is below 70%, then the studies are homogenous.
A forest plot was also made as this was a useful diagnostic tool in looking for heterogeneity in the studies included in a systematic review and meta-analysis. With this, it can support the result of the I2. A forest plot displays a range of information. First, they present both the point estimate and uncertainty of effect sizes from every study in the meta-analysis, serving a useful summary function similar to tables of individual studies. Second, the inclusion of the vertical line for the mean effect size makes this information apparent. Third, this plot provides visual information regarding the heterogeneity of studies (Card, 2015).
As heterogeneity was measured, with the researcher assuming homogeneity between the remaining studies after satisfying the inclusion criteria, the models for computation used above were termed random-effects models (Card, 2015). Therefore, there was no adjustment in the results of the computation of the effect size and heterogeneity.
Publication bias is when studies with statistically significant results are more likely to get published than those with non-significant results (Pettigrew & Roberts, 2006). To check if there is a publication bias in the remaining studies, a funnel plot should be made. A funnel plot is simply a scatterplot of the effect sizes found in studies relative to their sample size (Card, 2015).
The application used in the meta-analysis is the CMA software. This comprehensive meta-analysis software was easy to use regardless if you are a researcher, the instructor, or a statistician.

Ethical Consideration

This study underwent rigorous, analytical evaluation and ethical review by the University of the Immaculate Conception - Research Ethics Committee (UIC-REC) that ensured that this study followed the key and required ethical procedures and standards. This study had no human participants, as this was a review of multiple types of research. But because of such circumstance, the researcher was also aware of the privacy of the data that were found in the said researches. As such, the researcher applies for the EXEMPT category in ethical review. Based on the National Ethical Guidelines for Health and Health-Related Research 2017, protocols that do not involve human participants nor identifiable human tissue, biological samples, and data (e.g., meta-analysis protocols) shall be exempted from the ethical review. Protocols that involve the use of publicly available data or information were also qualified for the exemption.

Chapter 3

RESULTS AND DISCUSSION

This chapter presents the summary of the included studies, analysis, and interpretation of the research findings based on the review question stated in Chapter 1. The presentation begins with the study selection backed-up by a schematic diagram, followed by an explanation of the features of the studies, and the qualitative summary. This chapter further examines if there is a significant difference in the prevention of antimicrobial resistance between patients admitted in the hospital with and without Physicians – Pharmacists Team intervention in antimicrobial stewardship from the multiple interventional studies investigated shown in the PICO table and meta-analysis plots and statistical figures.

Study Selection

The flowchart for the selection of the studies is shown in Figure 2. The gathering of studies from the different electronic databases reached 351 studies. After deliberation of the relevance of titles and abstracts, 266 studies were excluded since the titles reflected issues with the designs implemented. They were irrelevant studies because they were identified as purely observational studies or experimental studies without the specified interventions; were done in the community or dealing with outpatients or those after hospital discharge, systematic reviews, not Physicians – Pharmacists Team interventions and thse studies do not reveal relevant information fit for the study. Only 85 studies remained for review, and out of it, 44 were identified as duplicated studies, thus being excluded. Out of 41 remaining studies, 17 studies were excluded since they were cohort studies where observations were made without interventions. Twenty-four studies remained, and 11 studies were excluded from the systematic review as they have abstracts only, or no full text of the article was available. There was one study identified with a sample size of less than 50. With that, there were remaining 12 studies that met the prescribed sample size of 50 and above, considering the total sample sizes of the experimental and control group. In all, the thorough stepwise deliberations narrowed the number of studies from initially 351 identified studies to only a total of 12 studies included and these were subjected for the systematic review analysis and meta-analysis.

From the initial 351 studies, 12 studies were selected for systematic review and meta-analysis. The chosen studies' designs were either randomized controlled trial (RCT) or quasi-experimental studies. There were two RCTs and 10 quasi-experimental studies utilized for this systematic review. The RCT is a study design that randomly assigns participants into an experimental group or a control group.

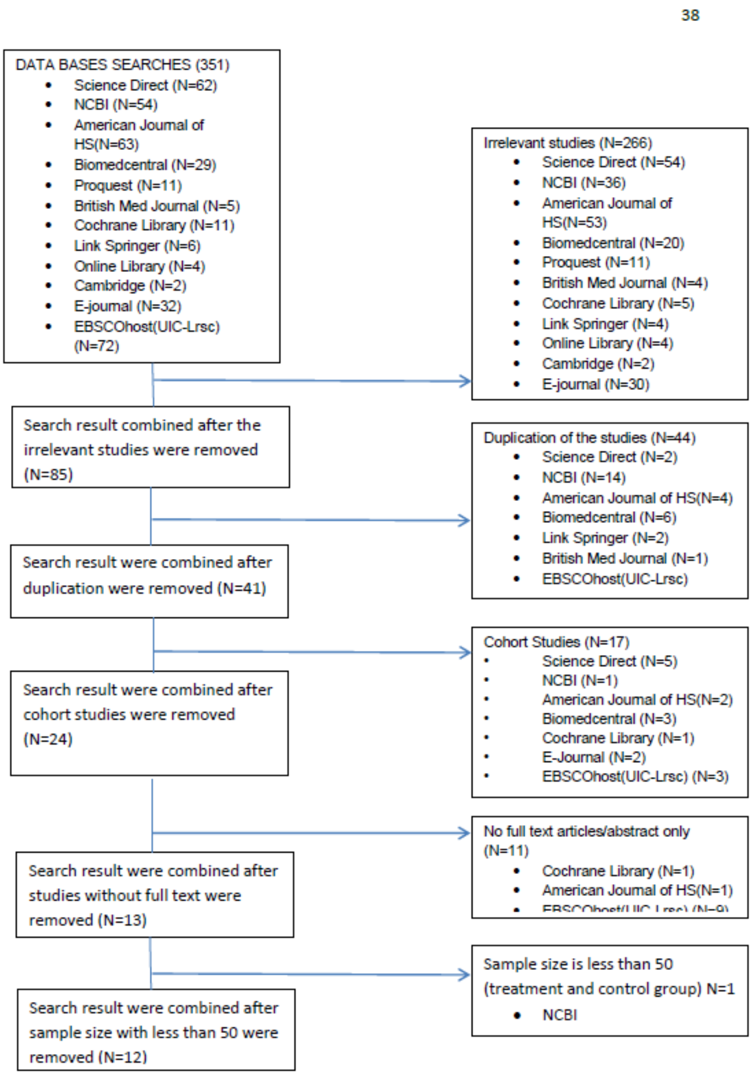

Figure 2. Flow Chart for the Study Selection

RCT is the most applicable design to review since it seeks to measure and compare the outcomes after the participants receive the interventions. Quasi-experimental research involves manipulating an independent variable without the random assignment of participants to conditions or orders of conditions. A quasi-experimental design is also fit to review because it identifies a comparison group that is similar to the treatment (experimental) group in terms of baseline (pre-intervention or control) characteristics.

General Features of Primary Studies

Considered for Preliminary Screening

Initially, there were 351 studies reviewed. The information extracted from those studies were the authors, the number of authors, year study was published, the name of hospital or country the research was conducted, language used, design, control group mean, treatment or experimental group mean, experimental or treatment group sample size, control group sample size, p-value, F or T-Test value, total population, patient, and the website. These individual studies' URL were presented in Appendix A, and all the information extracted were exhibited in Appendix B.

Specific Features of the Included Studies

Finally, from 351 studies, 12 of these studies met quality inclusion criteria and were included in the systematic review and meta-analysis. Table 1 exhibits the features of these selected studies.

Table 1
Features of the Included Studies

TITLE	AUTHORS; YEAR PUBLISHED; COUNTRY	PUBLISHER; URL	DESIGN	SAMPLE SIZE (n)	OUTCOME INDICATOR	MEAN	SMD	p-VALUE
1. Impact of pharmacist-led antibiotic stewardship interventions on compliance with surgical antibiotic prophylaxis in obstetric and gynecologic surgeries in Nigeria.	Abubakar, U., Syed Sulaiman, S. A., & Adesiyun, A. G.; 2019 Nigeria	PLOS ONE; https://www.ncbi.nlm.nih.gov/pubmed/30845240	Quasi-experimental	exp-238 con-226	Antibiotic utilization: DDD of surgical antibiotic prophylaxis	exp-12.8 con-16.6	0.365	p= 0.000
2. Effects of an automatic discontinuation of antibiotics policy: A novel approach to antimicrobial stewardship	Bolten, B. C., Bradford, J. L., White, B. N., Heath, G. W., Sizemore, J. M., & White, C. E. 2019 Kentucky, USA	AJHP American Society of Health-System Pharmacists; https://academic.oup.com/ajhp/article-abstract/76/Supplement_3/S85/5550351	Quasi-experimental	exp-162 con-162	Total number of antibiotic days per patient	exp-6.6 con-7.6	0.307	p= 0.006
3. Effect of an intervention targeting inappropriate continued	Choe, P. G., Koo, H. L., Yoon, D.,	Biomed Central; http://web.a.ebscohost.com.u	Quasi-experimental	exp-1,244 con-1,249	Amount of empirical vancomycin (DDDs/	exp-19.99 con-23.9	0.113	p= 0.005

empirical parenteral vancomycin use: a quasi-experimental study in a region of high MRSA prevalence.	Bae, J. Y., Lee, E., Hwang, J.-H. & Kim, N. J. 2018 Switzerland	iclrsc.remotexs.co/ehost/detail/detail?vid=0&sid=b775c5d6-316d-42de-8b7f-2ad2991190a9%40sessionmgr4007&bdata=JnNpdGU9ZWhvc3QtbGl2ZQ%3d%3d#AN=129090393&db=afh			1000 patient-days) Amount of inappropriate continued empirical vancomycin (DDDs/1000 patient-days)	 exp-5.8 con-8.0		 p= 0.009
4. A noninferiority cluster-randomized controlled trial on antibiotic postprescription review and authorization by trained general pharmacists and infectious disease clinical fellows	Rattanaumpawan, P., Upapan, P., & Thamlikitkul, V. 2018 Thailand	SHEA-The Society for Healthcare Epidemiology of America; https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01955125/full?highlightAbstract=pharmacist%7Cwithdrawn%7Ca	RCT	exp-303 con-307	Length of hospital stay DDD per prescription of targeted antibio-tics DDD per prescription of overall antibiotic 28-d overall mortality	exp-19.81 con-20.40 exp-13.49 con-12.86 exp-46.03 con-41.43 exp-61 con-82	0.027	p= 0.74 p=0.58 p=0.32 p=0.06

		ntimicrobial%7Cantimicrobi%7Chospital%7Chospit						
5. Impact of a pharmacist-driven care package on Staphylococcus aureus bacteremia management in a large community healthcare network: A propensity score-matched, quasi-experimental study	Smith, J. R., Frens, J. J., Snider, C. B., & Claeys, K. C. 2018 North Carolina, USA	Diagnostic Microbiology and Infectious Disease; https://www.sciencedirect.com/science/article/abs/pii/S0732889317303073	Quasi-experimental	exp-172 con-86	Bacteremia > 7 days	exp-3 con-4	0.300	p= 0.024
6. Formalization of an antimicrobial stewardship program in a small community hospital	Lockwood, A. R., Bolton, N. S., Winton, M. D., & Carter, J. T. 2017 Montana, USA	AJHP American Society of Health-System Pharmacists; https://academic.oup.com/ajhp/article-abstract/74/17_Supplement_3/S52/5102292?redirectedFrom=fullt	Quasi-experimental	exp-56 con-68	Vancomycin : DOT per order (days)	exp-1.43 con-2.93	0.664	p= 0.000

		ext						
7. The effect of antibiotic stewardship interventions with stakeholder involvement in hospital settings: a multicentre, cluster randomized controlled intervention study	Wathne, J. S., Kleppe, L. K. S., Harthug, S., Blix, H. S., Nilsen, R. M., … Smith, I. 2018 Norway	BiomedCentral; https://aricjournal.biomedcentral.com/articles/10.1186/s13756-018-0400-7#Bib1	RCT	exp-523 con-1,279	Length of stay	exp-6.5 con-7.2	0.151	p= 0.004
8. Impact of an antimicrobial stewardship initiative on time to administration of empirical antibiotic therapy in hospitalized patients with bacteremia.	Bias, T. E., Vincent, W. R., Trustman, N., Berkowitz, L. B., & Venugopalan, V. 2017 New York, USA	AJHP American Society of Health-System Pharmacists; http://web.b.ebscohost.com.uiclrsc.remotexs.co/ehost/detail/detail?vid=0&sid=979bf8e9-8909-40cb-9d82-61aacab630da%40pdc-v-sessmgr03&bdata=JnNpdGU9ZWhvc3QtbGI2Z	Quasi-experimental	exp-71 con-62	Infection-related mortality, no. Overall time to first antibiotic	exp-8 con-16 exp-1:23 con-9:09	0.349	p= 0.047 p<0.001

		Q%3d%3d#AN=122330969&db=afh						
9. Effects of an operational multidisciplinary team on hospital antibiotic use and cost in France: a cluster controlled trial	Bevilacqua, S., Demoré, B., Erpelding, M.-L., Boschetti, E., May, T., May, I., Thilly, N. 2011 France	Int J Clin Pharm-Springer; https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00812241/full?highlightAbstract=pharmacist%7Cwithdrawn%7Cantimicrobial%7Cantimicrobi	Quasi-experimental	Exp-720 con-484	Antibiotic consumption	exp-3.3% con-33.6%	0.175	p= 0.003
10. Implementing a pharmacist-led sequential antimicrobial therapy strategy: a controlled before-and-after study	Dunn, K., O'Reilly, A., Silke, B., Rogers, T., & Bergin, C. 2011 Ireland	Int J Clin Pharm-Springer; https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00810802/full?highlightAbstract=antimicrobial%7Chospit%7Cstewardship	Quasi-experimental	exp-177 con-113	Median duration of IV antimicrobial treatment (hours)	exp-55.5 con-71.7	0.289	p= 0.017

		%7Cpharmaci%7Cwithdrawn%7Cantimicrobi%7Chospital%7Cpharmacis						
11. Effects of pharmaceutical counselling on antimicrobial use in surgical wards: intervention study with historical control group.	Grill, E., Weber, A., Lohmann, S., Vetter-Kerkhoff, C., Strobl, R., & Jauch, K.-W. ; 2011 Germany	Wiley Online Library; https://www.ncbi.nlm.nih.gov/pubmed/21452339	Quasi-experimental	exp-321 con-317	Length of antimicrobial therapy (day) Length of IV therapy (day)	exp-10 con-11 exp-8 con-10	0.353	p= 0.000 p>0.0001
12.Limited efficacy of a nonrestricted intervention on antimicrobial prescription of commonly used antibiotics in the hospital setting: results of a randomized controlled trial	Masiá, M., Matoses, C., Padilla, S., Murcia, A., Sánchez, V., Romero, I., … Gutiérrez, F. 2008 Spain	Eur J Clin Microbiol Infect Dis – Springer; https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00648035/full?highlightAbstract=pharmacist%7Cwithdrawn%7Cantimicrobial%7Cantimicrobi	RCT	exp-146 con-132	Total # of DDD of the targeted antibio-tics Total # of days receiving the targeted antibio-tics per patient	exp-8 con-10 exp-4 con-6	0.248	p= 0.040 p= 0.002

URL = Uniform Resource Locator

AJHP = American Journal of Health-System Pharmacy
Int J Clin Pharm = International Journal of Clinical Pharmacy by Springer
Eur J Clin Microbiol Infect Dis = European Journal of Clinical Microbiology & Infectious Diseases
DDD= Defined daily dose
SAB = *Staphylococcus aureus* Bacteremia (SAB)

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IV= Intravenous
CDI = Clostridium difficile infection
LOS = length of stay.
SOB = Shortness of breath
DOT= duration of therapy

The data in Table 1 were sought from electronic databases and varieties of websites of colleges and universities and covered different continents. It presents the features relevantly needed for thematic analysis and meta-analysis. The data were gathered from different electronic databases and were already published, generated, and written by different authors around the globe. The data obtained were the title, authors, the year study is published, country where the study was conducted, the publishing company, the link or uniform resource locator (URL), design, sample size of the control and experimental group, specific outcome indicator, the standard mean difference and the p-value.

The researcher thoroughly reviewed the features of the twelve included studies and summarized them in Table 2

Table 2
Profile of 12 included studies.

Profile		Number of studies	Study Number
Continent/ Country	Europe	6	
	Switzerland		3
	Norway		7
	France		9
	Ireland		10
	Germany		11
	Spain		12
	USA	4	
	Kentucky		2
	North Carolina		5
	Montana		6
	New York		8
	Africa	1	1
	Nigeria		
	Asia	1	4
	Thailand		
Number of Authors	7	3	3, 9 & 12
	6	3	2, 7 & 11
	5	2	8 &10
	4	2	5 & 6
	3	2	1 & 4
Year Published	2019	2	1 & 2
	2018	4	3, 4, 5 & 7
	2017	2	6 & 8
	2011	3	9, 10 & 11
	2008	1	12
Publishing Company	PLOS ONE	1	1
	AJHP	3	2, 6 & 8
	BMC	2	3 & 7
	SHEA	1	4
	Diagnostic Microbiology and Infectious Disease	1	5
	IJCP	2	9, 10
	Wiley Online Library	1	11
	EJCMID	1	12

Design	RCT Quasi-experimental	3 9	4, 7 & 12 1,2,3,5,6,8,9,10&11
Number of participants in experimental group group	>50; <100 >100;<500 >500; <1000 > 1000	2 7 2 1	6, 8 1,2,4,5,10,11&12 7, 9 3
Number of participants in control group	>50; <100 >100;<500 >500; <1000 > 1000	3 7 2	5,6 & 8 1,2,4,9,10,11&12 3 & 7

Comparison between control group and experimental group with respect to outcomes	Control > Experimental Control < Experimental	12 1	1, 2, 3, 4(LOS), 5,6,7,8,9,10,11&12 4 (DDD/Rx &28dM)
SMD	< 0	12	All 12 studies
p-value	< 0.05 >0.05	11 1	1,2,3,5,6,7,8,9,10,11&12 4

Table 2 presents the profile of the included studies. It includes different countries across different continents, number of authors, and year published, publishing company, design of the study, the total number of participants of experimental and control groups among 12 studies, comparison between the control group and experimental group with respect to outcomes, SMD and p-value.

Features of Twelve Studies. Specifically, six studies were identified to have been conducted in Europe across Switzerland, Norway, France, Ireland, Germany, and Spain; four all over America, such as Kentucky, North Carolina, Montana, and New York; and one in Thailand, Asia and Nigeria, Africa. Various individuals across the globe authored the studies chosen. There were three studies written by six and seven authors and two studies authored by three, four, and five persons. One of the inclusion criteria is to review studies published from 2000 to 2019. The twelve studies selected are recently published from the year 2008 to 2018. Two studies were published last 2019, four studies in 2018, another two studies were published last 2017, three studies last 2011, and one study was published last 2008.

The studies selected were from reputable publishing companies from America and Europe that are either for-profit or non-profit. There were three studies published by the American Journal of Health-System Pharmacy (AJHP), two were distributed by Biomed Central and International Journal of Clinical Pharmacy by Springer. The other remaining publishers were Plos One, Society for Healthcare Epidemiology of America (SHEA), Diagnostic Microbiology and Infectious Disease, Wiley Online Library and European Journal of Clinical Microbiology & Infectious Diseases which is an interdisciplinary journal devoted to the publication of communications on infectious diseases of bacterial, viral and parasitic origin. The description of each publishing company listed is discussed in Appendix C.

The selected studies' designs were either randomized controlled trial (RCT) or quasi-experimental studies. There are 2 RCTs and 10 Quasi-experimental studies utilized. All studies reflected sample sizes greater than 50 in both samples of experimental and control groups. Two studies have more than 50 but less than 100 experimental samples, seven of which was greater than 100 but less than 500, two studies had experimental samples were greater than 500, but less than 1000 and one study has more than one thousand sample size. Whereas in the control group sample size, three studies are having greater than 50 but less than 100, seven studies had greater than 500, but less than 1000 and 2 studies have more than 1000. This means all twelve selected studies met the inclusion criteria and produced a statistically significant result by utilizing a large trial of effective intervention (Faraone, 2018).

In table 1, outcome indicators of interest of the study are presented. These outcome indicators are outlined in DOH Antimicrobial Stewardship Program Procedural Manual in the hospital. The following are the outcome indicators: DDD of surgical antibiotic prophylaxis in antibiotic utilization, total number of antibiotic days per patient, amount of empirical vancomycin (DDDs/1000 patient-days), amount of inappropriate continued empirical vancomycin (DDDs/1000 patient-days), length of hospital stay, DDD per prescription of targeted antibiotics, DDD per prescription of overall antibiotic, 28-d overall mortality, bacteremia> 7 days, DOT per order (days) of vancomycin, length of stay, infection-related mortality (number) , overall time to the first antibiotic, antibiotic consumption, median duration of IV antimicrobial treatment (hours), length of antimicrobial therapy (day), length of IV therapy (day), total # of DDD of the targeted antibiotics, total # of days receiving the targeted antibiotics per patient. See Appendix D for a description of each outcome indicator.

Table 2 presents the relationship between the mean score of the experimental group and the control group. Out of the twelve studies, only one study (Study 4) has three outcome indicators that the mean score of the experimental group to control is from high to low, respectively. Study 4 also has one indicator with a high control group mean score and a low experimental group mean score. All other eleven studies have a high control group mean score lowered after post-intervention (experimental group).

Primary Study Indicators. Out of the twelve studies, only one study (Study 4) has three outcome indicators that the mean score of the experimental group to control is from high to low, respectively. Study 4 also has one indicator that has a high control group mean score to the low experimental group mean score. All other eleven studies have a high control group mean score lowered after post-intervention (experimental group). More importantly, according to Faraone (2018), if the improvement is associated with lower scores on the outcome measure, SMDs lower than zero indicate the degree to which intervention is more efficacious than traditional and SMDs greater than zero indicate the degree to which intervention is less efficacious than traditional.

Primary Study SMD. When indirect comparisons are conducted, meaning there is a meaningful comparison of interventions from different indicators, measuring effect size is essential to make sensible evaluations. The standard mean difference (SMD), also known as the effect size, is used to estimate the effect of the treatment. Accordingly (Faraone, 2018), the SMD of zero means that the new treatment and the placebo have equivalent effects. If improvement is associated with higher scores on the outcome measure, SMDs greater than zero indicate the degree to which treatment is more efficacious than placebo. SMDs less than zero indicates the degree to which treatment is less efficacious than a placebo. If improvement is associated with lower scores on the outcome measure, SMDs lower than zero indicate the degree to which treatment is more efficacious than placebo and SMDs greater than zero indicate the degree to which treatment is less efficacious than placebo. As observed in table 2, all twelve studies have lesser than zero SMD. This implied that the intervention is more efficacious than the traditional or conventional method.

Primary Study p-value. The studies gathered have p–values ranging from 0.000 to 0.740. P-values are the marginal significance within a statistical hypothesis test, presenting the probability of the occurrence of a given event. In this review, we only examined significance based on studies reporting p-values. Studies that measured outcomes of interest and found that the change in result values from pre- to post-intervention had a p-value of < 0.05 were classified as statistically significant. Studies with a change in result values that measured a p-value of ≥0.05 were classified as non-statistically significant. Table 2 shows that study 4 has p-values greater than 0.05, which means those indicators have no significant difference, whereas the other 11 studies have a p-value lower than 0.05. These data mean these interventions through their indicators have a significant difference.

Participants, Intervention, Comparator, and Outcomes (PICO) Analysis

This study utilized the PICO analysis to review the selected 12 studies further. In defining the SR review question in terms of the specific patient problem, PICO aided in finding clinically relevant evidence in the 12 studies selected. Moreover, the PICO Model is a format that helped define the research question. Table 3, the PICO table presents the title together with the authors, year, and country it was published; design of the study, participants or patients, interventions, comparator, and outcomes.

Table 3
Data for Participants, Interventions, Comparators and Outcomes (PICO) Analysis

TITLE; AUTHOR; YEAR PUBLISHED; COUNTRY	DESIGN	PARTICIPANTS/ PATIENTS (n)	INTERVENTIONS	COMPARATOR	OUTCOMES
1.Impact of pharmacist-led antibiotic stewardship interventions on compliance with surgical antibiotic prophylaxis in obstetric and gynecologic surgeries in Nigeria. Abubakar, U., Syed Sulaiman, S. A., & Adesiyun, A. G. 2019 Nigeria	Quasi-experimental	• Obstetrics and Gynecologic Surgeries Patients • Mean age : 32 y.o • Female • Surgical procedure: CS, Myomectomy, Hysterectomy, laparotomy or Laparoscopy • experimental group (n =238) • control group (n=226)	Development of Protocol, educational meeting and audit and feedback. Period: May – Dec. 2016 Duration (D): 3 months Done by: Clinical Pharmacist Targeted Antibiotics: Third generation cephalosporins	Antibiotic stewardship interventions (protocol, educational meeting and audit and feedback) compared to traditional practice	Control vs. Experimental • Antibiotic utilization: DDD of surgical antibiotic prophylaxis **16.6 vs. 12.8 (p=0.000)** There was a significant decrease in antibiotic utilization after the interventions. **SMD = 0.365** The intervention is effective than traditional practice
2. Effects of an automatic discontinuation of antibiotics policy: A novel approach to antimicrobial stewardship. Bolten, B. C.,	Quasi-experimental	• ICU and non ICU adult patients • Mean age: 62 y.o • Both male and female • PMH: CAP, HAP, COPD, SBP or ABSSSI	Implementation of an automatic discontinuation of antibiotics policy (ADAP) Period: Nov 2015 –	Antibiotic stewardship intervention (ADAP) compared to traditional practice	Control vs. Experimental • Total number of antibiotic days per patient **7.6 vs. 6.6 (p=0.006)** There was a significant decrease in total

Bradford, J. L., White, B. N., Heath, G. W., Sizemore, J. M., & White, C. E. 2019 Kentucky, USA		• experimental group (n =162) • control group (n=162)	April. 2016 Duration (D): 4 months Done by: Infectious Disease(ID) Pharmacist		number of antibiotic days per patient **SMD = 0.307** The intervention is effective than traditional practice.
3.Effect of an intervention targeting inappropriate continued empirical parenteral vancomycin use: a quasi-experimental study in a region of high MRSA prevalence. Choe, P. G., Koo, H. L., Yoon, D., Bae, J. Y., Lee, E., Hwang, J.-H. Kim, N. J. 2018 Switzerland	Quasi-experimental	• Adult patients from medial ward, medical ICU, surgical ward and surgical ICU. • Mean age :60 y.o. • Male • PMH: DM, Chronic Liver disease, Chronic Lung disease, Cerebrovascular disease, azotemia or neutropenia • experimental group (n =1,244) • control group (n=1,249)	Monitoring of appropriateness and direct discussion with the prescribing physicians . Period: March – Sep. 2015 Duration (D): 6 months Done by: General Pharmacist Targeted Antibiotics: Vancomycin Broad Spectrum	Antibiotic stewardship intervention (Monitoring by pharmacist of appropriate Vancomycin use) compared to frequently inappropriate-ly vancomycin used as empirical treatment.	1.Control vs. Experimental • The amount of empirical vancomycin (DDDs/1000 patient-days) **23.9 vs. 19.9 (p=0.005)** There was a significant decrease in the amount of empirical vancomycin (DDDs/1000 patient-days) **SMD = 0.113** The intervention is effective than traditional practice. 2.Control vs. Experimental • Amount of inappro-priate continued empirical

					vancomycin (DDDs/1000 patient-days) **8.0 vs. 5.8 (p=0.009)** There was a significant decrease in the amount of inappro-priate continued empirical vancomycin (DDDs/1000 patient-days)
4. A noninferiority cluster-randomized controlled trial on antibiotic postprescription review and authorization by trained general pharmacists and infectious disease clinical fellows. Rattanaumpawan, P., Upapan, P., & Thamlikitkul, V. 2018 Thailand	RCT	• Patient aged > 15 y.o who received atleast 1 dose of the targeted antibiotic. • Mean age :60 y.o. • Female • PMH: Chronic Lung disease, Cerebrovascular disease, CVD,DM, CKD, solid tumor, Neutropenia or HIV • experimental group (n =303) • control group (n=307)	Antibiotic postprescription review and authorization (PPRA) determined by trained general pharmacists Period: Feb. 1 – Sep. 30 2013 Duration (D): 8 months Done by: General Pharmacist Targeted Antibiotics: Piperacillin/Tazobactam Imipenem/Cilastatin Meropenem	Comparing the effectiveness of antibiotic postprescription review and authorization (PPRA) determined by trained general pharmacists with that of infectious disease (ID) clinical fellows	1.Control vs. Experimental • Length of hospital stay **20.40 vs. 19.81 (p=0.740)** There was **no** significant decrease in the length of stay. **SMD = 0.027** The intervention is effective than traditional practice. 2.Control vs. Experimental • DDD per prescription Of targeted

					antibiotics **12.86vs. 13.49 (p=0.58)** There was **no significant difference** in the DDD per prescription of targeted antibiotics 3.Control vs. Experimental • DDD per prescription of overall antibiotics **41.43 vs. 46.03 (p=0.74)** There was **no significant difference** in the DDD per prescription of over all antibiotics 4.Control vs. Experimental • 28-d overall mortality **82 vs. 61 (p=0.06)** There was **no significant decreased** in the 28-d overall mortality
5. Impact of a pharmacist-driven care package on Staphylococcus aureus bacteremia management in a large community healthcare network: A propensity score-matched, quasi-experimental study Smith, J. R., Frens, J. J., Snider, C. B., & Claeys, K. C. 2018 North Carolina, USA	Quasi-Experimental	• Adult patient > 18 with SAB • Mean age: 63 y.o • Male • PMH: DM, CKD, HIV or surgery • experimental group (n =303) • control group (n=307)	Pharmacist-driven, ASP intervention on SAB therapy. Period: Nov.2013 – Dec. 2015 Duration (D): 25 month3 Done by: Clinical Pharmacist only Targeted Antibiotics: Cefazolin, Nafcillin, Vancomycin, Daptomycin	Pharmacist –driven Antibiotic stewardship intervention (ASP intervention on SAB therapy) compared to traditional practice	Control vs. Experimental • Bacteremia > 7 days **4 vs. 3 (p=0.024)** There was a significant decrease in Bacteremia > 7 days **SMD = 0.300** The intervention is effective than traditional practice.
6. Formalization of an antimicrobial stewardship program in a small community hospital Lockwood, A. R., Bolton, N. S., Winton, M. D., & Carter, J. T. 2017 Montana, USA	Quasi-experimental	• Hospital patients who received one or more doses of antimicrobials in medical units and ICU. • Mean age: 63 y.o • experimental group (n =56) • control group (n=68)	Formalization of a fully integrated and multi pharmacist ASP • Deescalate therapy • Change to more appropriate therapy Period: March – June 30. 2016 Duration (D): 4 months	Comparison of Pharmacist intervention involving antimicrobial therapy before and after formalization of antimicrobial stewardship program	Control vs. Experimental • The mean DOT per order for parenteral vancomycin **2.93 vs. 1.43 (p=0.000)** There was a significant decrease in the mean DOT per order for parenteral vancomycin **SMD = 0.300**

			Done by: General Pharmacist Targeted Antibiotics: Vancomycin, Tazobactam		The intervention is effective than traditional practice.
7. The effect of antibiotic stewardship interventions with stakeholder involvement in hospital settings: a multicentre, cluster randomized controlled intervention study. Wathne, J. S., Kleppe, L. K. S., Harthug, S., Blix, H. S., Nilsen, R. M., … Smith, I. 2018 Norway	Quasi-experimental	• Adult patient from ID, pulmonary medical and gastronomy units • Mean age: 68 y.o • Both male and female • PMH: Pneumonia, LRTI, COPD, Sepsis, UTI or GIT infection • experimental group (n =71) • control group (n=62)	Audit with feedback Period: Feb – April 2014 Duration (D): 3 months Done by: General Pharmacist Targeted Antibiotics: Vancomycin Penecillin 3rd gen Cephalosporin	Pharmacist –driven Antibiotic stewardship intervention (Audit with feedback) compared to traditional practice	Control vs. Experimental • Length of stay **7.2 vs. 6.5 (p=0.004)** There was a significant decrease in the length of stay. **SMD = 0.300** The intervention is effective than traditional practice.
8. Impact of an antimicrobial stewardship initiative on time to administration of empirical antibiotic therapy in hospitalized patients with bacteremia. Bias, T. E., Vincent, W. R., Trustman, N., Berkowitz, L. B., & Venugopalan, V. 2017 New York, USA	Quasi-experimental	• age 18 years or older • infection occurred two or more days after hospital admission • Had a blood culture growing an organism other than common skin contaminants (i.e., coagulase-negative staphylococci, *Bacillus* species) • Mean age: 68 y.o • Female • experimental group (n =71) • control group (n=62)	Rapid administration of antimicrobials by an infectious diseases specialist (RAIDS) protocol. (ID physician, a pharmacist, and a microbiology laboratory director) Period: Dec.2010 – Feb. 2011 Duration (D): 3 months Done by: ID Pharmacist	Study was conducted for adult in-patients who received antibiotics following RAID protocol compared with those patients without RAID protocol.	1.Control vs. Experimental • No. of infection-related mortality **16 vs. 8 (p=0.047)** There was a significant decrease in the number of infection-related mortality **SMD = 0.349** The intervention is effective than traditional practice. 2.Control vs. Experimental • Overall time to first Antibiotic **9:09 vs. 1:23 (p<0.001)** There was a significant decrease in the overall time to first antibiotic
9. Effects of an operational multidisciplinary team on hospital antibiotic use and cost in France: a cluster controlled trial Bevilacqua, S., Demoré, B., Erpelding, M.-L., Boschetti, E., May, T., May, I.,	Quasi-experimental	• Medical and Surgical ward patients • PMH: hemodialysis, CVD, Respiratory Diseases, Kidney Diseases, Liver diseases or GIT • Surgery: Digestive or Urology • experimental group (n =720) • control group (n=484)	Operational Multidisciplinary Antibiotic Team (OMAT) (An infectious disease physician and a clinical pharmacist) Period: July 2007 – June 2008 Duration (D): 12 months	Site 2 where OMAT was operational on all wards compared to Site 1 where OMAT was not implemented	Control vs. Experimental • Antibiotic consumption **33% vs. 3% (p=0.003)** There was a significant decrease in the antibiotic consumption **SMD = 0.175** The intervention is effective in Site 2 than in Site 1

Thilly, N. 2011 France			Done by: Clinical Pharmacist Targeted Antibiotics: Vancomycin, Ceftazidime, Cefepime Amikacin		
10. Implementing a pharmacist-led sequential antimicrobial therapy strategy: a controlled before-and-after study Dunn, K., O'Reilly, A., Silke, B., Rogers, T., & Bergin, C. 2011 Ireland	Quasi-experimental	• Adult patient who were prescribed IV antimicrobial drug in the 1st 4 days of admission from medical wards • Mean age: 74 y.o • Male • PMH: RTI, UTI, skin and soft tissue abdomen or infections • experimental group (n =177) • control group (n=113)	Application of stickers and criteria for switch to oral antimicrobial therapy to the drug chart Period: Dec 2006 – June 2007 Duration (D): 7 months Done by: Pharmacist Targeted Antibiotics: Co-amox Ciprofloxacin	Pharmacist –driven Antibiotic stewardship intervention (Application of stickers and criteria for switch to oral antimicrobial therapy to the drug chart) compared to conventional practice clinical pharmacist (reviewing drug charts and contacting prescribers to discuss a switch to an oral antimicrobial continued)	Control vs. Experimental • Median duration of IV antimicro-bial treatment (hours) **71.7 vs. 55.5 (p=0.017)** There was a significant decrease in the antibiotic consumption **SMD = 0.289** The intervention is effective than the conventional practice
11. Effects of pharmaceutical counselling on antimicrobial use in surgical wards: intervention study	Quasi-experimental	• Adult patient from surgical wards • Mean age: 62 y.o • Female • Surgery: Abdominal, vascular or Thoracic	Clinical pharmacist reviewed the prescriptions and give advice on medication. • Discontinuation of therapy	Patients receiving pharmaceutical intervention compared to historical control group	1.Control vs. Experimental • Length of antimicro-bial therapy(day) **11 vs. 10 (p=0.000)**
with historical control group. Grill, E., Weber, A., Lohmann, S., Vetter-Kerkhoff, C., Strobl, R., & Jauch, K.-W. ; 2011 Germany		• experimental group (n =321) • control group (n=317)	• Intravenous/oral sequential therapy • Adjustment to standards • Choice of agent • Adjustment of dosage • Therapeutic drug monitoring Period: Aug 2007 – Jan 2008. Duration (D): months 7 Done by: Clinical Pharmacist Targeted Antibiotics: Ciprofloxacin Piperacillin/ Tazobactam		There was a significant decrease in the length of antimicro-bial therapy(day) **SMD = 0.353** The intervention is effective than historical practice. 2.Control vs. Experimental • Length of IV therapy (day) **10 vs. 8 (p>0.001)** There was a significant decrease in the length of IV therapy (day)
12.Limited efficacy of a nonrestricted intervention on antimicrobial prescription of commonly used antibiotics in the hospital setting: results of a randomized	RCT	• Adult patient from medical and surgical wards • Mean age: 68 y.o • Male • PMH: Neoplasia, DM, COPD, Pneuomonia, LRTI, Fever and neutropenia	Antibiotic regimen counselling targeted to match local antibiotic guidelines by pharmacist. Period: Jan 7 – June 30 2006 Duration (D): 3	Pharmacist –driven Antibiotic stewardship intervention (Antibiotic regimen counselling) compared to traditional practice	1.Control vs. Experimental • Total # of DDD of the targeted antibiotics **10 vs. 8 (p=0.040)** There was a significant decrease in total # of

controlled trial Masiá, M., Matoses, C., Padilla, S., Murcia, A., Sánchez, V., Romero, I., … Gutiérrez, F. 2008 Spain		• experimental group (n =146) • control group (n=132)	months Done by: General Pharmacist Targeted Antibiotics: Carbapenem Vancomycin		DDD of the targeted antibiotics **SMD = 0.248** The intervention is effective than historical practice. 2.Control vs. Experimental • Total # of days receiving the targeted antibiotics per patient **6 vs. 4** **(p=0.002)** There was a significant decrease in the Total # of days receiving the targeted antibiotics per patient

CS - Caesarean Section
CAP – Community Acquired Pneumonia
HAP – Hospital Acquired Pneumonia
SBP – Spontaneous Bacterial Peritonitis
ABSSSI – Acute Bacterial Skin and Skin Structure Infection
CVD- Cardivascular Disease
SAB- *Staphylococcus areus* Bacteremia
ID- Infectious Disease
PMH- Patient Medical History
DOT – Duration of therapy
LRTI – Lower Respiratory Tract Infection
COPD – Chronic Obstructive Pulmonary Disease
UTI – Urinary Tract Infection
GIT – Gastrointestinal Tract
DM – Diabetes Mellitus
DDD – Defined Daily Doses

Table 3 presents the Participants, Interventions, Comparator and Outcomes (PICO) analysis with the following details, title of the study together with the name of the authors, year and country the study was published; design of the study; participants or patients involved in the post-intervention; the interventions implemented for each study, comparator used among control groups and the relevant outcomes. Participant's demographic and medical history and sample size were also presented. Table 3 also shows the period and duration the intervention was conducted, pharmacists, who led the study, and the target antibiotics utilized.

Design. Quasi-experimental and Randomized Controlled Trials designs were employed in all the studies. All in all, there are 9 Quasi-experimental studies and 3 RCTs. Quasi-experimental research is an empirical interventional study used to estimate the causal impact of an intervention on the target population without random assignment. At the same time, RCT is a trial in which participants are randomly assigned to two or more groups: at least one (the experimental group) receiving an intervention that is being tested and another (the comparison or control group) receiving an alternative treatment or placebo. RCT design allows an assessment of the relative effects of interventions.

Participants. Someone who takes part in the experimental or control group is called a participant or patient. All 12 studies employed adult participants aged 35 to 73 years old. These participants were patients from medical wards, surgical wards, or intensive care units (ICU). Four studies employed patients from medical wards, three studies utilized patients from both medical wards and ICU, two studies had surgical ward patients, another two studies had both medical and surgical patients, and one study employed patients form ICU only. Patient medical history from medical wards comprised of common diseases of respiratory, kidney, liver lungs, endocrine, cardiovascular, cerebrovascular, gastrointestinal tract and other infections from the skin and soft tissues and abdomen while surgeries are done for patients in the studies are either digestive, urology, abdominal, vascular, thoracic, obstetric or gynecologic surgeries. The four studies

consisted of female participants. There are four studies in which purely males were involved, two studies compose of both female and male participants, and the remaining two studies did not identify the gender.
Interventions. The intervention caused any difference in outcomes between the experimental and control groups**.** Physicians – Pharmacists Team interventions in antimicrobial stewardship programs were employed in all chosen studies to prevent antimicrobial resistance. Five of the chosen studies used to Audit and Feedback intervention. Audit and Feedback intervention is a prospective audit with direct intervention, and feedback to the prescriber involves the clinical evaluation of the individual prescription of antimicrobials for appropriateness, followed by the immediate and direct communication with prescribers to optimize treatment for patients. Three studies used Point of Care (POC) interventions. POC interventions occur routinely at the ward level with direct feedback to the prescriber or attending physician at the time of prescription or laboratory diagnosis. It improves patient management and outcomes and is an excellent opportunity to educate clinical staff on appropriate prescribing. POC interventions include dose optimization, de-escalation of antimicrobial therapy, intravenous to oral (IV-to-PO) antimicrobial switch therapy, and rapid administration of antimicrobials.

Lastly, three used different interventions such as Automatic Stop Order, Antimicrobial Restriction and Pre-authorization and Pharmacist-driven, ASP intervention on SAB therapy. Automatic Stop Order policy authorized the ASP team to automatically halt antibiotic treatment in cases involving inappropriate duplicate antimicrobial coverage or excess duration of treatment. This policy will prevent unnecessary exposure or prolonged antimicrobial exposure, thus preventing patients from the emergence of drug-resistant organisms and adverse effects. Antimicrobial Restriction and Pre-authorization require clinicians to obtain approval for the use of selected antimicrobials before prescribing. These antimicrobials are typically last-line antimicrobials that demand to preserve their use to conditions they are indeed indicated. This strategy is also helpful in minimizing unnecessary patient exposure to toxicities and costs associated with inappropriate therapy. Pharmacist-driven, ASP intervention on SAB therapy is SAB management based on predefined intervention led by clinical pharmacists and infectious diseases physicians. ASP intervention on SAB therapy was associated with increased adherence to core SAB care metrics and reduced relapse and mortality. The interventions included among 12 studies employs developmental steps from simple counseling (2008) to more advance and great approach (2018 to 2019)—the interventions in which a pharmacist-led will also use collaborative operations with other AMS teams. Appendix E presents the description and summary of the procedure of how the interventions are implemented in the study.
Comparator. The comparator captures what would have been the outcomes if the intervention had not been implemented. The comparison may be a standard practice, traditional practice, conventional practice, or no intervention at all. Among all of the 12 studies, seven studies were using the traditional method or conventional method. The experimental group in the remaining four studies were compared to before and after the implementation or formalization of interventions. The last one used different strategies, Post Prescription Review, and the trained pharmacist does authorization was compared to Post Prescription Review and Authorization by Fellow Clinicians.
Outcome. These are the outcomes the study used to measure and compare after the participants received the interventions. The SMD of the ten studies differ from each other, 0.027 being the smallest value of SMD and 0.664 being the highest value. Out of the 12 studies, 11 studies showed all of their outcome indicators have a significant difference. One study showed its outcome indicator has no significant difference. The outcome indicators of Audit and Feedback interventions showed all significant differences, which means the AMS Program on Audit and Feedback done by Physicians – Pharmacists Team is an

effective intervention in preventing AMR. These outcome indicators include antibiotic utilization, course, consumption or use, DDDs/1,000 patient days of vancomycin, and inappropriate consumption of antimicrobials. All outcome indicators of Point of Care (POC) Intervention have also shown significant difference, and again this shows Physicians – Pharmacists Team intervention in AMS on POC is an effective intervention in preventing AMR. These outcome indicators include DOT per order, injection-related deaths, and duration of therapy. Pharmacist intervention, ASP intervention on SAB therapy, demonstrates that pharmacist-led intervention decreased time to appropriate antibiotic treatment and is associated with enhanced adherence to established markers of therapeutic efficacy in SAB. This intervention was also associated with a lower rate of readmission due to SAB.

Table 4
Profile of the Intervention and Outcomes based on DOH Antimicrobial Stewardship Program Manual of Procedures

Intervention	Outcome (Control vs Experimental)	Study Number	Number of studies
Audit and Feedback	There was a significant decrease in antibiotic utilization after the interventions. **(Control vs. Exp.16.6 vs. 12.8 (p=0.000))** The intervention is effective than traditional practice. **SMD = 0.365**	1	6
	1There was a significant decrease in the amount of empirical vancomycin (DDDs/1000 patient-days) **23.9 vs. 19.9 (p=0.005)** The intervention is effective than traditional practice. **(SMD = 0.113)** 2.There was a significant decrease in the amount of inappropriate continued empirical vancomycin (DDDs/1000 patient-days) **(8.0 vs. 5.8 (p=0.009)**)	3	
	There was a significant decrease in the length of stay.(**7.2 vs. 6.5 (p=0.004))** The intervention is effective than traditional practice. **(SMD = 0. 151)**	7	

	There was a significant decrease in the antibiotic consumption. 33% **vs. 3% (p=0.003)** The intervention is effective in Site 2 than in Site **SMD = 0.175**	9	
	1.There was a significant decrease in the length of antimicrobial therapy(day) **11 vs. 10 (p=0.000)** The intervention is effective than historical practice. **SMD = 0.353** 2.There was a significant decrease in the length of IV therapy (day) **10 vs. 8 (p>0.001)**	11	
	1.There was a significant decrease in total # of DDD of the targeted antibiotics**10 vs. 8 (p=0.040)** The intervention is effective than historical practice. **SMD = 0.248** 2.There was a significant decrease in the Total # of days receiving the targeted antibiotics per patient. **6 vs. 4 (p=0.002)**	12	
Point of Care	There was a significant decrease in the mean DOT per order for parenteral vancomycin. **0.93 vs. 1.43 (p=0.000)** The intervention is effective than traditional practice. **SMD = 0.300**	6	3
	1.There was a significant decrease in the number of infection-related mortality. **16 vs. 8 (p=0.047)** The intervention is effective than traditional practice. **SMD = 0.349**	8 &	
	2.There was a significant decrease in the overall time to first antibiotic. **9:09 vs. 1:23 (p<0.001)** There was a significant decrease in the antibiotic consumption. **71.7 vs. 55.5 (p=0.017)** The intervention is effective than the conventional practice. **SMD = 0.289**	10	
Automatic Stop Order	There was a significant decrease in total number of antibiotic days per patient.**7.6 vs. 6.6 (p=0.006)** The intervention is effective than traditional practice. **SMD = 0.307**	2	1

Antimicrobial Restriction and Pre-authorization	1.There was no significant decrease in the length of stay. **20.40 vs. 19.81 (p=0.740)** The intervention is effective than traditional practice. **SMD = 0.027** 2.There was **no significant difference** in the DDD per prescription of targeted antibiotics. **12.86vs. 13.49 (p=0.58)** 3. There was **no significant difference** in the DDD per prescription of over-all antibiotics. **41.43 vs. 46.03 (p=0.74)** 4.There was **no significant decreased** in the 28-d overall mortality **82 vs. 61 (p=0.06)**	4	1
ASP intervention on SAB therapy.	There was a significant decrease in Bacteremia > 7 days. **4 vs. 3 (p=0.024)** The intervention is effective than traditional practice. **SMD = 0.664**	5	1

Table 4 presents the profile of the intervention and outcomes based on the DOH Antimicrobial Stewardship Program Manual of Procedures. It includes the intervention, comparison of control and experimental mean, p-value and outcomes, study number, and the number of studies that utilized the corresponding intervention. The interventions among the twelve selected studies were categorized into five, namely: Audit and Feedback, Point of Care, Automatic Stop Order, Antimicrobial Restriction and Pre-authorization and ASP intervention on SAB therapy.

Intervention: Audit and Feedback. Audit and feedback had the highest number of 6 among 12 studies interventions used to prevent AMR. Statistically, amount of empirical vancomycin (DDDs/100 patient-days), Length of hospital stay, antibiotic consumption, Length of antimicrobial therapy, Length of IV therapy, total # of DDD, or targeted antibiotics and the total number of days receiving the targeted antibiotics per patient decreased significantly. Thus, Audit and feedback are more effective than traditional practice. To prevent AMR

Intervention: Point of Care. Three studies used point of care intervention. Statistically, DOT per order for parenteral vancomycin, the number of infection-related mortality, and overall time to the first antibiotic decreased significantly. Thus, Point of Care intervention is more effective than traditional practice to prevent AMR

Intervention: Automatic Stop Order. Automatic Stop Order significantly decreased the total number of antibiotic days per patient. Thus, it is more effective than traditional practice to prevent AMR.

Intervention: ASP Intervention on SAB. ASP intervention on SAB therapy also significantly decreased the bacteremia greater than seven days. Thus, it is more effective than traditional practice to prevent AMR. The author claimed this as the first study to have a pharmacist-led intervention to be a cornerstone of care, as others have been based on physician or multifaceted intervention. Perhaps most importantly, the data further support the use of antimicrobial stewardship to reduce not only antibiotic exposure but also improve patient care and outcomes.

Intervention: Antimicrobial Restriction and Pre-Authorization Done by a Trained Pharmacist. However, Antimicrobial Restriction and Pre-authorization done by trained pharmacist does not show any significant effect. There was no significant decrease in Length of stay, DDD per the prescription of targeted antibiotics, and overall antibiotics and 28-day overall mortality. Though, SMD shows that it is more than the comparator.

The only intervention that revealed no significant difference is Post Prescription Review and Authorization done by trained pharmacists. The study has demonstrated that general pharmacists who have undergone a short ID training course can safely implement an antibiotic approval program. However, the study could not confirm the noninferiority of a pharmacist PPRA in the targeted antibiotic consumption nor demonstrate noninferiority in terms of favorable clinical response. This study was conducted in Thailand. It faces a shortage of ID specialists and ID clinical pharmacists; thus, the study sought to determine whether trained general pharmacists could effectively implement an antibiotic approval program. Furthermore, there was no significant difference in the consumption of the targeted antibiotics, antibiotic expenditure, and other important treatment outcomes. From these findings, the strategy of using general pharmacists trained in the above manner appears safe; however, it may not be efficient in reducing antibiotic consumption as an ID clinical fellow implements antibiotic approval.

Table 5
Profile of Outcomes with Significant Effect Based on WHO Outcome Measures or Indicators

	Outcomes	Number of studies	Number of Interventions	Interventions
Primary Outcomes (Antimicrobial Usage)	antibiotic utilization	2	2 1	Audit and feedback Point of care
	in the amount of empirical antibiotic (DDDs/1000 patient-days)	1	1	Audit and feedback
	amount of inappropriate continued empirical antibiotic (DDDs/1000 patient-days)	1	1	Audit and feedback
	length/DOT of antimicrobial therapy	2	1 1	Audit and feedback Automatic Stop order
	length or days of IV therapy	2	1 1	Audit and feedback Point of care
	Total # of DDD receiving the targeted antibiotics per patient	1	1	Audit and feedback
	Total # of days receiving the targeted antibiotics per patient	1	1	Audit and feedback
	overall time to first antibiotic	1	1	Point of care
Secondary Outcomes (Patient/microbiology outcomes)	length of stay	1	1	Audit and feedback
	Bacteremia>7days	1	1	ASP intervention on SAB therapy
	number of infection-related mortality	1	1	Point of care

Table 5 presents the profile of outcomes with a significant effect based on WHO outcome measures or indicators. WHO classifies outcomes of measures into primary, which refer to the antimicrobial usage and secondary outcomes regarding patient or microbiology outcomes. The table also shows the different interventions and the number of times they were used.

Out of the 12 studies, 11 studies have primary outcomes based on antimicrobial usage, 6 of that 11 studies have relevant outcomes related to the following: antibiotic utilization, DOT of antimicrobial therapy, and days of IV therapy. The other remaining five studies include a significant decrease in the amount of empirical antibiotics (DDDs/1000 patient-days), amount of inappropriate continued empirical antibiotics (DDDs/1000 patient-days), the total number of days receiving the targeted antibiotics per patient and overall time to first antibiotic. Moreover, 3 out of 12 studies have secondary outcomes, specifically 2 of that are related to patient outcomes (Length of stay and number of infection-related to mortality) and one on microbiology outcome(Bacteremia>7days). The interventions involved are Audit and feedback, Point of Care, and ASP intervention on SAB therapy.

There are 11 primary outcomes, and there are only three secondary outcomes revealed. Audit and feedback and point of care are the interventions both utilized with primary and secondary outcomes. To top it all, Audit and feedback intervention has numerous outcomes both for primary and secondary.

Meta-Analysis

After a systematic and rigorous integration of the available evidence, this study utilized meta-analysis to provide a precise and robust summary estimate. Meta-analysis is the quantitative analysis of the results included in an SR. In practice, this implies combining the results of several individual clinical trials using specialized statistical methodology. Besides, meta-analysis provided useful listing and exploration of bias sources, aided in quantifying between-study heterogeneity, and proposed some potential explanations for dissecting genuine heterogeneity from bias. More importantly, meta-analysis, effect size holds the prime importance, when it comes to analysis.

The result of meta-analysis is presented in a forest plot, where each study is shown with its effect size and the corresponding 95% confidence interval (Figure 3).

Figure 3
Forest Plot for the Standardized Mean Differences Between the Control and Experimental Groups of RCTs and Quasi-Experimental Studies

Meta-Analysis of the RCTs and Quasi-Experimental Studies on Pharmacist-Driven AMS Programs to Prevent AMR in the Hospita

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study						
Abubakar et al.	0.365	0.094	0.009	0.181	0.548	3.893	0.000
Bolten et al.	0.307	0.112	0.012	0.088	0.526	2.750	0.006
Choe et al.	0.113	0.040	0.002	0.034	0.191	2.807	0.005
Rattanaumpanawan et al.	0.027	0.081	0.007	-0.132	0.186	0.332	0.740
Smith et al.	0.300	0.133	0.018	0.040	0.560	2.259	0.024
Lockwood et al.	0.664	0.185	0.034	0.301	1.027	3.582	0.000
Wathne et al.	0.151	0.052	0.003	0.049	0.253	2.903	0.004
Bias et al.	0.349	0.175	0.031	0.005	0.692	1.990	0.047
Bevilacqua et al.	0.175	0.059	0.003	0.059	0.290	2.968	0.003
Dunn et al.	0.289	0.121	0.015	0.052	0.526	2.389	0.017
Gril et al.	0.353	0.080	0.006	0.196	0.509	4.419	0.000
Masia et al.	0.248	0.121	0.015	0.012	0.484	2.056	0.040
	0.234	0.039	0.001	0.158	0.310	6.045	0.000

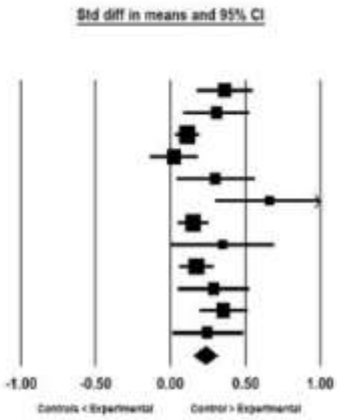

Figure 3. Forest Plot for the Standardized Mean Differences Between the Control and Experimental Groups of RCTs and Quasi-Experimental Studies

Forest Plot. Figure 3 shows the forest plot for the standardized mean differences (SMDs) in the measured outcomes between the control and experimental groups of the RCTs and quasi-experimental studies assessing the effectiveness of certain interventions to prevent AMR reviewed in this study.

Effect Size and the Null Effect Vertical Line. In this figure, the x-axis indicates the effect size being compared among the selected studies, specifically SMD in this systematic review since the outcomes are expressed as continuous variables, expressed in different units. Each SMD value was computed based on the mean difference between the control and experimental groups divided by their "pooled" standard deviation. The treatment or intervention is considered effective if the experimental group's mean is lesser than that of the control. As shown, the x-axis is conveniently set at a range of -1.0 to +1.0. The vertical line that coincides with 0.00 is the line of null effect and, as such, indicates no significant difference in the outcomes between the control and experimental groups (Borenstein et al., 2011). The SMDs to the right denotes an effective intervention, that is, the measured outcome for the control is greater than that of the experimental. Meanwhile, SMDs to the left of the ―null effect‖ line favors the control.

SMDs and 95% Confidence Intervals of Individual Studies. Figure 3 also reveals the SMDs of the 12 studies reviewed, as represented by the black boxes, with their corresponding 95% confidence intervals, as represented by the ―whiskers‖ on both sides of each black box. The individual SMD, as the effect size is indicated for each study and the 95 % confidence interval, is also shown.

For instance, study 6 (Lockwood et al., 2017) has shown the greatest SMD = 0.664 among the 12 studies. Its confidence interval at 0.301 to 1.027, implying that within this range, one can be 95% certain that the true SMD lies. Further, a closer examination of the figure reveals that studies 3 (Choe et al., 2018), 7 (Wathne et al., 2018), 9 (Bevilacqua et al., 2011), and 11 (Grill et al., 2011) are relatively "bigger" studies and as such are represented by black boxes of larger sizes, and hence, have a greater number of participants, establishing a "narrower" confidence interval. Among the 12 studies, there is one--- study 4 (Rattanaumpawan et al., 2018) whose confidence interval crosses the vertical line of at 0.00, indicating that this study fails to establish the significance of the difference. The rest of the individual studies have significant SMDs as indicated by their p-values and as validated by their "whiskers" not crossing the vertical line of the "null effect."

Overall SMD. As shown by the black diamond in Figure 3, the overall SMD = 0.234 with p-value = .000, and it is described as a significant "small" effect, as suggested by Cohen. This result indicates that the experimental group outcome is 0.234 lower than the control group's outcome, implying the intervention's effectiveness. Correspondingly, the 95% confidence interval is 0.158 to 0.310, which indicates it is of 95% certainty that the true SMD lies within this range of values.

Heterogeneity. Heterogeneity in meta-analysis refers to the variation in study outcomes between studies.

Table 6
Heterogeneity

Model	Effect size and 95% confidence interval						Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	12	0.189	0.022	0.000	0.146	0.233	8.556	0.000	26.096	11	0.006	57.848	0.009	0.007	0.000	0.094
Random	12	0.234	0.039	0.001	0.158	0.310	6.045	0.000								

Table 6 presents the statistical parameters generated by the Comprehensive Meta-Analysis (CMA) software.

Q-test. The Cochran's Q = 26.096 with p-value = .006 indicates that the individual studies' SMDs do not statistically evaluate the same effect size, with respect to the overall SMD. It suggests that there are indeed genuine differences underlying the results of the studies. Although the power of Q, in this case, is not high due to the limited number of included studies, there is a hint of heterogeneity of these studies. (Sutton et al., 2000)

I2-test. The I*2* statistic describes the percentage of variation across studies that are due to heterogeneity rather than chance. As revealed in the same table, this collection of studies has established an I*2* = 57.85%. This value denotes moderate heterogeneity, which implies that the variability across the studies that may be used as a basis for further subgroup analysis. (Borenstein et al., 2017) is a measure of the dispersion of true effect sizes between studies in terms of the scale of the effect size. It is also an estimate of the variance of the true effect sizes. also represents the absolute value of the true variance (heterogeneity) (Borenstein et al., 2011). In this study, the CMA software generated that the true effect sizes between the 12 studies are dispersed at 0.009 in terms of the scale of the effect size.

Funnel Plot and Publication Bias. It is crucial to examine the results of each meta-analysis for evidence of publication bias. An estimation of likely size of the publication bias in the review and an approach to dealing with the bias is inherent to the conduct of many meta-analyses. The funnel plot provided a graphical evaluation of the potential for bias and was developed by Light and Pillemer (1984) and discussed in detail by Egger and colleagues (1997). A funnel plot is a scatterplot of treatment effect against a measure of study size. If publication bias is not present, the plot is expected to have a symmetric inverted funnel shape, as shown in Figure 4.

Figure 4
Funnel Plot

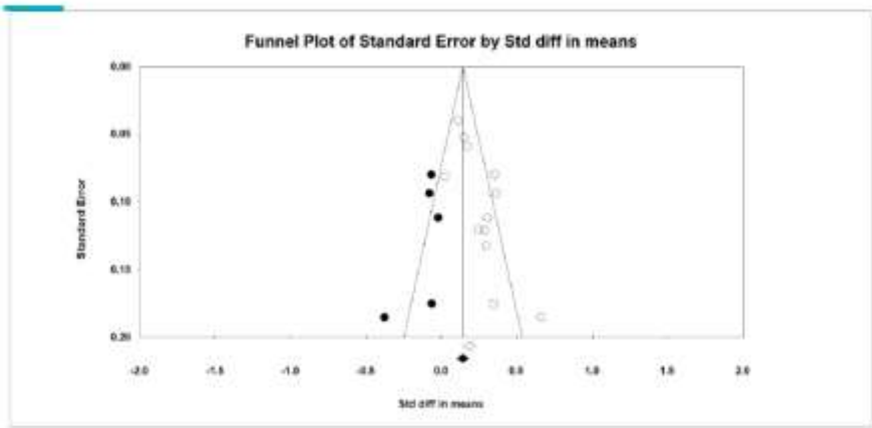

Figure 4 shows the funnel plot to describe the publication bias with respect to the 12 studies selected for this meta-analysis. A publication bias pertains to the failure to include all relevant studies because they were not published and were therefore not accessible. Publication bias will result in asymmetry of the funnel plot. As shown in figure 4, there is a publication bias since the dots representing the studies selected did not establish symmetry with respect to the vertical line, representing the total overall estimate or the standard mean difference revealed by the 12 studies. Asymmetry of funnel plots is not solely attributable to publication bias, but may also result from clinical heterogeneity among studies (Haidich, 2010). However, the five filled plots on the left side are five studies not found by the researcher that will help reduce the publication bias.

An early approach to publication bias was Rosenthal's Fail-safe N, as shown in Table 7.

Table 7
Classic fail – safe

Classic fail – safe N	
Z-value for observed studies	9.33823
P-value for observed studies	0.00000
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	12.00000
Number of missing studies that would bring p-value to > alpha	261.00000

Table 7 presents the generated data from the CMA software. These values revealed vital information to measure the publication bias of this meta-analysis done in the 12 studies selected. Suppose a meta-analysis reports a significant p-value based on studies. The researcher is concerned that studies with smaller effects are missing, and if all the missing studies were retrieved and included in the analysis, the p-value for the summary effect would no longer be significant. Rosenthal (1979) suggested that we compute how many missing studies we would need to retrieve and incorporate in the analysis before the p-value became nonsignificant.

Table 7 values reveal vital information to measure the publication bias of this meta-analysis done in the 12 studies selected. It shows that there are 261 studies that are missing that would bring the p-value to a number greater than 0.05. It implies that at least 261 studies with nonsignificant effects are needed to make the overall effect or SMD value nonsignificant. The failsafe number estimates the number of 261 additional studies that are required to turn the effect size from the included and additional studies combined insignificant, that the _new' combined effect size is essentially zero.

Implications to Pharmacy Practice

The current study evaluates the different Physicians – Pharmacists Team interventions in antimicrobial stewardship to prevent antimicrobial resistance among those patients admitted in the hospital utilizing systematic and meta-analysis methods. The outcome shows that Audit and Feedback, Point of Care, Automatic Stop Order and ASP Intervention on SAB therapy prevented antibiotic resistance.

The study also discovered among the Physicians – Pharmacists Team interventions, Audit and Feedback showed a very beneficial intervention in the prevention of antimicrobial resistance. This outcome was in agreement with a Japanese study done by Kimura et al. (2017) entitled ―Long-term efficacy of comprehensive multidisciplinary antibiotic stewardship programs centered on weekly prospective audit and feedback‖. He concluded that antibiotic stewardship program (ASP) can have sufficient efficacy by multidisciplinary collaborations and various supplemental strategies in conjunction with prospective and audit feedback and that this strategy contributed to maintaining the long-term effectiveness of ASPs. In another study entitled, Antimicrobial stewardship: A review of prospective audit and feedback systems and an objective evaluation of outcomes by Chung et al. (2013), she stated that among the various interventions, the prospective audit and feedback strategy will probably be the most widely implemented in view of its clear advantages—particularly with regards to lack of opposition from prescribers. And because of the nature of antibiotic prescribing, it may prove more effective to incorporate behavior change strategies in addition to current existing interventions, particularly for the prospective audit and feedback strategy.

The current study also found that Antimicrobial Restriction and Pre-Authorization intervention both through PICO analysis and Meta-analysis, may not be as efficient in reducing antimicrobial resistance as implemented by an Infectious Disease (ID) clinical fellow but the strategy of using general pharmacists trained appears safe and using trained general pharmacists could be an alternative to ID specialists when resources are limited.

Furthermore, implementation of the above two interventions (Audit and Feedback and Antimicrobial Restriction and Pre-Authorization) require personnel dedicated to the ASP. In most academic and medium-to-large community hospitals, formation of an ASP with either of these strategies would be possible. On the other hand, in smaller hospitals where dedicated personnel may not be available, some of the pharmacy driven interventions mentioned previously can be implemented, as they require less resources and effort. These have been referred to as ―low hanging fruit‖ interventions as they are the simplest to implement and yet have been shown to have a positive impact (Lam et al., 2017). Such interventions include Point of care interventions and ASP Intervention on SAB therapy. Point of care interventions include dose optimization and de-escalation of antimicrobial therapy (Study 6), intravenous to oral (IV-to-PO) antimicrobial switch therapy (Study 8), and rapid administration of antimicrobials (Study 10). ASP Intervention on SAB therapy (Study 5) demonstrated that a pharmacist-led, ASP intervention can have drastic impact on SAB care in an institution where such an intervention did not previously exist. It claims as the first study to have a pharmacist-led intervention as the cornerstone of care, as others have been based on physician or multifaceted intervention.

The study also highlights collaboration of multidisciplinary health professionals namely pharmacist, doctors and microbiologist as one team in the prevention of AMR through different AMS program. This finding is in agreement with the few reports published to date. Gums et al. (1999) were the first to reveal that a multidisciplinary team approach, including ID physicians, microbiologists and pharmacists, played a crucial role in controlling antibiotic use at hospital. All other published studies (Demoré et al., 2017; Hulscher & Prins, 2017; Lesprit & Brun-Buisson, 2008) have assessed the impact of multifaceted intervention programmes involving implementation of multidisciplinary teams. However, since 1988 the largely opinion based Infectious Diseases Society of America guidelines (Marr et al., 1988) have recommended that multidisciplinary antimicrobial teams should be established in all hospitals. Later, the World Health Organization (WHO 2010) report on overcoming antimicrobial resistance similarly encouraged the introduction of such teams. In general, the acceptance and partnership with doctors is one factor in the success of pharmacist‘s interventions to prevent AMR.

The reviewed studies have also underlined the contribution of pharmacist to improve the quality of antimicrobial treatment. A pharmacist with or without specialized training or a general pharmacist practitioner takes a vital role as one of the member in the Antimicrobial Stewardship Program Team to prevent AMR. This position paper highlights the critical importance of pharmacists with training in antimicrobial stewardship in an effective antimicrobial stewardship program. As outlined by the American

Society of Health-System Pharmacists‘ (ASHP) Statement on the Pharmacist‘s Role in Antimicrobial Stewardship and Infection Prevention (American Society of Health-System Pharmacists‘ (ASHP), 2010), pharmacists take prominent roles in antimicrobial stewardship programs due to their unique expertise, understanding of, and influence over antimicrobial use within an organization. This stance is further supported by Center for Disease Control and Prevention‘s (CDC, 2015). It is written in its Core Elements document (CDC, 2015), that successful stewardship programs must have not only physician leadership and accountability but also drug expertise from a pharmacist leader. CDC's made it clear that in addition to the physician who will be responsible for outcomes within the institution's ASP, facilities must identify a single pharmacy leader who will co-lead the program. "I think the CDC has done a nice job of elevating the role of the pharmacist by singling them out as necessary co-leaders of antimicrobial stewardship programs," says Dodds-Ashley (2017). "The Core Elements guidance clearly gives us a seat at the table and I think it's tremendous that it is well recognized that pharmacy is a key element to ASPs."

Evaluation of Physicians – Pharmacists Team intervention in antimicrobial stewardship is based on their performance on antimicrobial usage, as well as on patient outcomes (Table 2.3). However, because antimicrobial stewardship is highly variable, establishing specific targets and performance criteria requires the synthesis of data from different settings, making this study ideal for a meta-analysis study. Using this approach, we found that the overall effect size of intervention to control is 0.234 which means that all interventions done by Physicians – Pharmacists Team compared to traditional are more effective in preventing AMR.

Chapter 4

CONCLUSION AND RECOMMENDATIONS

This chapter presents the conclusions drawn from the findings of the study, as well as some recommendations deduced from the conclusions as well as some recommendations deduced from the results and conclusions.

Conclusion

The findings of the systematic review and meta–analysis revealed that there is a significant difference between patients admitted in the hospital with and without Physicians – Pharmacists Team intervention in antimicrobial stewardship. Except for one intervention, Post Prescription Review and Authorization done by trained pharmacist, that is inconclusive compared to Post Prescription Review and Authorization done by ID clinical fellow. Generally, the results emphasized that the Physicians – Pharmacists Team interventions in antimicrobial stewardship such as Audit and Feedback, Point of Care, Automatic Stop Order and ASP intervention on SAB therapy are more effective than the conventional methods. Thus, these Physicians – Pharmacists Team interventions in antimicrobial stewardship will significantly reduce, lessen, slows down or prevent the emergence of antimicrobial resistance. Furthermore, among the various interventions, the prospective audit and feedback strategy will have the greater chance to be widely applied because of its clear advantages—lack of opposition from prescribers, avoidance of loss of autonomy and the opportunity to educate individuals rather than only restrict utilization.

Recommendations

This study has a great implication in the health care system especially in the pharmacy profession specifically in the rational utilization of antimicrobial agents in the hospital. Physicians, pharmacists or clinical pharmacist and other health care professionals working in the hospital have a vital role in the prevention of antimicrobial resistance. In our country, the Department of Health implemented the AMS

Program appointing different health care professional as member of the AMS team assuming several roles and responsibilities. Thus, the following are recommended:

An appropriate action or strategic plan based on the findings of the study may be developed. This plan may include the following:

Communication is a key component of the success of an ASP. Clear, simple communication may show the vision and the benefits of the program, with core clinical messages. (Ababa, 2018) Hospitals may follow at least the following communication approaches. One Approach is to identify and communicate to prescribers' specific situations where antimicrobial should be withheld and guidance in relation to the duration of antimicrobial use, which is often an area of misuse. The importance of communicating, sharing and learning from data is also important. Face-to-face meetings with prescribers, where there is an opportunity for reflection about their prescribing practices, or attending multidisciplinary teams, conferences, etc., are all important in promoting learning about prudent prescribing. Discussions during ward round in the presence of multidisciplinary team are important. Thus, close collaboration of operational teams with all members competencies are acknowledged and their cross-disciplinary activities are accepted in reducing and optimizing antimicrobial use.

ASPs can have sufficient efficacy by multidisciplinary collaborations and various supplemental strategies in conjunction with prospective Audit and Feedback (Kimura et al., 2017). We believe this strategy contributed to maintaining the long-term effectiveness of our ASPs. Thus, Audit and Feedback is highly recommended intervention.

According to Centers for Disease Control and Prevention (CDC, 2015) successful stewardship programs must have not only physician leadership and accountability but also drug expertise from a pharmacist leader. The Core Elements guidance elevates the role of the pharmacist by singling them out as necessary co-leaders of antimicrobial stewardship programs and that pharmacy is recognized as a key element to ASPs (Doods-Ashley et al., 2017). Likewise, in smaller hospitals where dedicated personnel may not be available, pharmacy driven interventions such as Point of care interventions and ASP Intervention on SAB therapy may be implemented, as they require less resources and effort and pharmacist leadership as drug experts are at best.

Effective surveillance of AMR using screening of patients for certain Multi Drug Resistant Organism (MDROs, such as carbapenemase-producing Enterobacteriaceae (CPE), Methicillin Resistant Staphylococcus aurues(MRSA)) can provide critical information for the team of ASP for effective decision making (Arensman et al., 2019). Each hospital may appoint a specialist antimicrobial pharmacist or infectious pharmacist to hospital trusts as surveillance approach to identify AMR.

Mortality associated with Staphylococcus aureus bacteremia (SAB) has prompted the development of ―bundle‖-based approaches to improve outcomes. Components of bundled strategies include appropriate antibiotic selection, early source control, documenting negative cultures, echocardiogram, and adequate treatment duration. (Marx, 2019) Other countries with their Antimicrobial Stewardship Program (ASP) began prospective monitoring of SAB patients. Thus, DOH may attempt to include the ―bundled‖ to SAB treatment and other common resistant pathogens as one action element.

Centers for Disease Control and Prevention (CDC) indicated that antibiotic resistant bacteria infect 2 million patients in the United States each year, resulting in 23,000 deaths and $20 billion in healthcare costs. Resistant infections prolong length of hospital stay by 24% and increase costs by 29% versus susceptible infections (Butt et al., 2019). There are several studies concluding the beneficial outcome of ASP to total costs. Another study of an ASP in a 77-bed facility demonstrated a reduction in the percentage

of patients on antimicrobial therapy, the median duration of antimicrobial therapy, and a 25% reduction of total inpatient antimicrobial costs (Gordon et al., 2018). Thus, future SR-MA studies may evaluate effectiveness of AMS program in the total cost of hospitalization and cost of drug expenditure.
In order to have evidence based antimicrobial stewardship program, further research as well as regular evaluation and monitoring are needed to identify the best strategies for the prevention and containment of antimicrobial resistance. (Ababa, 2018). Future studies may evaluate effectiveness of pharmacist-driven AMS program to prevent AMR in the community setting.
Finally, further researchers on related variables may also be conducted through systematic review and meta – analysis approach to help establish reliable conclusions on examined variables.

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