A META-ANALYSIS OF ANTIBIOTIC RESISTANCE PREVALENCE AMONG HOSPITAL AND COMMUNITY- ACQUIRED INFECTIONS

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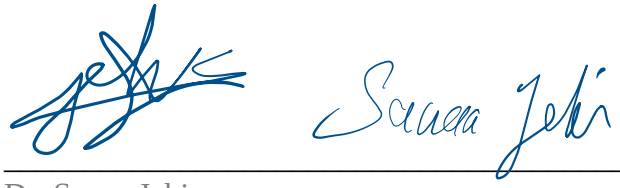

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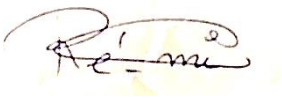

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Abstract

Antibiotic resistance and prevalence of hospital (HAI) and community-acquired (CAI) infections are significantly increasing in the world, though very few studies are addressing this topic in Lebanon. Therefore, this meta-analysis aims to identify antibiotic (AB) resistance prevalence among hospital and community acquired infections. Literature databases were searched for antibiotic resistance, HAI, and CAI in Lebanon from 2010 to 2020. To be eligible for inclusion, studies had to report data in Lebanon published between 2010 and 2020, antibiotic resistance in microorganisms responsible for either HAI or CAI. Consequently, data published out of this time frame, other than Lebanese population, and consortiums were excluded. Thus, sixty-six articles were identified at first, from which six articles were duplicates, and 46 studies excluded. Following full-text assessment, only seven studies were included and used to compile the metadata. Data were analyzed using Review Manager (Cochran RevMan) with the random effects-model for dichotomous data, Mantel-Haenszel, and 95% CI. Antibiotic resistance was more prevalent ($p<0.00001$) in HAI than CAI. Gram-positive and gram-negative bacteria showed significant ($p<0.0001$) resistance to AB. However, analysis of microorganisms' sensitivity to multiple antibiotics was significant ($p<0.00001$) despite the high heterogeneity ($I^2=98\%$) of the data. Our results indicate that antibiotic resistance is more prevalent in HAI compared to CAI. Gram-negative and gram-positive bacteria both showed resistance to antibiotics whereas antibiotics are still considered to be effective and susceptible by the organisms. Therefore, in order to overcome high rates of antibiotic resistance and maintain the effectiveness of antibiotics, awareness about such life-threatening topic and adherence to international guidelines should be more frequent.

Keywords: Nosocomial infections, meta-analysis, antibiotic resistance.

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List of Abbreviations

AB: Antibiotic(s)

ABR: Antibiotic resistance

CAI: Community-acquired infections

CA-UTI: Community-acquired urinary tract infections

CA-MRSA: Community-acquired methicillin resistant *Staphylococcus aureus*

DA-HAI: Device-associated hospital-acquired infections

ESBL: Extended-spectrum beta-lactamase

HAI: Hospital-acquired infections

HA-MRSA: Hospital-acquired methicillin resistant *Staphylococcus aureus*

HA-UTI: Hospital-acquired urinary tract infections

ICU: Intensive care unit

LA-MRSA: Livestock-acquired methicillin resistant *Staphylococcus aureus*

MDR: Multidrug resistant

MRSA: Methicillin resistant Staphylococcus aureus

PICO: Patients – interview – comparison – outcome

PRISMA: Preferred reporting items for systematic reviews and meta-analysis

QUORUM: Quality reporting of meta-analysis

VRE: Vancomycin–resistant *Enterococci*

Introduction

Bacterial infections are considered to be one of the ten most common causes of death worldwide especially that antibiotic resistance is rising to a point where the pipeline of antibiotics (AB) for gram-negative bacteria is becoming limited. In fact, since the 1990s, the development of antibiotics has slowed down to a frightful point where only six AB were approved since 2003 while the epidemic misuse of antibiotics led to the emergence of multidrug-resistant (MDR) organisms (Donadio et al., 2010; Eid and Berbari, 2013; Abayasekara et al., 2017). Acquired infections are significantly increasing in communities and hospitals where significant endemicity of resistance was reported. In Lebanon, the fact that antibiotics are over the counter lead to a major increase in AB misuse or abuse (Daoud, 2018). More importantly, it is reported that 50% of prescribed AB are not always necessary nor optimal (Sosa et al., 2010). As a result, the emergence of bacterial resistance was reported in gram-positive and gram-negative bacteria alike (Donadio et al., 2010). Further, commonly reported microorganisms like *E. coli, Klebsiella* spp., *Acinetobacter* spp., *Salmonella* spp., *P. aeruginosa*, and *Enterococci* have increased resistance to several AB like nitrofurantoin, cefoxitin, imipenem, ciprofloxacin, oxacillin/methicillin, ampicillin, and their combination. Neveretheless, the degree of resistance depends on their usage (Donadio et al., 2010; Daoud, 2018 ; Moghnieh et al., 2019).

Despite the large number of studies done on antibiotic resistance in community-acquired infections and nosocomial infections worldwide, no meta-analysis study focused on assessing the previous research studies and derived conclusions from their research body

particularly in Lebanon. In the current circumstances with the antibiotics being abused as they are over the counter, it is necessary to observe how antibiotic resistance is developing in Lebanon, and further pinpoint the origin of this issue to eventually develop proper guidelines for the management of antibiotic use and abuse.

Literature Review

I. Antibiotics and their application and mode of action

1. Application and use of antibiotics.

Antimicrobials are drugs used since the 19th century for their ability to kill or inhibit microorganisms. AB were initially produced by microorganisms capable of selectively inhibiting or killing other microorganisms without affecting the host. In 1928, Alexander Fleming accidentally discovered the first AB, penicillin, a naturally produced AB by *Penicillium notatum*, a non-pathogenic fungus to humans (Penicillin, accessed November 18 2020).

After this discovery "the golden age of AB discovery" has started and the search for other organisms producing antimicrobials successfully started. Several antimicrobials produced by microorganisms such as fungi or bacteria were discovered. Nonetheless, drugs were not only limited to natural synthesis but chemical modifications took place and resulted in a larger number of antimicrobials (Mohr, 2016; Hutchings et al., 2019). The first synthetic AB was discovered in the early 1900's by the cooperation of Paul Ehrlich with Alfred Berteim and Sahchiro Hata under the trade name Salvarsan which is no longer used. Additionally, new classes of AB started with the discovery of sulfa drugs, then beta-lactam, and other AB summarized in Table 1 (Mohr, 2016; Hutchings et al., 2019).

Antibiotics can be subdivided into two groups as shown in table 2. AB that kill bacteria are called bactericidal whereas those that slow their growth are referred to as bacteriostatic as represented in figure 1 (Muheim, 2017). Furthermore, the use of bactericidal and bacteriostatic together has been reported to have an antagonistic effect, rather than increasing the efficiency

or enlarging the spectrum of such drugs. In addition, many bactericidal require actively growing bacteria in order to be able to effectively kill it. However, a single AB could have both bactericidal and bacteriostatic activities, thus making it hard to classify AB clearly (Muheim, 2017) (Bollenbach, 2015).

Furthermore, antimicrobial's spectrum of activity varies from a broad spectrum to a narrow one. For instance, sulfonamide is a synthesized drug that acts on a large spectrum and it affects parasites and bacteria (NIDDKD, 2012; Muheim, 2017). On the other hand, some bacteria, like Penicillin used to treat gram-positive bacteria, was showing lack of effectiveness due to developing resistance (Utili, 2001; Muheim, 2017). As a result and in order to target a larger spectrum of gram-positive bacteria and gram-negative bacteria, modifications were carried out on natural antibiotics. Some AB, such as the ones in figure 2, have a very broad spectrum that could be used for both gram-positive and gram-negative, in this way, the range of bacteria that can be affected is larger (Muheim, 2017; University, n.d.).

The broad spectrum of beta-lactam's activity is represented in table 3. For example, imipenem is reported to affect several common microorganisms. Furthermore, cephalosporin got evolved from being used for low spectrum and gram-positive into affecting a very large spectrum with the third and fourth generation of this AB that involves gram-negative bacteria as well (Wisher, 2012; Muheim, 2017).

Antimicrobials are not used only in human medicine but in agriculture and animals as well. In the USA, the usage of AB in agriculture is less than 0.5% of total AB use (McManus et al., 2002). In addition to their therapeutic effect, AB in animals can be used for their prophylactic or metaphylactic effect, as preventative or growth promoters (van den Bogaard and Stobberingh, 1999; Phillips et al., 2004). However, growth promoters have been forbidden for several years in several developed countries such as the European Union. Yet, this is not the case in Lebanon (Abdelnoor et al., 2013; van Tricht et al., 2018; University, n.d.).

AB resistant bacteria like *E. coli, Salmonella spp., Campylobacter*, and *enterococci* from animals can infect and colonize the human body through the food chain or through contact. Nevertheless, bacterial resistance genes can be transferred from animals to the intestinal flora of humans (van den Bogaard and Stobberingh, 1999). Moreover, seafood and potable water might be a source of infection. As for contaminated foods, like fruits, vegetables, and poultry, they have major direct contact with the soil which its microbiota is considered an origin for resistant genes (Abdelnoor et al., 2013).

2. Mechanisms of Antibiotic action

With a variation in bacterial structure, AB have a varying penetrating effect. The cell envelope is a complex structure involved in several major cellular processes like its protection and cellular shape maintenance. Bacteria are composed of an internal membrane and a thick layer of peptidoglycans,yet not all bacteria are limited to this structure. The outer membrane of gram-negative bacteria makes AB penetration harder (Silhavy et al., 2010; Zgurskaya et al., 2015).

In order for AB to reach their intracellular target, they need to cross one or both membranes according to the bacteria (Silhavy et al., 2010). AB target essential cellular processes for cell survival such as the ones involved in cell growth and replication as shown in figure 2. Targets of antibiotic action include various bacterial components.

In fact, detergents and some AB target the outer cell membrane of only gram-negative bacteria. Other AB such as penicillin, inhibit cell wall synthesis, in other words they impair the ability of the bacteria to replicate. As a result, the bacteria will stop growing and will eventually be killed. AB like fluoroquinolone and metronidazole inhibit bacterial growth by affecting its DNA replication thus acting on its genetic material. Moreover, AB can interfere with the cell protein factory, RNA-polymerase, thus affecting transcription. Along with interfering in the RNA transcription, this would cause interference in the cell's system. Thus, protein synthesis would not be achieved due to the inhibition of ribosomal binding (Kohanski et al., 2010; Muheim, 2017; University, n.d.). Equally important, some AB, like sulfonamide and trimethoprim, act as antimetabolites thus interfere with the cell's metabolism. Otherwise stated, such AB mimic the substrate and result in inhibiting nucleic acid synthesis (Kohanski et al., 2010; Bhattacharjee, 2016; Muheim, 2017; University, n.d.).

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3. **Importance and prevalence of nosocomial infections**

Hospitals represent a rich environment of bacterial flora that originated either from the hospital itself, nosocomial, or from the community as embodied in admitted patients. In addition to the pathogens patients are exposed to in the community, they are exposed to virulent pathogens from the flora of other sick patients inside the hospital's threatening environment (Brusselaers et al., 2011). Hospital-acquired infections (HAI), known as nosocomial infections, are defined as infections acquired after 48 hours of hospital admission. Nosocomial infections can be due to all pathogens but bacterial infections are the most common (Berche et al., 1991; Al-Hajje et al., 2012; Xia et al., 2016). Thus, nosocomial infections create major problems in the healthcare system especially with the rate at which they are increasing. During a hospital stay, 5 to 10% of hospitalized patients acquire nosocomial infections (Brun-Buisson and Girou, 2000; Xia et al., 2016; Abayasekara et al., 2017). Generally, the bacteria responsible for HAI are resistant to multiple AB , therefore, treating infections is challenging and difficult (Matta et al., 2018).

Several factors increase the risk of getting nosocomial infections. In some cases, it depends on the patient himself and his particular case, such as if he has advanced age, diabetes, obesity, and/or immunosuppression. Other factors are related to the pathogen itself such as its virulence and its resistance profile, and the hospital units admitted to (Intensive Care Unit, Pediatrics, and Emergency room) as well as the procedures taken (endoscopy, surgery…) (Al-Hajje et al., 2012).

Besides nosocomial infections, multidrug resistance is a major concern these days. This resistance is mainly due to inappropriate empiric antimicrobial treatment that targets the MDR

pathogens causing infections (Figueiredo Costa, 2008). Similarly, AB of broad-spectrum are excessively used, sponsoring the emergence of MDR (Abayasekara et al., 2017; Matta et al., 2018).

Moreover, *Staphylococcus aureus*, a gram-positive coccus, is considered as one of the most common hospital-acquired pathogens due to its ability to withstand harsh environments for extended periods, allowing the infection of susceptible individuals through contact of either persistently or transiently colonized people and increases morbidity (Ben-David et al., 2008).

Frequent nosocomial infections such as endocarditis, meningitis, urinary tract infections, neonatal infections, and wound infections are caused by *Enterococcus faecalis, E.coli, and Klebsiella spp (Savas et al., 2006; Flores-Mireles et al., 2015; Anderson et al., 2018)*. Normally, *Enterococcus faecalis* are found in healthy individuals but only in low numbers in the oral sites. As they increase in number they cause oral diseases like gingivitis, periodontitis, caries, and endodontic infections. Besides its pathogenicity and presence in oral sites, they are present in the gastrointestinal tract as commensal microorganisms in humans and animals (Anderson et al., 2018).

In addition to *S. aureus* and *Enterococci*, *EnterobacteriaceaePseudomonas spp*, and *A. baumannii*are well known to cause HAI (Brusselaers et al., 2011; Kanj et al., 2012; Ismail et al., 2016).

A major source of nosocomial infections is the devices used for certain procedures in the human body (Kanj et al., 2012; Ismail et al., 2016; Kanafani et al., 2019). Hospital infection control and quality assurance are affected by the DA-HAI (device associated to hospital-acquired infection) surveillance in the ICU mainly. In the ICU, patients' safety is under the threat

of DA-HAI which have major impact on patients' morbidity and mortality resulting in referring to it as the epicenter of infections. Also, it is known for being the epicenter of resistance development, especially that in this factory antimicrobial resistance might be highly created, disseminated, and amplified. Moreover, due to the procedures and drugs taken, 20% to 30% of the ICU population get infected (Brusselaers et al., 2011; Kanj et al., 2012).

According to the Nosocomial Infection Surveillance System (NNIS) and National Healthcare Safety Network (NHSN), the criteria for DA-HAI surveillance is the determination of DA-HAI rates per 1000 device-days. This surveillance method is used as a guideline for the effective solving strategy for the infection control practitioners (ICP) about the problems that they can encounter. The International Infection Control Consortium (INICC) comprises a worldwide network of selected hospitals that provide the INICC with its databases on DA-HAI (Kanj et al., 2012).

4. **Testing for antibiotic resistance**

Resistance can be measured either molecularly or phenotypically. Genotypic testing is done in the laboratories through PCR or genomic sequencing which is considered as one of the main methods in testing for antibiotic resistance but it lacks practicality**.** Phenotypic testing, on the other side, is practical and provides quantitative and qualitative results. Quantitative results can be tested via the minimum inhibitory concentration (MIC)(mg/L) which is the lowest antimicrobial concentration that will inhibit the growth or kill the organism, it is also used to indicate the results on a scale in the E-test which is a diffusion test since it is a plastic strip that contains the antimicrobial (Reller et al., 2009; Kowalska-Krochmal and Dudek-Wicher, 2021).

This method remains nonstandard and expensive. Whereas, qualitative results indicate how a drug would act in vivo. In qualitative testing results are provided by classifying bacteria into resistant, intermediate, and susceptible. There are different standards in susceptibility testing methodology also known as the international European or American guideline such as CSLI and EUCAST, respectively (Reller et al., 2009; Khan et al., 2019). Furthermore, this testing method is considered to be the most basic method to measure the antimicrobial activity against the organism. More importantly, qualitative results can be obtained from the quantitative results.

Disk diffusion assay is a qualitative measurement based on the inhibition zone diameter and was invented by Kirby and Bauer in 1956. This method, also referred to as Kirby-Bauer method, was used for antimicrobial susceptibility testing (Biemer, 1973; Reller et al., 2009; Khan et al., 2019). With time, the susceptibility testing evolved toward a dilution method which gives quantitative results. Dilution is done either using broth dilution or agar dilution. All these methods are extremely sensitive and their results are influenced by several factors that vary from the size of the inoculum, contents and acidity of medium, as well as incubation time and temperature (Reller et al., 2009; Khan et al., 2019).

5. **Development of Antibiotic resistance**

Bacteria can be intrinsically resistant and they can acquire this resistance through mutation in their genome via point mutations, deletions, inversions, or others (Coates et al., 2002; Barlow, 2009). For instance, a point mutation can have major effect on the cell's function especially if it is located in housekeeping genes as it would affect cell's growth or its

metabolism. DNA gyrase is an essential enzyme for replication and any minor change, even in one nucleotide would make a major difference. In fact, to be more specific, mutations in some DNA gyrase sites have an effect on quinolone, thus leading to quinolone resistance (Jaktaji and Mohiti, 2010; University, n.d.)

Intrinsically, resistant bacteria are able to transfer resistance to daughter cells through vertical transmission. Whereas acquisition can be due to the DNA horizontal transfer which is based on different mechanisms that result in the transmission from the donor to the recipient as represented in figure 4 (Dzidic and Bedeković, 2003; Munita and Arias, 2016; Muheim, 2017). In other words, this unidirectional transfer can take place by transformation where the free DNA is released from a cell and taken up by another, or transduction in which the DNA transfer is mediated by a virus, or by conjugation in which requires cell-to-cell contact in order to transfer the DNA. Naked DNA can be acquired in a recipient bacteria depending on its species and more specifically on its competence which varies between species, this process is known as transformation. Chemical and physical processes provide the competency of bacteria so it would become able to uptake this naked DNA, yet some species like *E. coli* are already competent. Additionally and more importantly, horizontal gene transfer forms a major problem since it has a major contribution in the spread of resistant genetic elements (Dzidic and Bedeković, 2003; Clark, 2013).

Horizontal transfer can occur via transposons, integrons, gene cassettes, and mainly plasmids. Those mobile genetic elements transfer resistant genes between bacteria either in the same species or in different species. The first identified mechanism for gene resistance capture was the integrons which disseminated among Gram-negative bacteria. Plasmids are

small, circular, double-stranded DNA molecules that are different from the chromosomal DNA (Partridge et al., 2018).

The fate of the transferred DNA is not always the same. This DNA may be degraded, replicated, or recombined. Degradation takes place due to the restriction enzymes which are known as restriction endonuclease. Replication is done only if the recipient has an origin of replication. Nevertheless, the DNA could be recombined with the host chromosome and becomes an endogenous resistance which means that this will be transmitted to the daughter cells (Dzidic and Bedeković, 2003; Madigan et al., 2014; Munita and Arias, 2016).

Acquired resistance occurs in several mechanisms like enzymatic inactivation, reduced intracellular accumulation, decreased influx and/or increased efflux of the drug. In addition to the effect on the drug, some mechanisms modify the cellular target. Alternatively said, the bacteria modify their target site to avoid the action of AB. This results in decreased affinity for the antibiotic molecule, overexpression of sensitive target for a more resistant one, and protection of the binding site so the antibiotic won't reach it (Cox and Wright, 2013; Munita and Arias, 2016).

Intrinsic resistance is based on resistance encoded in the bacterial own chromosome, not a gene that came in. This resistance can be due to some enzymes, or a lack of affinity for the target, or different cell walls (Kapoor et al., 2017; University, n.d.).

II. Antibiotic resistance development and testing

Antibiotic resistance can be due to several mechanisms but the main ones are decreased cell permeability, alteration or replacement of the target, enzyme inactivation, and active export and they are represented in figure 5. In fact, active export is facilitated with the pumps,

their presence provides multi-resistance because they can pump more than one type of drugs (Coates et al., 2002; Blair et al., 2015; Kapoor et al., 2017).

Resistance level can be affected by several factors including variation in the natural level of resistance of the species, involvement of a resistance gene or mutation, the expression of the gene in the strain, and the presence of other genes or mutations not directly involved in AB resistance (University, n.d.).

Antibiotic resistance in Gram-negative is developed in several ways and mainly through carrying genes coding for enzymes such as beta-lactamases (Dzidic and Bedeković, 2003; Matta et al., 2018). Beta-lactamases hydrolyze and inactivate beta-lactam antibiotics (Matta et al., 2018).

Cross-resistance

Cross-resistance provides resistance by a single molecular mechanism for drugs that are similar or related, such as avoparcin and vancomycin (Colclough et al., 2019; University, n.d.). For instance, cross-resistance is applied on colistin and polymixin B because they are drugs from the same family which means bacteria can resist (Napier et al., 2013).

Resistance to Tetracycline

Tetracycline is an antibiotic commonly used in animals and in humans. This broad-spectrum antimicrobial affects gram-positive and gram-negative bacteria by targeting the ribosome 30S subunit and blocks the protein synthesis. Tetracycline genes are numerous and

they are mostly known as *tet* in addition to numbers and letters. For instance, tet(A), tet(32), and tet(X) are responsible for active efflux, ribosomal protection, and enzymatic modification respectively (Hedayatianfard et al., 2014; University, n.d.). Furthermore, in 1994, major methicillin-resistant bacterial strains showed 60% to 90% resistance to tetracycline; these included *Staphylococcus aureus, Streptococcus agalactiae,* MDR *Enterococcus faecalis*, and *Streptococcus pneumonia* (Mohr, 2016).

Resistance to Vancomycin

Some bacteria, like *Lactobacillus* and *Leuconostoc,* have intrinsic resistance against vancomycin which is the first described glycopeptide(Courvalin, 2006). Most commonly identified genes responsible for resistance are vanA, vanB, and vanC. vanA as other genes (vanR, vanS, vanH, vanX, and vanZ) are located on mobile genetic elements and more specifically they are located on transposons that reside on plasmids (Cetinkaya et al., 2000; Dzidic and Bedeković, 2003; Courvalin, 2006; Mohr, 2016). More importantly, vanA effectiveness depends on vanH which is responsible for its substrate production. In fact, vanA is the most reported gene for vancomycin resistance in Europe (Cetinkaya et al., 2000; Dzidic and Bedeković, 2003; Mohr, 2016).

Co-resistance

Co-resistance targets unrelated drugs, like tetracycline and sulphonimide, due to different resistance mechanisms that are located in the same genetic element (Manson et al., 2010; Tadesse et al., 2012; University, n.d.). A single plasmid contains various resistance genes.

For instance, one plasmid may provide resistance to vancomycin (vanA), tetracycline (tcr), and erythromycin (ermB) at once (Conwell et al., 2017). Therefore, despite the differences between AB families, the bacteria acquiring this plasmid will become resistant. More importantly, the plasmid is able to transfer from one bacteria to another. Therefore, the bacteria becomes resistant since the plasmid acquires resistant genes.(University, n.d.).The prevalence of such organisms is increasing (Cantón and Ruiz-Garbajosa, 2011).

Resistance to β-lactam

With the use of beta-lactam AB, cells formed a resistance mechanism. Resistance mechanisms are decreased cell permeability, altered targeted site, and enzymatic inactivation of the drug. By decreasing the cell permeability, the drug becomes unable to penetrate the periplasmic space thus not affecting the cell. By altering the target site, the bacteria modifies the target site so the drug won't interact with it any longer. And by the enzymatic inactivation of the drug, the cell produces enzymes that will act on the drug and result in inactivating it. More importantly, bacteria holds a possibility to export drugs outside of the cells (Heesemann, 1993; Xia et al., 2016; University, n.d.). This mechanism is very common between *E. coli* and other *Enterobacteriaceae*. As represented in table 4, β-lactam drugs are inactivated by several classes of enzymes that have different substrates. Those enzymes are Extended-Spectrum Beta-Lactamase (ESBL), AmpC, and Carbapenemase (Xia et al., 2016; University, n.d.).

Bacteria resistant to beta-lactams can vary in mechanisms, modes of acquisition, and species as well. For instance, resistance in *Streptococci* might be acquired either by conjugation or transformation and it leads to enzymatic inactivation and target modification, respectively.

On the other hand, *Pseudomonas spp.* resist beta-lactam by reducing the permeability (Heesemann, 1993).

Beta-lactamases are numerous and within each group there are many enzyme types, like the ones resistant to penicillin and some cephalosporins. Beta-lactamases genes are represented as *bla*. OXA, oxacillinase enzymes, can be detected using genotypic and phenotypic methods (University, n.d.). In a recent study conducted in Iran, the most prevalent beta-lactamase gene was bla_{TEM} and it was found in nosocomial *A. baumannii* (Abdar et al., 2019).

Genes encoding Beta-lactamase exhibit mutation to single nucleotides. Those genes are present in major gram-negative bacteria like *E. coli*, *K. pneumonia*, *A. baumannii*, and *P. aeruginosa*. The following families constitute the enzymes responsible for resistance. This family is encoded by bla_{TEM}, bla_{SHV}, bla_{VEB} genes which are derived from narrow-spectrum beta-lactamases (Xia et al., 2016; Bajpai et al., 2017).

Resistance to Methicillin

Methicillin, this semisynthetic penicillin-derivate that was introduced to the market in 1960, is a beta-lactam AB but with time bacteria developed resistance and a new virulent strain, Methicillin-Resistant Staphylococcus aureus (MRSA), appeared in 1961 (Miall et al., 2001).

S. aureus became resistant by modifying the drug target which was earlier treated with drugs based on enzymatic inactivation mechanism. PBP2, a protein that holds the peptidoglycan by acting on the peptide chain, has a high affinity to beta-lactam AB. This AB connects to this protein thus disables the cross-linking of peptidoglycans which leads to the cell's death due to inappropriate cell wall (Mohr, 2016; Hassoun et al., 2017; Siddiqui and

Koirala, 2018; University, n.d.). Nonetheless, MRSA acquired resistance through PBP2a which is a new form of PBP2 (Łeski and Tomasz, 2005). Therefore, the drug will not interact with any target and the protein will continue to cross-link the peptidoglycan layers. More importantly, bacteriophages were responsible for the transfer of this resistance between *S. aureus* organisms. This can be detected through genotypic and phenotypic methods. In fact, not all penicillin-resistant *S. aureus* are MRSA (Mohr, 2016; Hassoun et al., 2017; Siddiqui and Koirala, 2018). mecA/mecC are genes responsible for MRSA (Denmark Technical University G2, n.d.) (Ballhausen et al., 2014)

Resistance to Colistin

Colistin is an anti-microbial that belongs to the class of polymixin. This drug was introduced in the 1960s but its use has been limited due to the side effects they cause (Nation and Li, 2009). However, it is still used in the veterinary medicine and the animal industry (University, n.d.). Yet, it was used in the last decade due to the emergence of MDR bacteria. Colistin is considered one of the most important antibiotics since it is one of the last resort antibiotics (Nation and Li, 2009; Li et al., 2020). In fact, it is intrinsically present in some bacteria such as *Acinetobacter, Pseudomonas aeruginosa, Haemophilus influenza,* and other species as well. Gram-positive bacteria are intrinsically resistant to this antibiotic.

Colisitin acts through an interaction with a lipopolysaccharide of the bacterial cell membrane leading to the leakage of the cellular content. Thus, any mechanism that is able to modify the target may lead to resistance. Colisitin resistance has two different mechanisms, chromosomal point mutations and the mcr genes. The mutation occurs in systems that are

associated with the synthesis and maintenance of lipopolysaccharide (Aghapour et al., 2019). Moreover, mcr genes were discovered for the first time in 2015 and they are harbored in plasmids. Thus, they have a very high potential of being transmitted between organisms and other species as well (Li et al., 2020) (University, n.d.). More importantly, resistance can be detected through genotypic and phenotypic methods (University, n.d.).

III. Nosocomial infections and antibiotic resistance

Recent reports showed (Al-Hajje et al., 2012; Xia et al., 2016; Abayasekara et al., 2017) that soil microbiota and livestock are great reservoirs of resistant antimicrobial genes. These can be transmitted to clinical patients via clinical pathogens (Abdelnoor et al., 2013). Health centers are considered to be a habitat for numerous virulent pathogens like bacteria and viruses. These microorganisms are responsible for hospital or healthcare-acquired infections (HAI) during or as a result of hospitalization also called nosocomial infections. These also include infections acquired during admission (Berche et al., 1991; Al-Hajje et al., 2012; Xia et al., 2016).

1. Importance and prevalence

Countries with limited resources have lower prevalence of HAI compared to developing countries (Alp et al., 2011). Nosocomial infections are caused by numerous resistant bacteria but mainly by *Staphyloccocus aureus* and its methicillin-resistant strain which is known as MRSA, extended-spectrum beta-lactamases (ESBL) producing Gram-negative bacilli like *Pseudomonas spp.* and vancomycin-resistant *Enterococci* (VRE) (Dzidic and Bedeković, 2003; Xia et al., 2016; Matta et al., 2018; Siddiqui and Koirala, 2018). HAI are mostly due to gram-negative bacteria and MDR strains which are increasing with time. As a

result of the massive use of broad-spectrum AB in the healthcare, bacteria became resistant and selective pressure was applied (Matta et al., 2018).

Recently, in Lebanon the attention on nosocomial infections prevalence, resistance, and effect on the community is growing. In 2014, comparing hospital acquired urinary tract infections (HA-UTI) with community acquired urinary tract infections (CA-UTI) showed that CA-UTI had more prevalent ESBL-producing strains in male patients and patients with diabetes mellitus, urinary catheterization and benign prostatic hyperplasia. Furthermore, results showed that HA-UTI patients are older than CA-UTI patients (65 years old and 61 years, respectively) and females are more prone to develop UTI compared to males 59.7% vs 42.1% (Soubra et al., 2014). The ventilator and the catheter are considered the main devices associated with HAI. More precisely, the ventilator is associated with pneumonia which is the highest in the ICU and the catheter is associated with UTI and related bloodstream infections which were the highest in the respiratory care unit. The most common organisms causing ventilator-associated pneumonia (VAP) are *A. baumannii, P. aeruginosa, and E. coli* and the ones causing catheter-associated urinary tract are *E. coli and K. pneumonia* (Kanj et al., 2012). Moreover, according to a study in a Lebanese hospital, the ICU is the reservoir for most of HAI and more precisely it accommodates 72% of the HAI. Eighty-nine percent of those HAI are gram-negative organisms and another study also reported that 95% of the reported organisms causing VAP are gram negative (Al-Hajje et al., 2012; Kanafani et al., 2019).

According to Matta et al. (2018), HAI/bacteria had higher rates of resistance than CAI and these rates increased with age and immunosuppressed patients and decreased with chronic obstructive pulmonary disease.

2. **Antibiotic resistance and reports**

In the ICU and the surgical department, the most frequent bacteria to be isolated is MRSA and its most common source is wounds (Dzidic and Bedeković, 2003). Even though *Staphyloccocus aureus* acquired resistance after a short time of methicillin introduction, it subdivided the species into two groups either sensitive or resistant due to the enzyme degrading beta-lactamase (Miall et al., 2001). Most global *S. aureus* bacteria cases are due to MRSA which is a global healthcare problem. Nonetheless, MRSA bacteremia incidence has decreased (van Hal et al., 2012; Mohr, 2016; Hassoun et al., 2017). Furthermore, MRSA can be divided into different categories which also witnessed a decrease over time as represented in figure 6. Some of these categories are HA-MRSA (hospital acquired), CA-MRSA (Community acquired), and LA-MRSA (Livestock associated)(Hassoun et al., 2017)(Denmark Technical University G2, n.d.). According to Matta et al. (2018), 12.9% of MRSA are causing HAI.

Acquired infections are majorly caused by gram-negative bacteria, nevertheless, HAI are characterized by producing beta-lactamase. *Acinetobacter baumanniii*, major contributor to nosocomial infection, is one of the most significant resistant bacteria. *Acinetobacter*, *Klebsiella pneumonia,* and *Pseudomonas aeruginosa* are carbapenemase producers and they are MDR strains, increasingly isolated in hospitals. Also, the resistance that *E. coli* have to beta-lactam is due to the fact that they are plasmid-borne ESBL. More importantly, this resistance trait is

present in approximately all strains of *Enterobacteriaceae* (Dzidic and Bedeković, 2003; Matta et al., 2018). Those enzymes hydrolyze most beta-lactams such as penicillin, extended-spectrum cephalosporin, and monobactam (Bush and Bradford, 2016). Nevertheless, beta-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam inhibit ESBLs (Dzidic and Bedeković, 2003; Matta et al., 2018). *Klebsiella spp* are known to be ESBL producers but their rate varies within time as well as geographic areas. For instance, it was reported that from 1990 to 1993 in the ICU of 400 hospitals in the United States, ESBL producing *Klebsiella spp* increased from 3.6% to 14.4%. In Europe in 1995, ESBL producing *Klebsiella spp* occurred between 20%-25% of the ICU patients, and in France in particular it occurred between 30%-40% (Emery and Weymouth, 1997; Quinn, 1998).

Enterococcus are well recognized in nosocomial infections especially that they are increasing due to the increased use of wide spectrum AB (Hunt, 1998; Remschmidt et al., 2018). These commensal bacteria developed resistance to several AB especially vancomycin. Highly compromised patients such as the ones in the ICU, for instance, are most likely to get infected with VRE. Those bacteria have resistance toward numerous antibiotics such as beta-lactam, aminoglycoside, and ampicillin and this resistance is based on PBP (Dzidic and Bedeković, 2003).

In fact, *E. faecalis* is intrinsically resistant and harbors different acquired resistance traits as well. Nonetheless, it uses horizontal gene transfer to acquire and spread genetic elements. Therefore, horizontal gene transfer results in the emergence of MDR *Enterobacteriaceae* (Dzidic and Bedeković, 2003). In addition to this, emergence of VRE is due to the lack of boundaries between the domains like hospitals and community, and people and animals. Equally important, these bacteria are able to form biofilms (Anderson et al., 2018).

IV. Meta-analysis steps and procedures

Meta-analysis is a tool used in biological research. Its usage emerged in the late 1970s, in order to conduct quantitative, formal, and epidemiological summary of existing studies, where inference is needed from a multitude of designs and findings. In contrast to a review, a meta-analysis is a statistical analysis subset of systematic review which identifies, evaluates, and summarizes the findings of all individual studies. This type of study encompasses a large review of the literature that might be complex, conflicting, and adds unforeseeable errors. Above all, by combining results of different studies, it gives rise to more precise results from its outcome. More importantly, statistical power would be increased due to the combination of parallel study results. Thus, the advantages of studies are several, mainly overcoming bias, high precision, and transparency since all the results would be revealed, and the precision improved (Crombie and Davies, 2009; Haidich, 2010). More importantly, the outcome of a meta-analysis can answer new questions that are not posed by individual studies and it can generate new hypotheses. Moreover, meta-analysis and systematic review have the highest quality of evidence and they are the most reliable compared to other study types like case-controlled studies and cohort studies (Haidich, 2010).

1. Steps and standards for a reliable meta-analysis

Well-constructed and answerable clinical questions are based on several components that are known as PICO (Patients/Population and setting of interest (community – hospital – age – race) – Intervention/Exposure (risk factors) – Comparison group(s) – Outcome). Thus, this model helps in identifying the question and answering it. In other words, breaking down the

research question into those components is essential for the researcher and the readers in order to identify the elements (JPT et al., 2021).

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement is an evidence-based of minimum set of items for reporting in systematic review and meta-analysis. Alternatively said, this reporting guideline reveals the transparency of the search method, it indicates qualitative and quantitative information. The meta-analysis results are presented in a distinct way that sets them apart from usual studies. Figure 7 represents how PRISMA statement offers a four-phase flow diagram for results presentation. This flow diagram represents the stages of the study with the number of studies used in each stage. More specifically, it shows the number of studies identified at first, the duplicated studies, the included ones, the excluded ones, the reasons for exclusions are also represented (Moher et al., 2009). This guide replaced Quality of Reporting of Meta-analyses (QUOROM) which is another checklist. A comprehensive search strategy, nowadays using at least one major electronic database such PubMed and Google Scholar is required in this reporting system (Haidich, 2010). The search strategy is not only limited to database search but it is a sequence of requirements (Basu, 2017). Above all and before starting with the search, a clear and narrow question should be determined. As the question becomes very precise the studies addressing it would be fewer (Hopkins', 2020)

This sequence varies from the keywords used in the search, included papers, excluded papers, and the criteria chosen (Crombie and Davies, 2009; Kumari, 2019). However, the first requirement is to choose the right keywords in order to identify the desired studies. Not all studies would be included in the meta-analysis due to certain exclusion criteria chosen by the

author. During the stage of initial development of the study protocol, the inclusion and exclusion criteria would be defined (Haidich, 2010; Kumari, 2019). Nonetheless, the exclusion criteria would be provided so the reasons behind the rejection would be clear (Kumari, 2019). A well-known quoted definition (Huque, 1988) about meta-analysis is "a statistical analysis which combines or integrates the results of several independent clinical trials considered by the analyst to be "combinable". Determining whether studies are combinable or not is a very delicate matter. Furthermore, deciding if the studies are combinable is essential to get a non-bias meta-analysis. One way for bias testing is by using Begg's funnel plot. A non-bias meta-analysis would have a symmetrical funnel plot (Dear and Begg, 1992; Egger et al., 1997; Chen et al., 2011; Matcham et al., 2013). Moreover, the summary effect measure significance is determined by the p-value from the Z test which is known as the test for overall effect. More precisely, the summary effect measure is considered significant with a $p<0.05$ (JPT et al., 2021).

Another important factor in a meta-analysis is statistical heterogeneity. The source of this heterogeneity lies in the clinical or methodological diversity. In other words, methodological diversity is the variability in the participants, interventions, and outcomes. Heterogeneity can be determined by Chi^2, p-vale, and I^2. A low p-value shows evidence of heterogeneity. I^2 levels are divided into 4 categories: 0%-40% indicates unimportant heterogeneity, 30%-60% moderate heterogeneity, 50%-90% substantial heterogeneity, and 75% to 100% considerable heterogeneity (Higgins et al., 2003; JPT et al., 2021)

Meta-analysis results are presented in a distinct way that sets them apart from usual studies. Figure 7 represents how PRISMA statement offers a four-phase flow diagram for results presentation. This flow diagram represents the stages of the study with the number of studies

used in each stage. More specifically, it shows the number of studies identified at first, the duplicated studies, the included ones, the excluded ones, the reasons for exclusions are also represented (Moher et al., 2009).

2. **Statistical methods for a meta-analysis**

Depending on the aim of the meta-analysis, different analysis techniques can be used. Before starting the data interpretation, it is important to understand the types of the collected data from the studies in order to measure the effect or their association (Hopkins', 2020).

Studies incorporated in a meta-analysis are assumed to be similar or to at least have enough in common in order to synthesize the information. On the other hand, meta-analysis wouldn't be an option if the studies were not combinable. The effect of the studies can be determined in a forest plot as represented in figure 8. In other words, a forest plot represents the results from individual studies and the results of the meta-analysis as well. The square represents a study and its size, meaning that a larger square has increased weight and decreased variance. Nonetheless, the diamond in the forest plot represents the effect and the confidence interval of the meta-analysis (JPT et al., 2021).

Each study is summarized by an estimate of effect, treatment of effect, or association. To get the estimated effect measure, risk ratio and odds ratio must be calculated. There are two statistical methods for meta-analysis, the fixed-effect model and the random-effects model. In contrary to random effects models, in the fixed-effect model, the true effects of the studies are assumed to coincide, so it is assumed that all studies are measuring the same effect size as represented in figure 9a. The overall effect measure is estimated as an average but in meta-analysis, it is known to be the weighted average. The weight reflects the varying

importance of each study, in other words, more weight is assigned to studies having more information, and information is affected by the sample size or the number of events that occurred in that study and other factors. Thus, more information will lead to increased precision in the study and in the meta-analysis as well. The observed effect size varies from one study to the next because of the random error inherent in each study. The width of the curve reflects the variance in the study. Thus, wider spread indicates larger variance whereas shorter spread reflects a study with higher precision. The true effect of the meta-analysis is represented in Figures 9b and 9c as θ (Hopkins', 2020) .

To estimate the population effect, calculations like the weight of each study (W), weighted mean (M), variance of the summary effect (V_M), and the standard error of the summary effect (SE_M) from the observed effects must be done (Hopkins', 2020).

Materials and methods

1. **Search strategy and databases**

The search was done using Google Scholar and PubMed on articles reporting antibiotic resistance, nosocomial infections, and community acquired infections in Lebanon between 2010 and 2020. The following keywords were chosen since they aim the studies that would be reporting the desired topic. The used keywords in the search strategy were: “Lebanon”, “nosocomial infections”, “nosocomial”, “hospital acquired infections”, “community acquired infections”, “antibiotic resistance”, and “antimicrobial resistance”. Furthermore, including Lebanon in each search was essential in order to limit the results to the Lebanese citizens since other populations are excluded. After database search, titles were screened in the first place and abstracts in the second place.

2. **Eligibility criteria of research papers**

The search results including either hospital or community-acquired infections with prevalence statistics were included in the meta-analysis. Targeted population specifically included Lebanon and hospital or community-acquired infections. All irrelevant populations, i.e. not Lebanon, pooled consortium data, or infections not linked to hospital or community-acquired resistance were discarded. The inclusion criteria consisted of the prevalence of antibiotic resistance in either hospital-acquired infections or community-acquired infections. As for the exclusion criteria, it included irrelevant population (i.e. international studies and the ones done out of Lebanon), irrelevant timing of data publication (i.e. studies published before 2010 and after 2020), duplicates (there is an overlap between databases or even in the same database), and consortiums because they showed no specific data about Lebanon.

3. **Data compilation**

Data for incidence of antibiotic resistance, specific bacteria and source of the infections were compiled from each study and collated in an excel file. Antimicrobials were grouped by classes, and bacteria were classified based on Gram staining and resistance of susceptibility and compared within community or hospital acquired.

Review Manager 5.4.1 (The Cochrane Collaboration, 2020) was used for metadata analysis and draw the forest plots. The data reporting the resistance, or the susceptibility of the organisms was needed. Otherwise stated, the rate of bacterial resistance/susceptibility to an AB was used.

Few studies were quantitative and reported antibiotic resistance in hospital acquired and community acquired infections. Most of the studies were mainly focusing on the prevalence on HAI or CAI whereas resistance to AB was a supplementation. Compiling data was challenging first for the fact that data were heterogeneous and second because studies were not precisely reporting the prevalence of AB resistance and the prevalence of HAI or CAI. Consequently, the number of included studies was limited, five studies reported AB resistance and HAI/CAI and two studies reported mainly the prevalence of HAI.

4. **Statistical analysis**

The data type used in this thesis was dichotomous and the prevalence was reported by 95% confidence intervals. Not all studies were homogeneous since there was heterogeneity in the prevalence rate in the studies, thus Random Effects Model was used as the analysis model.

In addition to the latter method, the Mantel-Haenszel method was used as the statistical method and risk difference as the effect measure.

Nonetheless, 0 was replaced by 1 for the studies that did not examine the source of infection to enable the estimation of the effect measure. However, in forest plots comparing studies in figures 11, 13, and 14, the empty spaces represent no data.

Results and Discussion

Database searches were conducted using a variety of relevant keywords. Sixty studies were identified from Google Scholar while only 6 were returned from PubMed. Same articles resulting from different keywords search and from several databases were considered as duplicates and therefore only one retained. Therefore, from 60 screened articles, only 14 were eligible for full-text assessment. Seven articles did not meet the inclusion criteria and as a result 7 articles are included in the meta-analysis. The PRISMA model was summarized in figure 10.

In Lebanon, community (CAI) and hospital (HAI) acquired infections are caused by a variety of antibiotic resistant or susceptible organisms, as summarized in table 5. Resistant organisms, like *E. coli, K. pneumonia,* and *Enterococcus* can be found in the hospital and in the community environment, whereas *Proteus spp.* is only found in community and *A. baumannii* and *Coagulase negative staphylococcus* are found in hospital environment only. Though the included studies were unexpectedly low in numbers namely because many researchers did not report actual frequency of resistant organisms, rather just the occurrence, or did not publish, or simply not enough interest in researching such a topic. From the meta-data, 2 studies reported CAI and HAI together, 3 studies reported only CAI, and 2 studies reported only HAI as shown in table 6.

We were originally aimed to compile our meta-data directly from hospital databases in order to have a large data but it was not possible due to this pandemic and the hectic situation of the hospitals. On various levels, COVID19 had a major impact of the healthcare system which became overwhelmed, thus we were limited to the published data which was limited to a certain period of time and certain population. Several consortiums and studies out of the set

timeframe were excluded. In the first place, this timeframe was chosen for the fact that studies could be recent and we would be able to observe the evolution/ progress of the numbers of bacteria and more importantly since COVID19 affected the antibiotic market. In other words, with the lack of knowledge and misconception about antibiotics, microorganisms, and antimicrobials people went over the misuse of AB to target COVID19. Nonetheless, better circumstances could lead to a greater and up-to-date meta-data. However, our metadata consisted of few studies reporting HAI and CAI and other studies reporting either HAI or CAI. Each study has its own weight which depends on its effect size. Simply put, studies having bigger size have more weight thus they would have a greater effect on the meta-analysis outcome. Furthermore, the outcome is affected by the homogeneity /heterogeneity of the data, mainly the result of the publication bias, chance, or the fact that studies are not similar enough to be combinable.

1. **Prevalence of antibiotic resistance in HAI and CAI**

Our meta-analysis using RevMan, presented in figure 11A, showed that antibiotic resistance is more prevalent in HAI. However, this prevalence is not significant since the summary effect measure passes through the null line (-0.17 , 0.27 and p=0.67). In other words, the difference found between the two groups is not statistically significant. This could be partially because the metadata did not show homogeneity due to the large variance. Here, heterogeneity is considered substantial since I^2= 74% and p-value=0.0008. Nonetheless, heterogeneity and publication bias lead to an asymmetrical funnel plot as shown in figure 11B.

Consequently, studies reporting only one source of infection were excluded since they were responsible for the observed heterogeneity. Therefore, only 2 studies were compared

and presented in figure 12A, and the results showed significant difference between AB resistance prevalence in CAI and AB resistance prevalence in HAI ($p<0.00001$) and moderate heterogeneity ($I^2=52\%$). Furthermore, as represented figure 12B, the funnel plot showed no evidence of publication bias.

Conclusively, AB resistance is more prevalent in HAI, similarly to other studies where the authors further showed that antimicrobial resistance and nosocomial infections are known to overlap (Jakab, 2010). According to a study in Lebanon, the use of inappropriate AB in hospitals is prevalent and the adherence to international guidelines for empiric AB prescriptions is low (32.6%) (Fahs et al., 2017). According to an Iranian study, MDR isolates are increasing their prevalence in the surgical site is alarming (Hemmati et al., 2020). In contrast, a study in Kuwait investigating hospital-acquired and community-acquired *C. difficile* reported no significant difference in the resistance against hospital-acquired and community-acquired *C. difficile* (Jamal and Rotimi, 2016*)*. However, according to Morehead and Scarbrough (2018) there is a chance of 50% to acquire *C. difficile* by spending more than 4 weeks in the hospital. Until 2001, there was no published data on HAI prevalence in Lebanon. However, back at that time, the rate of HAI occurrence in the Lebanese hospitals was similar to the one reported in the European countries (Azzam and Dramaix, 2001). According to an Australian study, the prevalence of HAI rate is affected by the hospital size. Bigger hospitals are associated with a higher rate of HAI (McLaws et al., 1988). Furthermore, the prevalence of HAI is significant in Morocco and Benin (Razine et al., 2012; Ahoyo et al., 2014). According to Razine et al. (2012), advanced age, longer length of hospital stay, presence of comorbity, use of invasive devices and AB were associated with nosocomial infections. In Saudi Arabia, gender had no effect on the risk of developing HAI, yet

the risk of developing HAI was 9.1 times higher among the patients admitted to the ICU. Furthermore, the length of stay exceeding 8 days caused a higher risk by 16.4 on developing HAI (Balkhy et al., 2006). According to a one-day prevalence survey in Accra, CAI were more prevalent than nosocomial infections (Newman, 2009).

2. Resistance of gram-positive and gram-negative bacteria

Moreover, the susceptibility and resistance of gram-positive and gram-negative were compared in figure 13. Both types of bacteria, gram-positive and gram-negative, showed significant resistance (-1.19, -0.50 and p<0000.1) because organisms that are resistant for at least 1 AB are considered resistant even if they are susceptible to other AB. According to another Lebanese study, gram-negative bacteria were more prevalent than gram-positive, however, gram-positive pathogens are remarkable (Salameh et al., 2017). In Vietnam, HAI are highly prevalent and they are mostly caused by carbapenem resistance gram-negative bacteria (Phu et al., 2016). At least 30% of nosocomial infections are due to gram-negative bacteria and they acquire AB resistance mainly in the existence of AB selection pressure (Peleg and Hooper, 2010) . According to Munita et al. (2015), gram-positive pathogens are evolving and showing AB resistance more frequently. Some major healthcare and community-associated gram-positive pathogens, like MRSA, *Streptococcus pneumoniae,* and *Enterococcus faecium* are few from several listed dangerous bacteria (Jubeh et al., 2020). In fact, according to a German study (Kizny Gordon et al., 2017), hospital water environments, like basins and toilets, are considered reservoirs for carbapenem-resistant organisms like *Pseudomonas spp., Klebsiella spp, A. baumannii,* and *E. coli*.

3. Susceptibility of microorganisms to antibiotics

Last, we used our metadata to compare the sensitivity of microorganisms to the various AB as represented in figure 14. Even though heterogeneity of the metadata was high (I^2=98%), the difference between the resistance or sensitivity to AB remained significant (-0.29, -0.23 and $p<0.00001$).

Resistance to carbapenem was slightly reported in Lebanon, however, in Germany from 2012 till 2017 carbapenem-resistant organisms were increasing (Kizny Gordon et al., 2017). Another study reported a variation between 82.9% and 15% in carbapenem resistance rates according to the organisms.

MDR is a crucial characteristic in bacteria and it was reported in Lebanon. MDR is also reported with significant numbers in the Lebanese food system (Kassem et al., 2020). Furthermore, in Mexico in 2011, a MDR *Acinetobacter spp*. outbreak developed an increase in HAI rate and HAI mortality (Cornejo-Juárez et al., 2015). Moreover, in Germany in 2011 as well, multidrug resistant organisms were not elevated but they were rising (Geffers and Gastmeier, 2011).

Conclusion and Implications

Antibiotic resistance and the prevalence of infections are significantly increasing. The community and healthcare/hospital environments have a major impact on the antibiotic resistance mechanisms and rate and the prevalence of infections. Hospital (HAI) and community-acquired infections (CAI) are particularly prevalent in Lebanon. In Lebanon in the last decade, few studies focused on the prevalence of HAI and CAI and the antibiotic resistance, nonetheless, some studies emphasized the prevalence of either type infections and the antibiotic resistance. A Meta-analysis is a quantitative study that evaluates the findings of previous studies and it encompasses a substantial review of literature that might be complex, conflicting. This statistical analysis combines similar studies to calculate their effect thus give rise to more precise results. Yet, there is no meta-analysis in Lebanon targeting this concern, and with very few published studies, our analysis has inherently many weakness and thus will require reobservation in light of more publications.

Despite the large number of studies targeting antibiotic resistance in Lebanon, our meta-data was limited since only few studies reported the prevalence of HAI and/or CAI and antibiotic resistance. More precisely, only Matta et al. (2018) and Soubra et al. (2014) reported HAI and CAI and other studies reported either HAI or CAI. Our meta-analysis showed that HAI are more prevalent than CAI. Gram-positive and gram-negative bacteria both showed significant resistance to antibiotics. Nevertheless, antibiotics are still considered to be effective and susceptible by the microorganisms. To conclude, this study is important to show the weaknesses in publication requirements of infections and antibiotic resistance reporting norms.

If such norms for publication or data sharing are implemented, insight and regulations for antibiotic use and abuse will be essential for regulatory and efficient infection treatment purposes.

Tables

Table 1: Classes of antibiotics reached the clinic.
Summarized from (Hutchings et al., 2019)

Year of isolation	Classes of AB
1935	Sulfonamides
1943	Polypeptide antibiotics
1943	Aminoglycosides
1962	Quinolones
1973	Fluoroquinolones
1987	Oxazolidinone
2010	Diarylquinolines

Table 2: Activity and origin of antibiotics (University, n.d.)

Activity	Class	Origin
Bactericidal	Aminoglucosides	Streptomuces, Micromonospora spp.
	Cephalosporins	Cephalosporium spp.
	Rifamycins	Amycolapsis mediterranei
	Penicillins	Penicillium spp.
	Quinolones	Synthetic
Bacteriostatic	Macrolides	Various Actinomycetes
	Phenicols	Streptomyces venezuelae
	Sulfonamides	Synthetic
	Tetracyclines	Streptomyces spp.

Table 3: Beta-lactam AB spectrum (University, n.d.)

AB \ Organism	*Staphylococcus*	*Streptococcus*	H. influenzae	E. coli	P. aeruginosa
Penicillin					
Ampicillin					
Cefuroxime					
Ceftazidime					
Imipenem					

Table 4: Substrate specificity of beta-lactams *(University, n.d.)*

	Penicillin	Early generation cephalosporin	Second and third-generation cephalosporin	Beta-lactam/Beta-lactamase inhibitor combination	Carbapenem
ESBL					
Carbapenemase					
AmpC					
Oxacillinase					

Table 5: Antibiotic-resistant organisms causing CAI and HAI in Lebanon

Organism	CAI	HAI
E. coli	(Moghnieh et al., 2014; Soubra et al., 2014; EL-HAJJ et al., 2016)	(Kanj et al., 2012; Soubra et al., 2014; EL-HAJJ et al., 2016; Ismail et al., 2016; Matta et al., 2018)
Enterococcus	(Soubra et al., 2014)	(Kanj et al., 2012; Soubra et al., 2014)
Enterobacteriaceae	(Soubra et al., 2014)	(Kanj et al., 2012; Soubra et al., 2014; Kanafani et al., 2019)
MRSA		(EL-HAJJ et al., 2016; Kanafani et al., 2019)
Klebsiella	(EL-HAJJ et al., 2016)	(EL-HAJJ et al., 2016)
K. penumonia	(Moghnieh et al., 2014; Soubra et al., 2014)	(Kanj et al., 2012; Soubra et al., 2014)
Proteus spp.	(EL-HAJJ et al., 2016)	
Pseudomonas	(Matta et al., 2018)	(Soubra et al., 2014; Ismail et al., 2016; Matta et al., 2018)
S. aureus		(EL-HAJJ et al., 2016; Ismail et al., 2016)
A. baumani		(Ismail et al., 2016; Kanafani et al., 2019)
Coagulase negative Staphylococcus		(Kanj et al., 2012)

Table 6: Search database

Database	Filter	Keywords combination	Results	Selected articles
Google Scholar	2010-2020	**Lebanon** AND **antimicrobial resistance**	8,480	23
		Antibiotic resistance AND **Lebanon** AND **nosocomial**	3,190	20
		Lebanon AND **community acquired infections**	17,100	15
		Lebanon AND **hospital acquired infections**	17,000	0
PubMed	2010-2020	**Lebanon** AND **antimicrobial resistance**	359	0
		Antibiotic resistance AND **Lebanon** AND **nosocomial**	20	2
		Lebanon AND **community acquired infections**	33	4
		Lebanon AND **hospital acquired infections**	78	duplicates

Figures

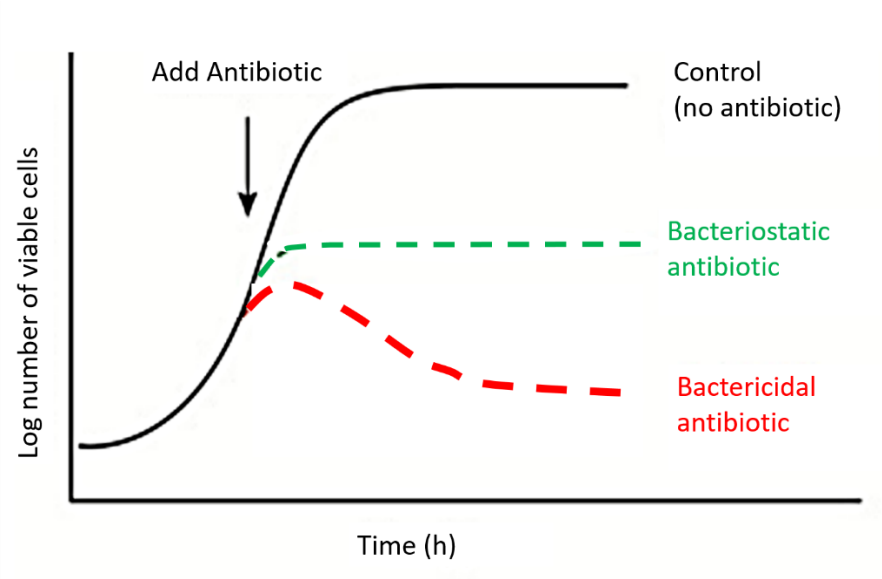


Figure 1: Bactericidal vs Bacteriostatic antimicrobials (Muheim, 2017)

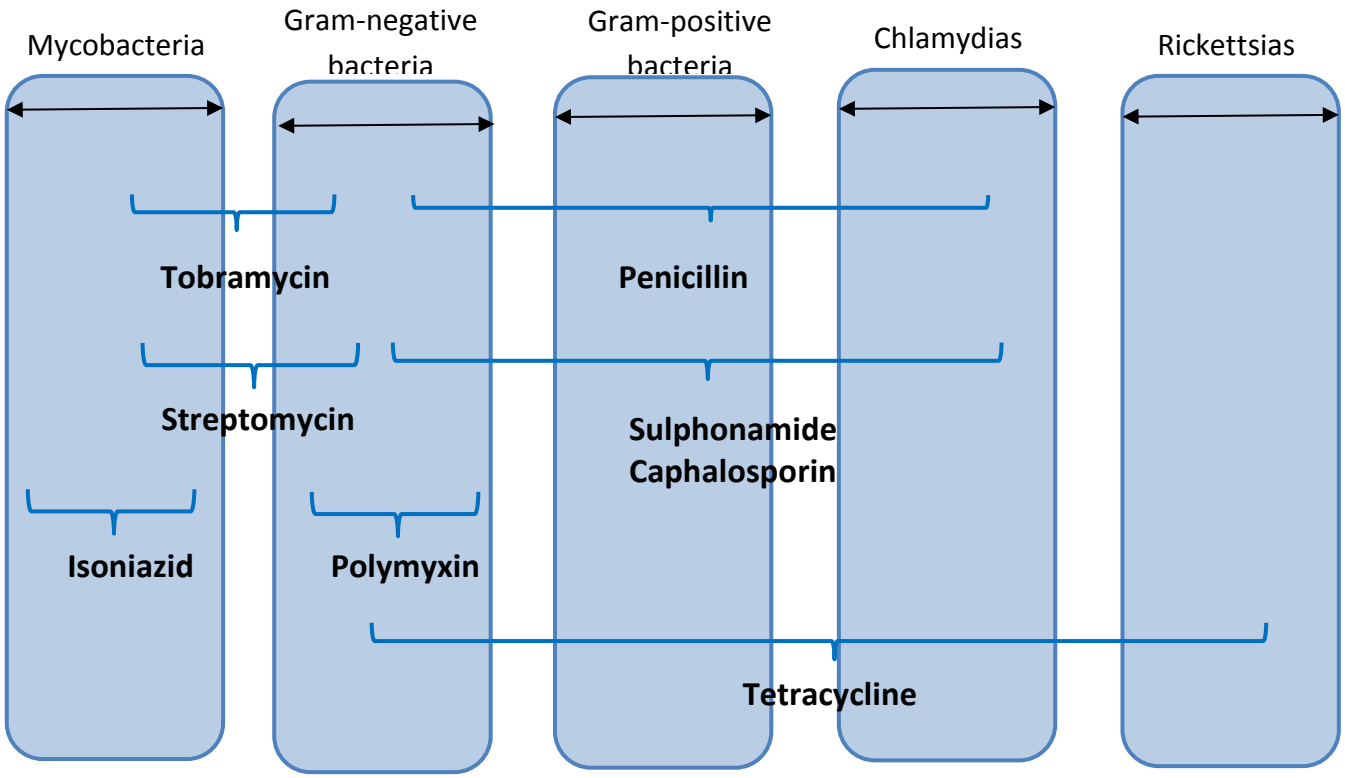


Figure 2: Antibiotics' spectrum of activity

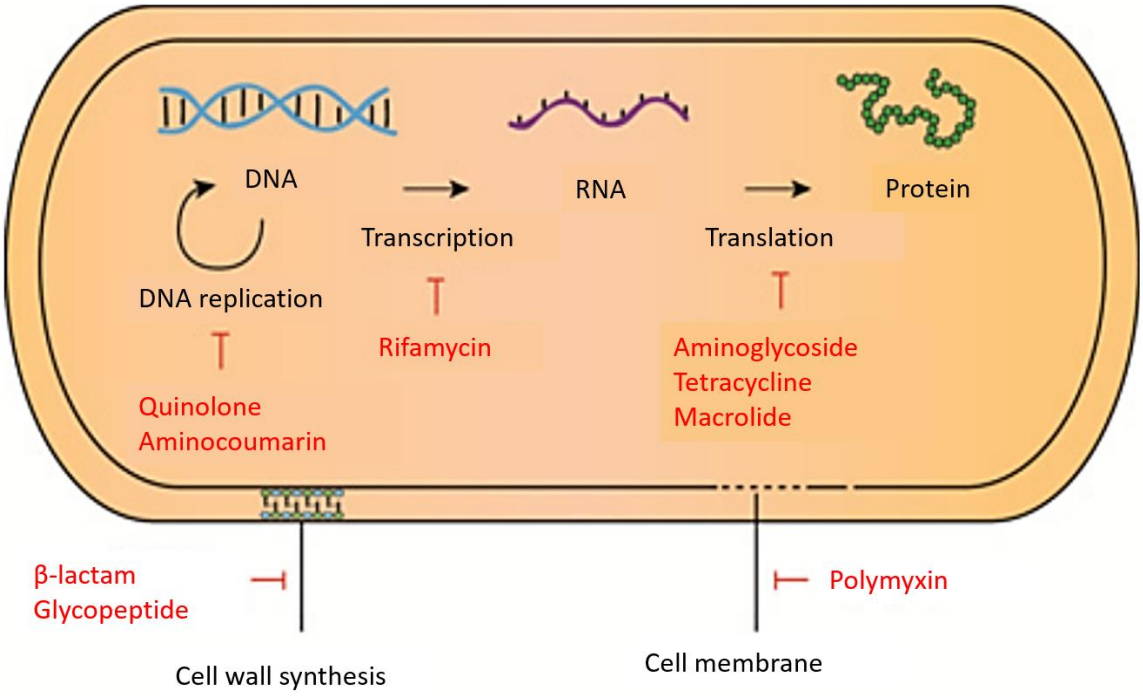


Figure 3: Inhibition of multiple cellular processes by AB (Muheim, 2017)

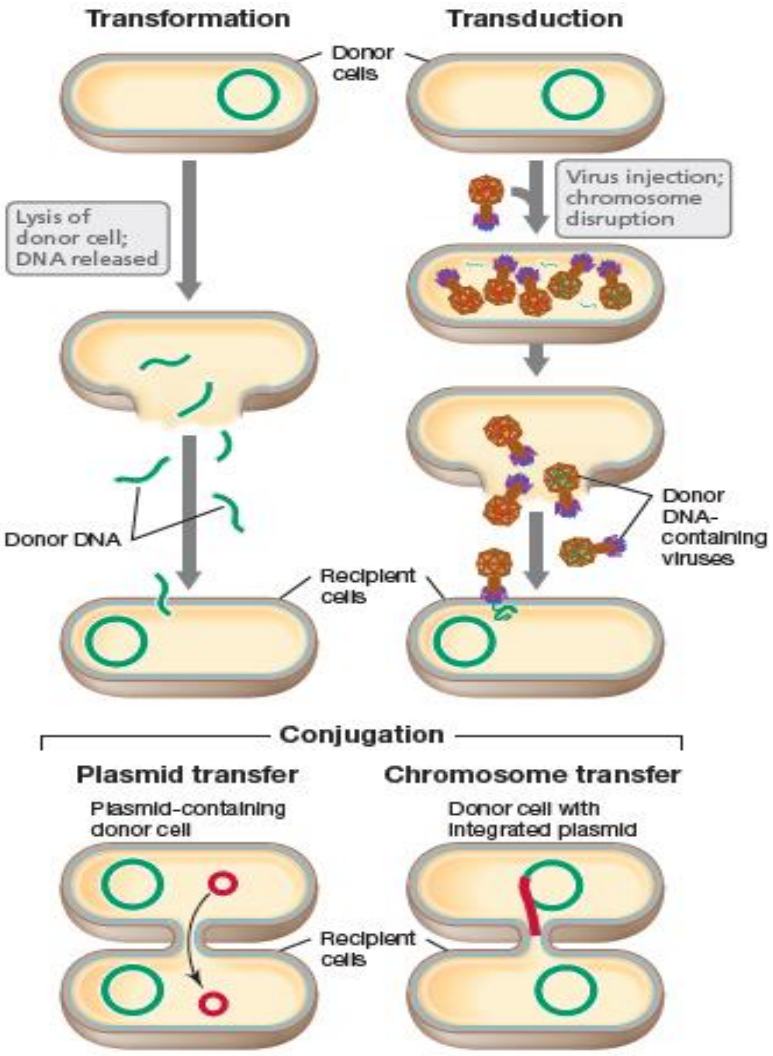


Figure 4: Processes of horizontal gene transfer from donor to recipient bacterial cell

(Madigan et al., 2014)

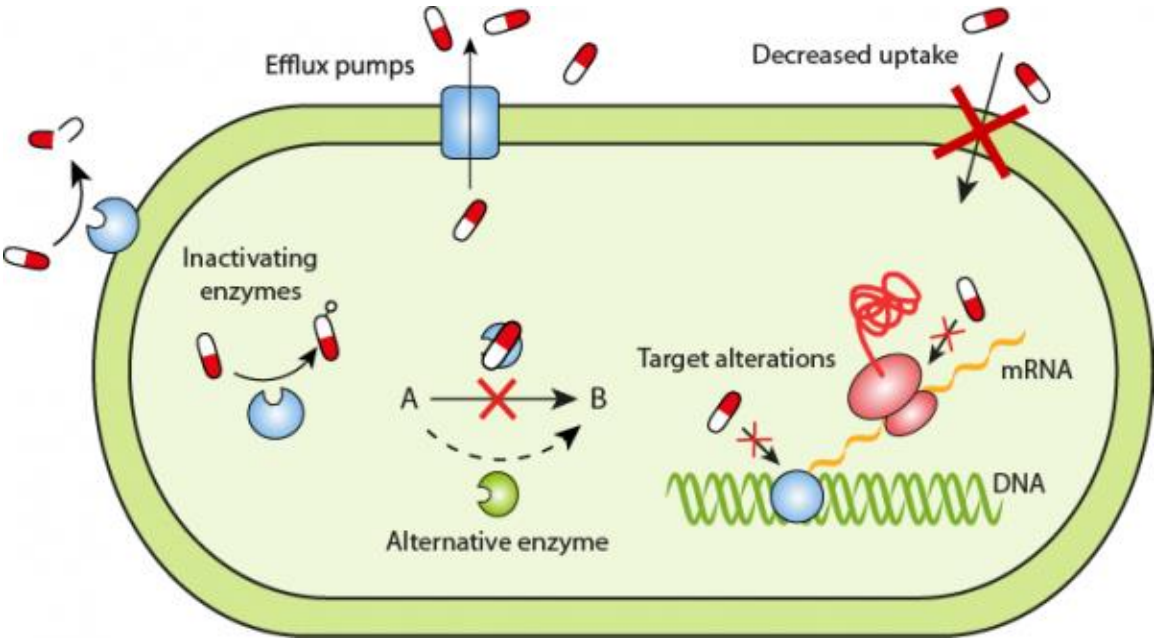


Figure 5: Mechanisms of antimicrobial resistance (Wistrand-Yuen et al., 2018)

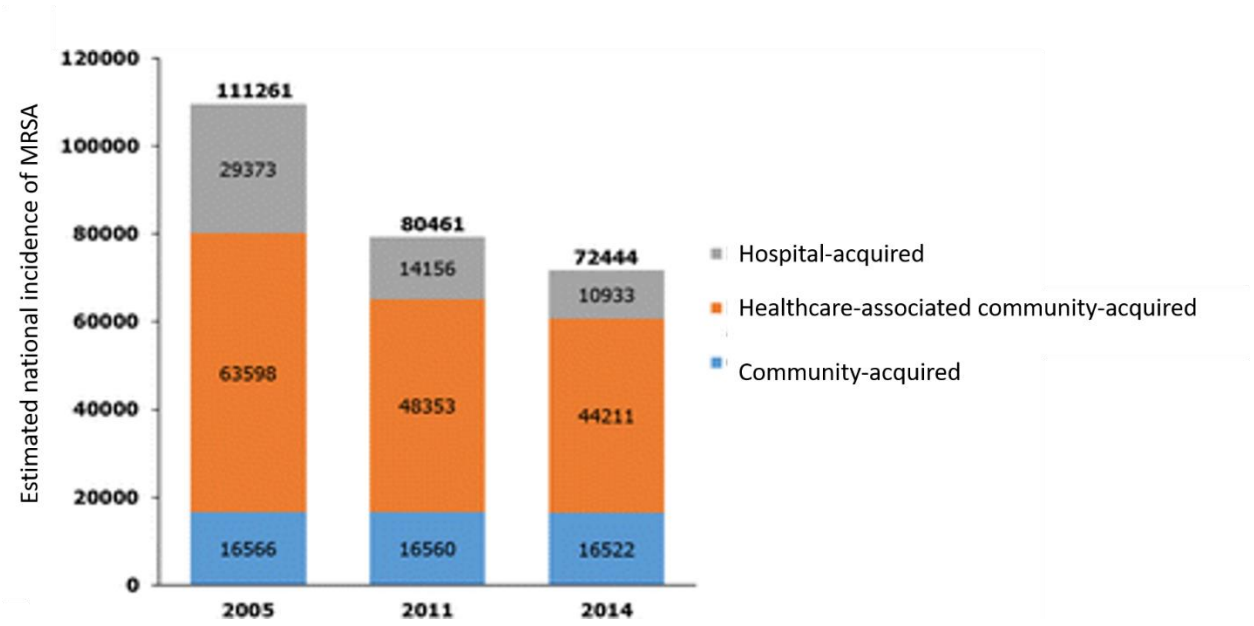


Figure 6: Estimated number of MRSA infections in the USA (van Hal et al., 2012)

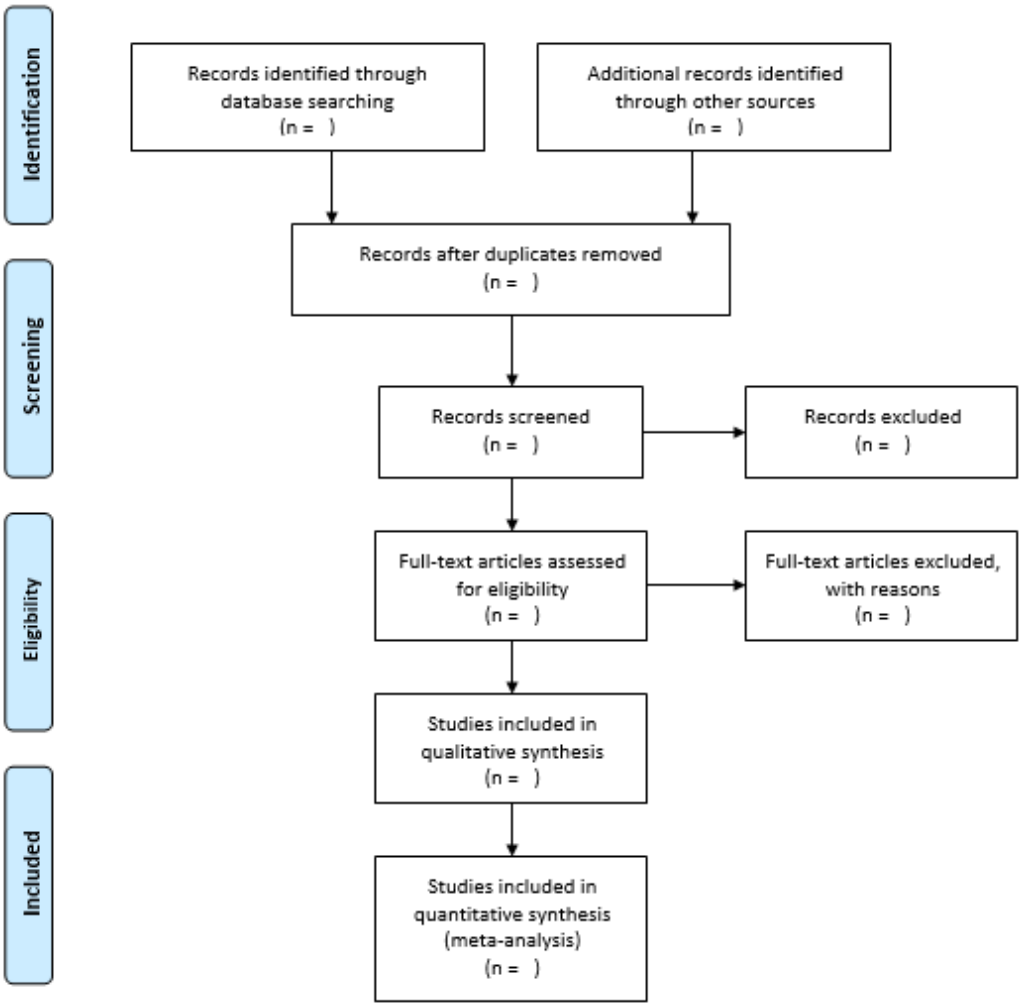


Figure 7: PRISMA 2009 flow diagram (Moher et al., 2009)

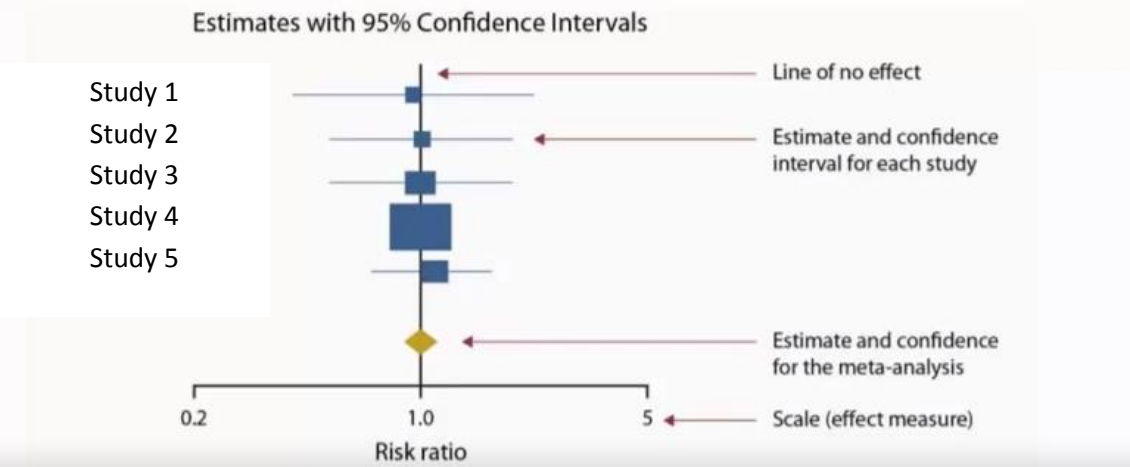
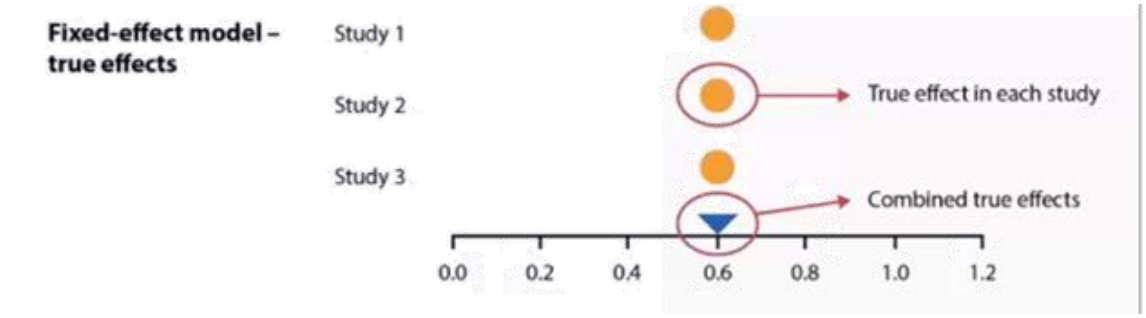
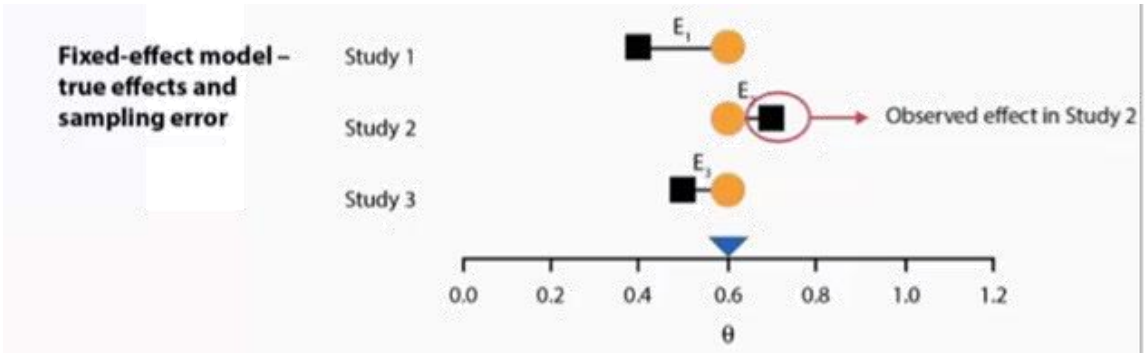


Figure 8: Forest plot labeling

A



B



C

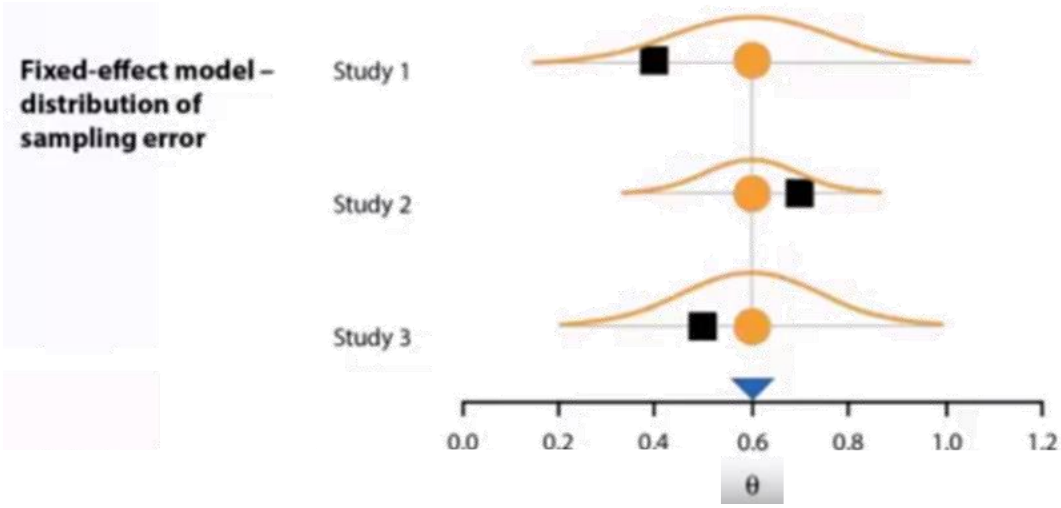


Figure 9: Fixed effect model (Hopkins', 2020)

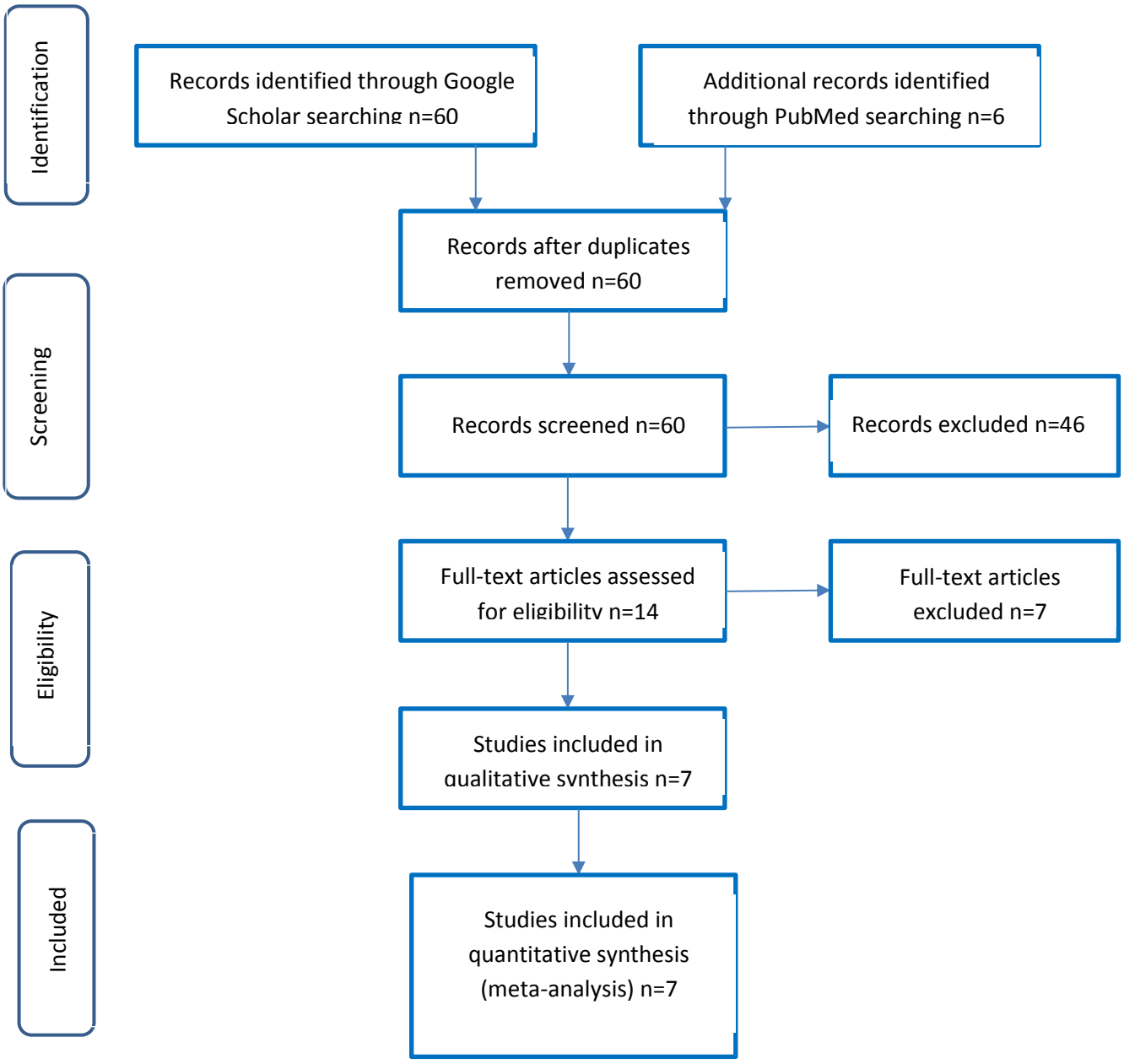
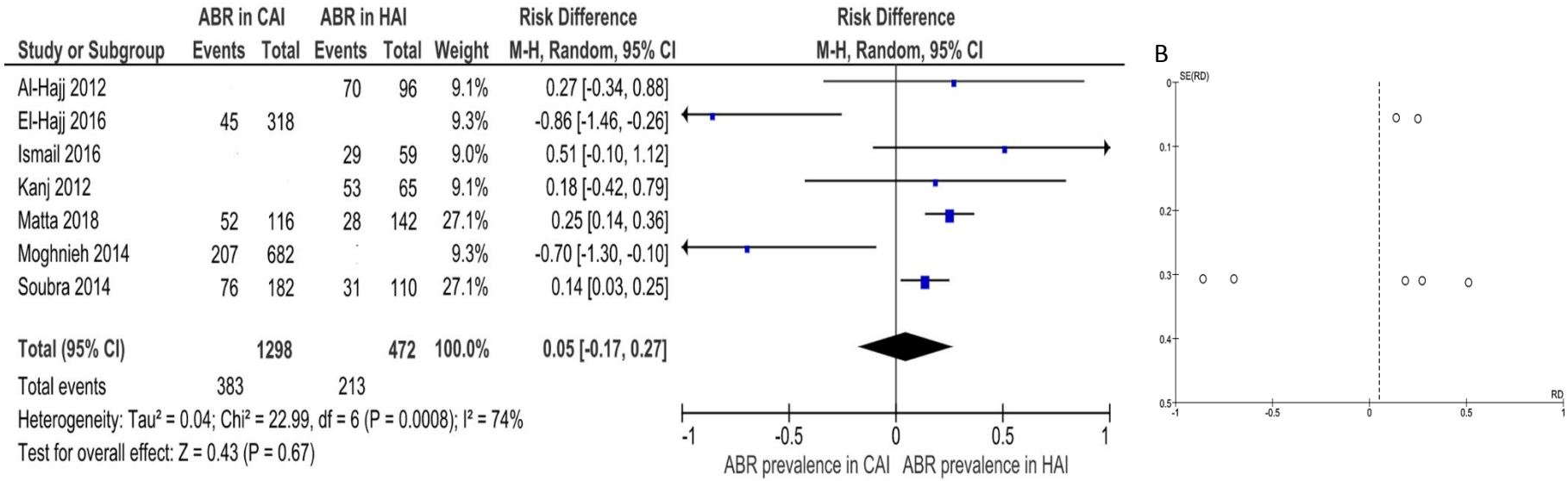


Figure 10: Search results under the PRISMA model

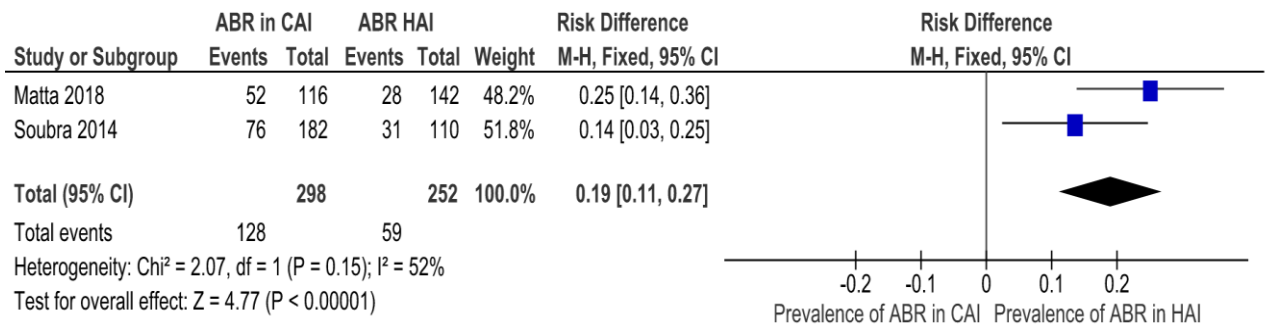
A



B

Figure 11*: Studies comparisons and forest plots. Comparison of all included studies (A). Comparison of the studies reporting CAI and HAI (B). ABR: antibiotic-resistant*

A



B

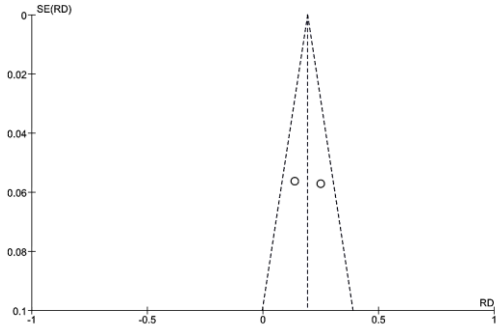


Figure 12*: Funnel plot for the studies reporting either/or CAI and HAI (A). Funnel plot for the studies reporting CAI and HAI together (B).*

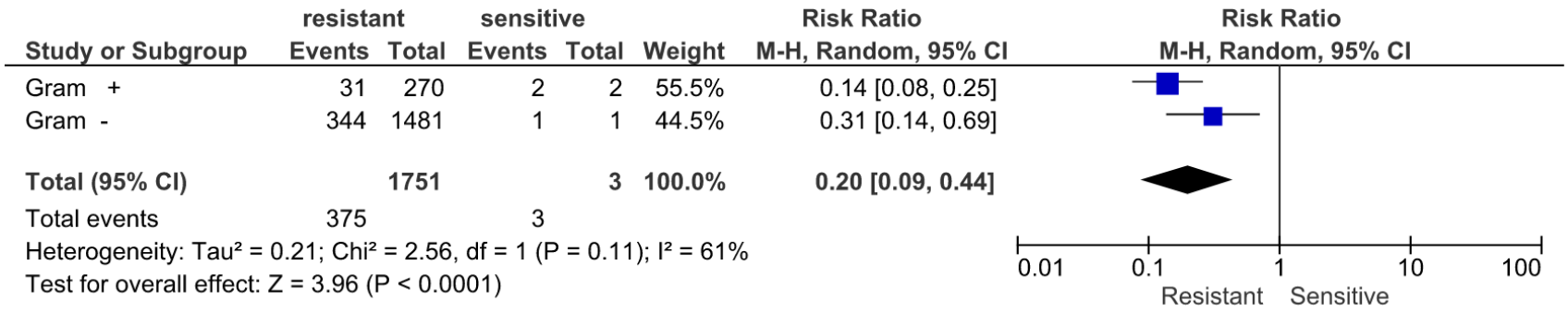
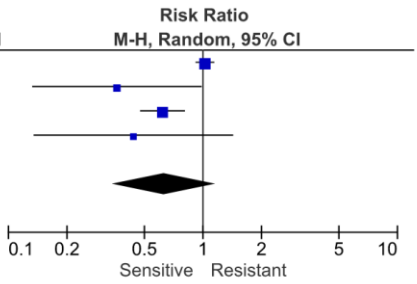


Figure 13*: Studies comparisons and forest plots. Comparison of all included studies (A). Comparison of the studies reporting CAI and HAI (B). ABR: antibiotic resistant*

Aminoglycosides

Study or Subgroup	Resistant Events	Resistant Total	Sensitive Events	Sensitive Total	Weight	Risk Ratio M-H, Random, 95% CI
Amikacin	42	47	618	708	34.2%	1.02 [0.92, 1.13]
Aminoglycosides	2	6	44	44	18.1%	0.36 [0.13, 0.98]
Gentamicin	28	52	199	229	32.5%	0.62 [0.48, 0.80]
Tobramycin	2	7	444	682	15.2%	0.44 [0.14, 1.42]
Total (95% CI)		**112**		**1663**	**100.0%**	**0.63 [0.34, 1.17]**
Total events	74		1305			

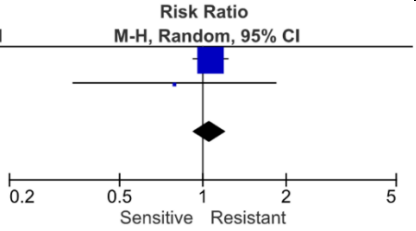
Heterogeneity: Tau² = 0.28; Chi² = 34.76, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.46 (P = 0.14)



Fluoroquinolones

Study or Subgroup	Resistant Events	Resistant Total	Sensitive Events	Sensitive Total	Weight	Risk Ratio M-H, Random, 95% CI
Ciprofloxacin	84	136	523	903	97.2%	1.07 [0.92, 1.23]
Fluoroquionolone	22	37			2.8%	0.79 [0.34, 1.83]
Total (95% CI)		**173**		**904**	**100.0%**	**1.06 [0.92, 1.22]**
Total events	106		524			

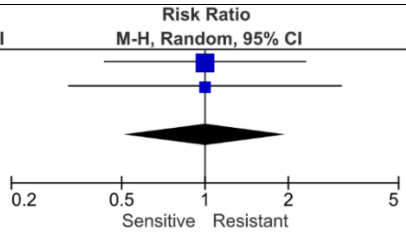
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)



Macrolides

Study or Subgroup	Resistant Events	Resistant Total	Sensitive Events	Sensitive Total	Weight	Risk Ratio M-H, Random, 95% CI
Clindamycin	5	5			64.7%	1.00 [0.43, 2.31]
Erythromycin	1	1			35.3%	1.00 [0.32, 3.10]
Total (95% CI)		**6**		**2**	**100.0%**	**1.00 [0.51, 1.96]**
Total events	6		2			

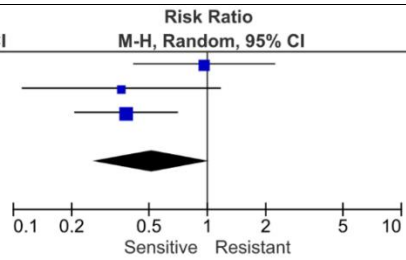
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



Cephalosporins

Study or Subgroup	Resistant Events	Resistant Total	Sensitive Events	Sensitive Total	Weight	Risk Ratio M-H, Random, 95% CI
Cefalotin	19	26			33.6%	0.96 [0.42, 2.22]
Cefepime	2	7	796	1004	22.9%	0.36 [0.11, 1.16]
Ceftriaxone	7	21	194	222	43.5%	0.38 [0.21, 0.70]
Total (95% CI)		**54**		**1227**	**100.0%**	**0.51 [0.26, 1.03]**
Total events	28		991			

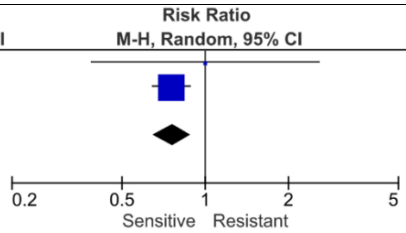
Heterogeneity: Tau² = 0.19; Chi² = 4.12, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 1.87 (P = 0.06)



Carbapenems

Study or Subgroup	Resistant Events	Resistant Total	Sensitive Events	Sensitive Total	Weight	Risk Ratio M-H, Random, 95% CI
Carbapenem	2	2			2.6%	1.00 [0.39, 2.58]
imipenem	42	57	919	940	97.4%	0.75 [0.65, 0.88]
Total (95% CI)		**59**		**941**	**100.0%**	**0.76 [0.65, 0.89]**
Total events	44		920			

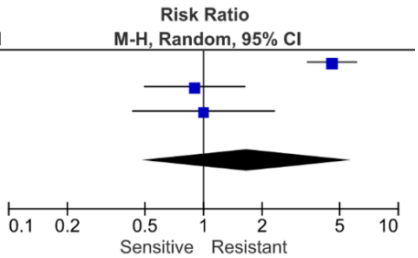
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 3.52 (P = 0.0004)



Penicillins

Study or Subgroup	Resistant Events	Resistant Total	Sensitive Events	Sensitive Total	Weight	Risk Ratio M-H, Random, 95% CI
Ampicillin	16	16	39	185	35.5%	4.57 [3.42, 6.10]
Methicillin	10	13	2	2	33.4%	0.90 [0.50, 1.62]
Penicillin	5	5			31.1%	1.00 [0.43, 2.31]
Total (95% CI)		**34**		**188**	**100.0%**	**1.66 [0.48, 5.73]**
Total events	31		42			

Heterogeneity: Tau² = 1.11; Chi² = 31.16, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.80 (P = 0.43)



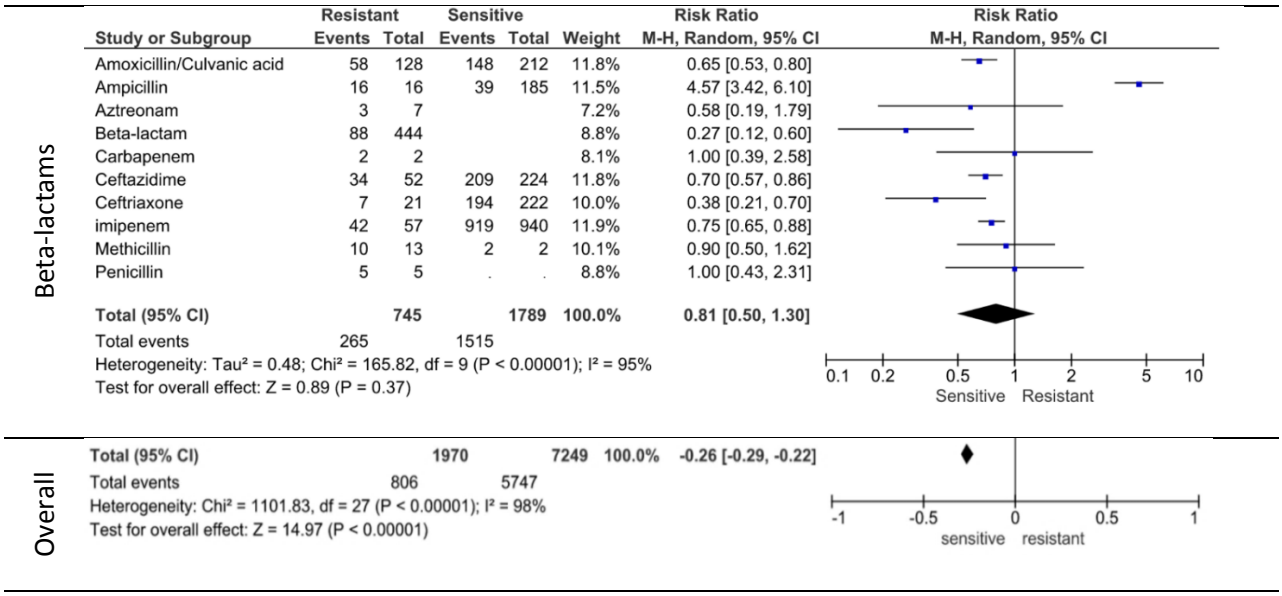


Figure 14*: Meta-analysis of the effectiveness of antimicrobials and their overall impact on microorganisms*

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