Navigating Antibacterial Frontiers: Landscape Analysis of Antibiotics, Resistance Mechanisms and Emerging Therapeutic Strategies

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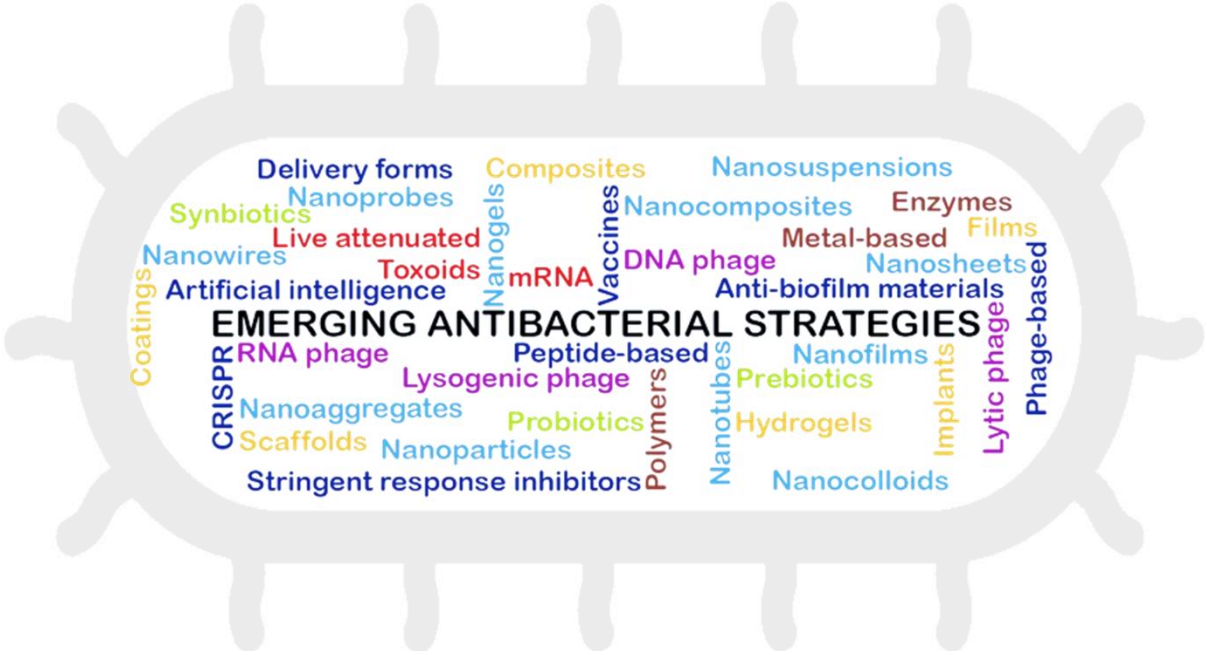
Abstract

Developing effective antibacterial solutions has become paramount in maintaining global health in this era of increasing bacterial threats and rampant antibiotic resistance. Traditional antibiotics have played a significant role in combating bacterial infections throughout history. However, the emergence of novel resistant strains necessitates constant innovation in antibacterial research. We have analyzed the data on antibacterials from the CAS Content Collection™, the largest human-curated collection of published scientific knowledge, proven valuable for quantitative analysis of global scientific knowledge. Our analysis focuses on mining the CAS Content Collection data for recent publications (since 2012). This article aims to explore the intricate landscape of antibacterial research while reviewing the advancement from traditional antibiotics to novel and emerging antibacterial strategies. By delving into the resistance mechanisms, this paper highlights the need to find alternate strategies to address the growing concern.



1. Introduction

The emergence of drug-resistant bacterial strains and their associated challenges continue to be responsible for a sustained economic burden to the whole world, exemplified by the fact that the World Health Organization (WHO) declared antimicrobial resistance (AMR) as one of the top ten primary health concerns affecting humanity.[1, 2] Bacterial infections comprise the majority of microbial infections due to their prevalence in diseases, public health impact, variability of virulence, development of resistance and ease of transmission, therefore, antibacterial agents are the most common method to prevent and treat these infections. The spectrum of antibacterial activity encompasses a wide range of bacteria, however, certain bacterial strains such as *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter sp., Escherichia coli* – collectively called ESKAPEE – have garnered public interest as they are known to 'escape' commonly used antibiotic treatment owing to multidrug resistance (MDR).[3-6] Data from the Centers for Disease Control and Prevention (CDC) for the year 2020 suggests that six out of the eighteen listed antimicrobial-resistant bacterial threats namely Vancomycin-resistant *Enterococcus* (VRE), Carbapenem-resistant *Acinetobacter baumannii* (CRAB), Methicillin Resistant *Staphylococcus Aureus* (MRSA), Carbapenem-resistant Enterobacterales (CRE), Multidrug-Resistant *Pseudomonas aeruginosa* (MDR-PA) and Extended-spectrum beta-lactamase (ESBL) producing Enterobacterales incur a collective cost of more than $4.6 billion annually.[7] MRSA strains remain a leading cause of infections worldwide, ranging from skin and soft tissue infections to more serious conditions such as bacteremia and endocarditis. Due to the rise in resistant species, some bacterial infections have become public health threads. For instance, tuberculosis, a serious lung disease requiring prolonged antibiotic therapy, is caused by *Mycobacterium tuberculosis* (MT). Many species of MT are resistant to the first-line oral antituberculosis agents isoniazid and rifampicin and are designated MDR TB.[8, 9] MDR TB requires the use of second-line drugs which require parenteral delivery and often have significant side effects, reducing the likelihood that treatment is completed and thus facilitating resistance. More extensively resistant variants such as extensively drug-resistant TB (XDR-TB) are resistant to second-line antitubercular therapies, and in rare cases, MT can be resistant to all available therapies (totally drug-resistant TB (TDR-TB).[10-12]. Similarly, community-acquired pneumonia (CAP), which results most commonly due to infection of *Streptococcus pneumoniae* and *Haemophilus influenzae*, is the major cause of pneumonia related deaths, especially in newborn population.[13, 14] Constantly evolving antibiotic-resistant bacterial species emphasize the need for a systematic literature review and analysis in the antibacterial field.

In this report, we provide an overview of the current knowledge on antibiotic resistance, antibiotics, and antibacterial materials. Furthermore, we provide a landscape of the antibacterial field based on data from the CAS Content Collection[15], the largest human-curated collection of published scientific knowledge, which has proven useful for quantitative analysis of global scientific publications. Our analysis focuses on mining the CAS Content Collection for recent documents (2012 onwards) to uncover trends in journal and patent publications, the use of various substances, and for providing insights linking antibiotics with bacteria and disease indications. Additionally, we review the antibiotic resistance mechanisms, diverse classes of antibiotics, their modes of action, and emerging antibacterial strategies. The overarching aim of this report is to serve as a useful resource for understanding the current state of the field of antibacterials and global research efforts in this field.

2. Antibiotic resistance

According to WHO, a resistant organism is one that is not killed/inactivated upon completion of the entire course of treatment. According to data presented by the Centre for Disease Control and Prevention (CDC), more than 2.8 million antibiotic-resistant (AMR) bacterial infections occur each year leading to >35,000 deaths per year.[16] According to projections made by the World Bank,[17] by the year 2050, 10 million people are projected to die due to MDR bacterial infections, incurring a loss of up to USD100 trillion to the global economy.[18] Antibiotic resistance occurs when bacteria evolve to render existing antibiotics ineffective, leading to difficult or ineffective treatment.[2, 19, 20] While many factors have led to the rise in MDR, one significant factor is the inability of antibacterial drug discovery and development to keep pace with bacterial drug resistance. Over 100 antibiotics are available for treating bacterial infections but overuse and misuse of antibiotics in both humans and livestock have also played a significant role in the rise of antibiotic resistance, as it creates a selective pressure favoring resistant strains.[21, 22] Inadequate prescription practices, a rise in self-medication, and non-compliance with prescribed antibiotic regimens can exacerbate these issues. Highly resistant bacterial strains include various Gram-positive bacteria such as *Enterococcus faecalis*, *Enterococcus faecium*, coagulase-negative *Staphylococci* (CNS), and Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and Gram-negative bacteria such as multidrug-resistant *Acinetobacter*, *Enterobacter*, *Escherichia coli*, *Pseudomonas aeruginosa, Klebsiella,* etc.[22-24]

Antibiotic resistance in bacterial species can be intrinsic or acquired. Intrinsic antibiotic resistance occurs primarily due to the inherent structural/genetic composition of a particular bacterial species while acquired antibiotic resistance arises due to the gain of new genetic material or from a mutation arising in the bacterial genome providing novel capabilities mediating survival in bacterial species.[25, 26] Mutations (contributing to acquired resistance) can be of several types - spontaneous, adaptive, and random, among others arise due to errors during replication or by inefficient repair of damaged DNA. In certain instances, selection pressure arising due to non-lethal antibiotics can result in hypermutations. In these cases, bacteria enter a state of high mutation rate called the 'hypermutable' state wherein they acquire mutations to survive. In certain cases, adaptive mutations can occur in non-dividing or slowly dividing cells due to selection pressure. These mutations are responsible for the development of antimicrobial resistance in bacteria under natural conditions. Vertical gene transfer is the transfer of genes from a parent bacterium to its offspring, while horizontal gene transfer is the transfer of genes between unrelated bacteria.[27] Horizontal gene transfer is the most prevalent method for antimicrobial resistance gene transfer, and it can take place by conjugation, transduction, or transformation.[28] Random genetic mutations can also lead to antibiotic resistance. For instance, the acquisition of the extended-spectrum β-lactamase cefotaximase, CTX-M-15 by a highly virulent strain of E. coli, ST131.[29] The rise in resistance can eventually lead to This has led to a rise in community-acquired antibiotic resistance in bacterial species.[30]

At the bacteria level, decreased drug uptake, increased antibiotic efflux pump expression, enzymatic inactivation, target alteration, alterations in bacterial metabolism to bypass antibiotic inhibition, and overproduction of drug targets are some common mechanisms of antibacterial resistance **(Figure 1)**.[31-35]

Decreased drug uptake: Gram-negative bacteria, unlike Gram-positive species, are naturally resistant to various drugs due to the presence of a bilayer, outer membrane that is impermeable/impenetrable to most drugs.[36] Structurally, the outer membrane contains lipopolysaccharides which stiffen bacterial membranes, reducing both membrane fluidity and permeability. Additionally, modifications in porins – diffusion channel-forming proteins – are also known to restrict the influx of antibiotics in bacteria by several mechanisms including size limitation, hydrophobicity, or charge-based drug repulsion. In certain cases, mutations lead to a

reduction in the expression/loss of porins. These mutations can result in reduced permeability/ complete exclusion of drugs from porins.[37, 38]

Efflux pumps: The permeability of antibiotics is affected by the type and number of efflux pumps present. Some bacteria have MDR efflux pumps which allow bacteria to reject and export toxic compounds and thus can also allow them to resist antibiotics. MDR pumps can be specific to one antibiotic or may target a broad spectrum of antibiotics. A variety of families of efflux pumps are present in bacteria, such as the ATP-binding cassette (ABC) family, the multidrug and toxin extrusion (MATE) family, the major facilitator superfamily (MFS), the small multidrug resistance (SMR) family, the resistance-nodulation-cell division (RND) superfamily and the proteobacterial antimicrobial compound efflux (PACE) family.[39, 40] These pumps are responsible for the majority of induced resistance in bacteria.

Modified drug target site: This is a common drug-resistant mechanism and occurs due to spontaneous mutation of bacterial genes and selection in the presence of antibiotics.[41] They can also occur due to enzymatic modification or by replacement of the original target. For instance, modifications in bacterial RNA polymerase and DNA gyrase result in resistance to the rifamycins and quinolones, respectively.[42-44] Similarly, vancomycin-resistant bacteria typically acquire resistance through modification of the drug's target site in bacterial cell walls, resulting in a reduction in the binding affinity of vancomycin, making it less efficient in disrupting cell walls.[45]

Target amplification: It involves increasing the production of target molecules that the antibiotic acts upon. It can be observed in the case of resistance to trimethoprim-sulfamethoxazole (TMP-SMX) due to mutations that can lead to an increase in the production of dihydrofolate reductase-drug target of trimethoprim.[46]

Enzymatic degradation/modification: Bacteria produce enzymes that can degrade antibiotics by modifying their structure (mostly through redox reactions or group transfer). For instance, ß-lactamases are a group of enzymes that deactivate ß-lactam antibiotics by hydrolyzing the ß-lactam ring.[47] ß-lactamases are mostly present in Gram-negative bacteria and a few Gram-positive ones such as *Staphylococcus aureus*, *Enterococcus faecalis,* etc.[48, 49] In *P. aeruginosa* beta-lactamases are present in their periplasmic spaces.[50, 51] Carbapenem-resistant Enterobacteriaceae (CRE) possess metallo-beta-lactamases such as New Dehli metallo-beta-lactamase-1, *Klebsiella pneumoniae* carbapenemase-2, and other metallo-beta-lactamases encoded by genes such as bla(NDM-1), bla(KPC), bla(IMP), and bla(CMY). Carbapenem-resistant Enterobacteriaceae are resistant not only to penicillins and cephalosporins but also to carbapenems, making them a serious global health threat.[52-55]

In certain bacterial species, one or combinations of these factors play a role in developing resistance. For instance*, A. baumannii* is resistant to carbapenems owing to a combination of decreased expression of porins, increased expression of three RND-type efflux pumps, and the presence of ß-lactamases.[56] Apart from resistance, certain bacteria also show 'tolerance' which is the ability of bacterial cells to withstand antibiotics due to them being in a physiological state of dormancy or slow growth.[57] In addition, certain sub-populations of bacteria, known as 'persisters' are non-growing and transiently tolerate antibiotic treatment.[57, 58] Persistent bacteria are often linked to chronic bacterial infections.[59] Some other mechanisms are used by bacteria to exhibit tolerance and virulence such as biofilm formation, endospores, adopting certain morphologies such as filamentous and L-form (cell wall deficient bacteria), using survival techniques such as quorum sensing, having secretory proteins and toxins such as type III secretion systems (T3SS), siderophores among others.[60-64]

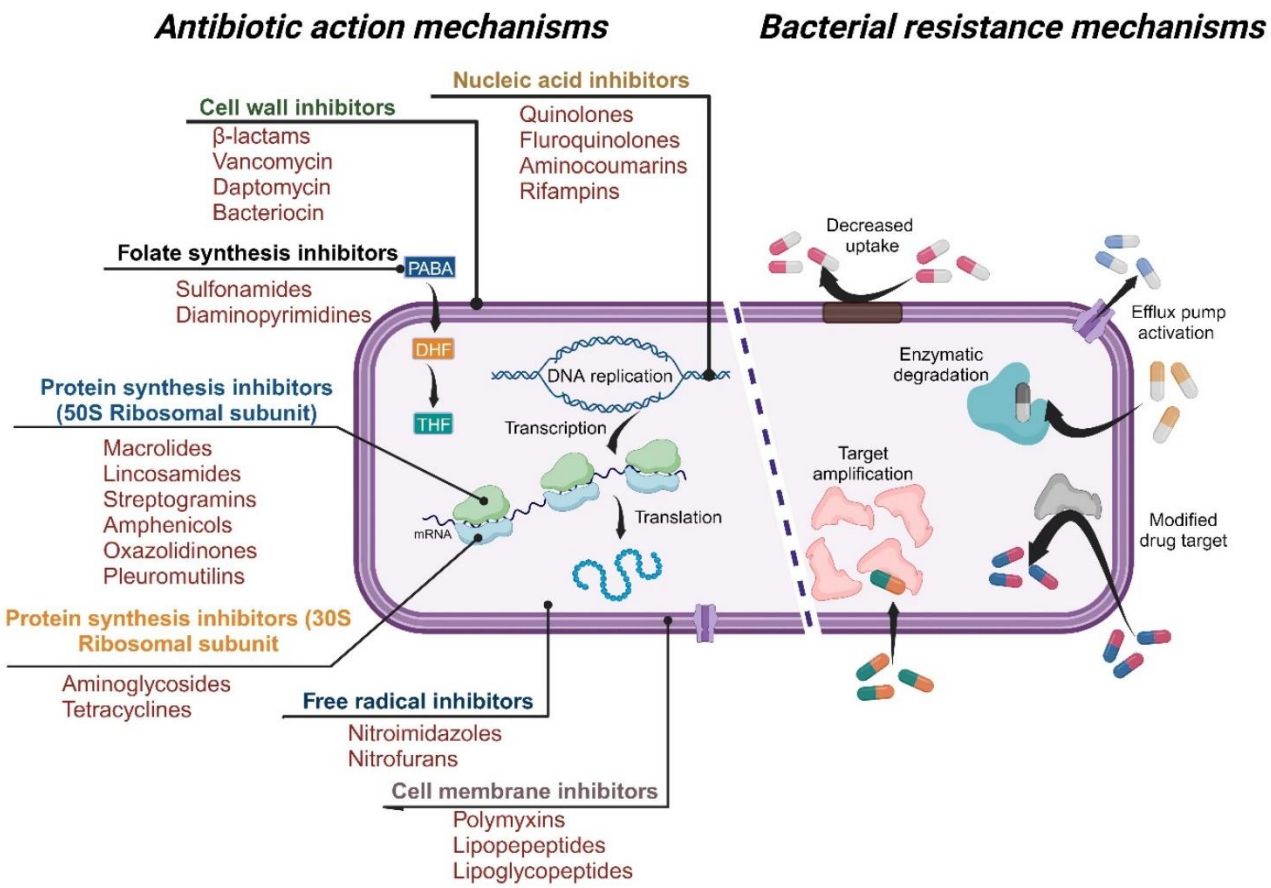


Figure 1: Illustration demonstrating action mechanisms of commonly used antibiotics (left side) and resistance mechanisms used by bacteria (right side) to evade the action of antibiotics (individual icons for creating illustration are sourced from www.biorender.com)

3. Antibiotics

This section describes traditional approaches used as antibiotics and novel approaches emerging to counter problems such as antimicrobial resistance in bacteria. Structures for antibiotic drugs mentioned in this section can be found in **Supplementary Table 1**.

3.1. Antibiotic classes

Sulfonamides: Sulfonamides form the core of the sulfa drugs, the first synthetic antibiotics discovered. They were discovered by Domagk as related arylazosulfonamides which were prepared as dyes but found to cure bacterial infections when given to people. Subsequent work showed that the azo compound found by Domagk underwent reductive cleavage to the active aminobenzenesulfonamide; the aminobenzenesulfonamide acts as a mimic of p-aminobenzoic acid, which inhibits dihydropteroate synthetase, an enzyme necessary for folate synthesis **(Figure 1**) and thus for growth and metabolism.[65] While bacteria can synthesize folates, mammals must obtain them through their diet; thus, bacteria are susceptible to folate inhibition but not mammals.[66] Sulfa drugs are bacteriostatic against both Gram-negative and Gram-positive bacteria but are not bactericidal. Seven sulfa drugs have been approved by the US FDA as antibiotics – sulfanilamide (1937, R = H), sulfadiazine (1941, R = 2-pyrimidinyl), sulfapyridine

(1942, R = 2-pyridinyl), sulfasalazine (1950 – an azo prodrug of sulfapyridine), sulfamethizole (1953, R = 5-methyl-1,3,4-thiadiazol-2-yl), sulfacetamide (1970, R = MeCO), and sulfamethoxazole (1982, R = 5-methyl-3-isoxazolyl) (**Supplementary Table 1**).[67] Bacteria have multiple resistance mechanisms for sulfonamides. Modification of dihydropteroate synthetase to prevent the binding of sulfonamides with substituents at the sulfonamide nitrogen in combination with other mutations to improve the activity of the mutant enzyme can restore growth to sulfonamide-inhibited bacteria.[68] Alternatively, acylation or hydroxylation of the aniline nitrogen of sulfonamides abrogates binding to dihydropteroate synthetase.[65]

Beta-lactams: First reported by Alexander Fleming in 1929[69], β-lactams are one of the most commonly prescribed drug classes.[70] Penicillin G, the "wonder drug" produced by the *Penicillium* fungus, is the oldest member of this family, clinically used in the 1930s and playing a very important role in saving lives during WWII.[71, 72] These drugs have an essential structural feature, a highly reactive four-membered amide ring known as a "β-lactam" or "azetidinone". The antibacterial properties of β-lactams come from their inhibition of bacterial transpeptidases that catalyze the cross-linkage of peptidoglycan, a main component in bacterial cell wall synthesis.[72, 73] These transpeptidases, known as penicillin-binding proteins (PBPs), irreversibly and covalently bind to β-lactams via the nucleophilic attack of the serine residue in the PBPs active site to the lactam carbonyl which results in a stable acyl-enzyme complex.[72, 74, 75] The structure, geometry, and stereochemical characteristics of β-lactams play a key role in this inhibition, for it mimics the enzyme-substrate, D-Ala-D-Ala dipeptide in peptidoglycans of the bacterial cell wall.[76] Gram-positive bacteria are more susceptible to β-lactams than gram-negative bacteria; mostly due to the higher concentration of peptidoglycan in the cell wall. This broad family of antibiotics can be divided into the structural classes shown in **Supplementary Table 1**.

While β-lactams have been highly successful antibiotics, their widespread use has led to antibiotic resistance. β-Lactamses, a family of hydrolytic enzymes that inactivate all β-lactams, are of particular concern due to high catalytic efficiency and rapid distribution via horizontal transfer on plasmids. β-Lactamase inhibitors (sulbactam, clavulanate, tazobactam, avibactam, and vaborbactam) have little antibacterial activity by themselves but can inactivate β-lactamases to restore the antibacterial activity of β-lactams. More recently, compounds incorporating two β-lactam groups have been developed as dual β-lactamase inhibitors and antibiotics to circumvent drug resistance.[73] Combining a β-lactam moiety with another class of antibiotic is another approach. For example, TD-1792 (Cefilavancin) is a novel covalently linked heterodimer of a glycopeptide (vancomycin) and a cephalosporin for the treatment of serious Gram-positive infections like acute bacterial skin and skin structure infection; it has completed phase II clinical trials in the US and is currently under the filling process in Russia.[77-80] Another approach is conjugating β-lactams to bacterial transporters like siderophores. A successful example of this is Cefiderocol, a siderophore-containing cephalosporin with activity against carbapenem-resistant and multidrug-resistant Gram-negative bacilli that is currently available commercially under the brand name Fetroja for the treatment of complicated urinary tract infections.[81, 82]

Aminoglycosides: The isolation of the first aminoglycoside with antibiotic properties, streptomycin, was first reported in 1944.[83] It was isolated from two strains of actinomyces related to *Streptomyces griseus*. Since then, many have been obtained via the fermentation of *Streptomyces* (neomycin from *S. fradiae*[84], kanamycin from *S. kanamyceticus*[85], tobramycin from *S. tenebrarius*[86, 87]) and *Micromonospora* (gentamicin *Micromonospora purpurea*[88], sisomicin from

Micromonospora inyoensis[89]) *or* through chemical modification of aminoglycoside scaffolds (amikacin[89-91], netilmicin[91, 92], arbekacin[92, 93], plazomicin[94-96]).
Aminoglycosides are hydrophilic molecules that have one or more aminated sugars joined in glycosidic linkages to a dibasic cyclitol (aminocyclitol), which is most commonly a 2-deoxystreptamine. [97, 98] They can be classified into two broad categories based on the aminocyclitol moiety: those with a deoxystreptamine ring and those without (streptomycin). This first category can be further divided based on the substitution of the deoxystreptamine ring: monosubstituted (apramycin), 4,5-di-substituted (neomycin, ribostamycin), and 4,6-di-substituted (gentamicin, amikacin, tobramycin, and plazomicin).[97, 99] This family of molecules is bactericidal and has a broad spectrum of activity against Gram-negative and Gram-positive bacteria, being particularly potent against *Enterobacteriacae*.[99, 100] They inhibit bacterial protein synthesis via binding to prokaryotic ribosomes.[98] The primary mechanism of action is via binding to the 16S ribosomal RNA at the tRNA acceptor aminoacyl-site (A-site) on the 30S ribosome, altering the conformation of the A-site. This inhibits the translation process by causing codon misreading and/or by hindering the translocation of tRNA from the A-site to the peptidyl tRNA, causing defective protein synthesis that can cause damage to the cell. [97, 99, 101] Some aminoglycosides can also block the elongation of translation or directly inhibit initiation.[100, 101]

The most prevalent resistance mechanism is the enzymatic modification caused by aminoglycoside modifying enzymes, specifically by aminoglycoside acyltransferases (AACs), aminoglycoside phosphotransferases (APHs), and aminoglycoside nucleotransferases (ANTs).[100, 102] Other resistance mechanisms are target site modification via methylation of 16S rRNA or chromosomal mutation; efflux, uptake and permeability mutations; and highly efficient membrane proteases.[100, 102] Strategies to combat this resistance, as well as new developments in these strategies have been discussed by Becker and Cooper,[102] Krause *et al*.[99, 100] and Tevyashova and Shapovalova.[103] In addition to resistance, adverse effects like ototoxicity, nephrotoxicity, and in some cases, neuromuscular blockade are also an issue.[104] Decreasing the associated toxicities is also a focus when it comes to developing new derivatives.[105-108]

Tetracyclines: Tetracyclines are a broad-spectrum bacteriostatic antibiotic class whose structure is based on a DCBA naphthacene core. Aureomycin, 6-chlorotetracycline, was the first member of this antibiotic class to be reported, discovered by Benjamin Minge Duggar at Lederle Laboratories in 1948.[109] This was followed by terramycin, reported in 1950 and discovered by Alexander Finley from Pfizer.[110] These first tetracyclines were natural products obtained from *Streptomyces* from soil samples, specifically via fermentation of *Streptomyces aureofaciens* (aureomycin) and *Streptomyces rismosus* (terramycin). Additional natural product tetracyclines are tetracycline (Teracyn) and demeclocycline, while other members of this class are semi-synthetic tetracyclines (lymecycline, methacycline, minocycline, rolitetracycline, sarecycline, omadacycline and doxycycline), glycylcyclines (tigecycline), and synthetic tetracyclines (eravacycline, TP-271).[111]
This class of antibiotics is effective against a wide range of Gram-positive and Gram-negative bacteria. Members of this family are effective against: *Yersinia pestis*, *Vibrio cholera*, *Salmonella enterica*, *Treponema pallidum*, *Legionella pneumophila*, *Bacillus anthracis*, *Borrelia burgdoferi*, *Borrelia afzelii*, *Borrelia garinii*, *Borrelia recurrentis*, *Mycobacterium tuberculosis*, *Coxiella burnetii*, *Rickettsia ricketsii*, *Mycobacterium lepra*, *Mycobacterium marinum*, *Mycoplasma pneumoniae*, *Staphylococcus aureus* (including MRSA), *Vibrio vulnificus* and vancomycin-resistant

enterococcus.[111, 112] Their main mechanism of action is the inhibition of protein synthesis in bacteria. They bind reversibly to the A site of the 30S ribosomal unit, interfering with the binding of the aminoacyl-tRNA to the acceptor site of the mRNA-ribosome complex which prevents the addition of new amino acids to the growing peptides and impairs the cells' ability to grow or replicate. Still, bacterial resistance has developed via reduction of intracellular concentration by active efflux, disruption of the interaction with the 30s subunit by ribosomal protective proteins (TetM and TetO), deactivation via hydroxylation of position C-11a (TetX and Tet 37), and mutation of the binding site.[112] Recent literature has further discussion on resistance, synthesis, photoactivation, new applications, modifications, and the new generation of tetracyclines.[113-120]

Polymyxins (Polymyxin B and Colistin): Polymyxins are lipopeptide antibiotics isolated from *Paenibacillus polymyxa*.[121] They contain a peptide lactam macrocycle core with an attached peptide terminally substituted with a lipid acyl group; their diamino-butane carboxylate moieties contribute positive change under biological conditions, rendering the polymyxin antibiotics pentacationic. Two polymyxins, polymyxin B and colistin, are in clinical use. Polymyxin B (as its sulfate) is used to treat infections of the urinary tract, meninges (when administered intrathecally), and bloodstream and as a topical or subconjunctival agent for eye infections caused by susceptible strains of *Pseudomonas aeruginosa*. It may be used for serious meningeal or urinary tract infections or bacteremia by susceptible strains of *Haemophilus influenzae, Escherichia coli, Aerobacter aerogenes*, or *Klebsiella pneumoniae* if less toxic antibiotics are not effective.[122] Colistin (as its penta-N-methanesulfonate prodrug) is used to treat acute or chronic infections due to sensitive strains of *Pseudomonas aeruginosa, Enterobacter aerogenes, Escherichia coli*, or *Klebsiella pneumoniae* (but not *Proteus* or *Neisseria* species) .[123, 124] The polymyxins have limited activity against *Acinetobacter, Pseudomonas aeruginosa, Klebsiella*, and *Escherichia coli* species because of resistance. *Acinetobacter* species can exhibit heteroresistance, in which a drug-resistant population coexists with a drug-susceptible population, making drug susceptibility testing difficult or impossible. The mechanism of polymyxin anti-bactericidal activity is not completely defined.[125] The binding of polymyxins to negatively charged lipopolysaccharide phosphates in bacterial membranes disrupts their outer membranes, causing membrane-membrane contact and lipid exchange between membranes with consequent loss of membrane integrity (because Gram-positive pathogens possess a cell wall that cannot be disrupted by polymyxins). Polymyxin also causes the buildup of reactive oxygen species in membranes, likely by inhibiting the inner membrane type II NADH-quinone oxidoreductase, which oxidizes and cleaves membrane lipids and further compromises bacterial membrane integrity.[121] Finally, polymyxins bind to and inactivate endotoxins.[126] Bacteria circumvent these mechanisms in a variety of ways. As for other antibacterial agents, efflux pumps can export polymyxins from bacteria. Bacteria modify their membranes to reduce their negative charge (and to hinder the binding affinity of cationic polymyxins) by incorporating amino group-containing components such as phosphoethanolamine and 4-amino-L-arabinose into lipopolysaccharides. The suppression of lipid A incorporation and replacement by amino-substituted components is controlled by the two-component system (TCS).[121] Bacteria also upregulate the production of proteins needed to maintain lipid asymmetry in the outer membrane. *Acinetobacter baumanii* can respond to polymyxins by removing lipid A from its membranes, preventing polymyxin binding; however, purging lipid A renders its membranes more permeable, making it susceptible to other antibiotics.

Polymyxins have significant toxicity on parenteral administration. Nephrotoxicity is observed often (30-60%) because tubular reabsorption concentrates colistin and polymyxin B in the kidneys and

generates toxic concentrations of polymyxins. The toxicity can be partially mitigated by co-administration of antioxidants. Neurotoxicity (with paresthesia, nausea and vomiting, neuropathy, or other sequelae) is observed in nearly 7% of patients. Extended exposure or conditions such as myasthenia gravis or renal dysfunction predispose to neurotoxicity. Skin hyperpigmentation and lung toxicity (for inhaled colistin or polymyxin B) are also observed.

Combinations of polymyxins with one or two other antibiotics (doripenem or meropenem, rifampicin, tigecycline, fosfomycin, vancomycin, or teicoplanin) have been used to circumvent resistance mechanisms. Analogs of polymyxins have entered preclinical work or clinical trials as antibiotics. For example, QPex Biopharma developed a polymyxin, QPX9003, in which the alkanoyl chain is replaced by a 2,4-dichlorobenzoyl moiety[127] with improved antibacterial activity and reduced nephrotoxicity; the compound showed appropriate toxicity, pharmacokinetic, and pharmacodynamic data from Phase 1 studies.[128] Spero Therapeutics developed N-aryl analogs of polymyxin B, developing the compound SPR206 which entered phase 1 clinical trials.[129] MicuRx Pharmaceuticals developed a lactone-containing analog of polymyxin, MRX8, which showed antibacterial activity against Gram-negative bacteria, including carbapenem-resistant *Acinetobacter baumanii*[130]; the compound is in Phase 1 clinical trials in the US.[131] Northern Antibiotics in Finland developed the polymyxins NAB739 and NAB815 and found them to be more effective against pyelonephritis in mice than polymyxin B[132]; a related polymyxin analog, NAB741, entered Phase 1 clinical trials in 2017.[133]

Chloramphenicol and Analogs (Amphenicols): Chloramphenicol is an antibiotic isolated from *Streptomyces venezuelae* in 1948[134] and approved by the US FDA in 1949.[135] It is a broad-spectrum antibiotic, inhibiting the growth of Gram-negative aerobic (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitides* and *gonorrhea*, *Brucella* species, and *Bordetella pertussis*) and Gram-positive and -negative anaerobic bacteria (cocci, *Clostridium*, and *Bacillus fragilis*); most *Escherichia coli* and *Klebsiella pneumoniae* are also susceptible to chloramphenicol. It is thus used for treating typhoid fever, bacterial meningitis, anaerobic bacterial infections, and rickettsial and mycoplasmic infections in susceptible strains or when other antibiotics are ineffective.[136, 137] Chloramphenicol binds to the 50S subunit of the bacterial ribosome at the peptidyltransferase center (PTC), inhibiting protein synthesis. Chloramphenicol, however, leads to dose-related reversible anemia, leucopenia, and thrombosis and also to an irreversible aplastic anemia which (while uncommon) is often fatal; analogs lacking the nitro group show dose-dependent reversible blood cell suppression but do not cause aplastic anemia.[138] The toxicity of chloramphenicol and its analogs is attributed to its damage to mitochondria via suppression of mitochondrial protein synthesis. Chloramphenicol is also associated with “grey baby syndrome”, cyanosis, and low blood pressure in neonates caused by the lack of liver-mediated metabolism of chloramphenicol. As a result, chloramphenicol is no longer approved for human use in the US. Chloramphenicol succinate was developed as a prodrug of chloramphenicol and approved by the US FDA but is no longer available; it has similar toxicity to chloramphenicol.[139] Thiamphenicol and florfenicol replace the nitro group of chloramphenicol with a methylsulfonylgroup, with a fluoro moiety replacing the hydroxyl group of chloramphenicol; while neither cause irreversible aplastic anemia, they still cause reversible bone marrow suppression, deprecating their use.[140] Further analogs of chloramphenicol have been studied to attempt to provide novel and useful antibiotics with reduced side effects. For example, the replacement of the chloramphenicol primary alcohol with an L-lysine amide yields a compound that bound strongly to the ribosome and inhibited puromycin effects on the ribosome, an inhibition characteristic of binding to the ribosome A-site.[141]

Macrolides: Macrolides are macrocycles, most commonly derived from polyketide metabolism, substituted with sugars. They have broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, including *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Legionella pneumoniae*, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pyogenes*, *Helicobacter pylori, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Mycobacterium avium/intracellulare, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae.* They are, however, generally inactive against *Escherichia coli* and *Klebsiella pneumoniae*.

At least six macrolides have been approved by the US FDA for treating bacterial infections. Erythromycin (discovered in 1952) is still used to treat a variety of infections, including skin infections, syphilis, and acne. Dirithromycin was approved in 1995[142] for bacterial infections related to chronic bronchitis and for uncomplicated skin or skin-structure infections by non-resistant *Staphylococcus aureus*, but was withdrawn in 2004.[143] Clarithromycin was approved in 2001: for acute bacterial exacerbation of chronic bronchitis in adults, acute maxillary sinusitis, community-acquired pneumonia, pharyngitis/tonsillitis, uncomplicated skin and skins structure infections, acute otitis media in pediatric patients, treatment and prophylaxis of disseminated mycobacterial infections, and *Helicobacter pylori* infection and duodenal ulcer disease in adults with methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*.[144] Azithromycin was approved in 2002 for treating acute bacterial exacerbations of chronic bronchitis, acute bacterial sinusitis in adults, uncomplicated skin and skin structure infections, urethritis and cervicitis in adults, genital ulcer disease in men, acute otitis media in pediatric patients, community-acquired pneumonia in adults and pediatric patients, pharyngitis/tonsillitis in adults and pediatric patients from Gram-positive and Gram-negative bacteria.[145] Fidaxomicin was approved in 2011 for treating *Clostridium difficile*-associated diarrhea.[146] Telithromycin is a ketolide (a macrolide in which a ketone replaces an aminocarbohydrate-substituted alcohol moiety).[147] It was approved by the US FDA in 2004 but withdrawn from sale in 2016 due to severe side effects (liver damage, respiratory failure in myasthenia gravis patients) and resulting restrictions on the approved indications for use.[148, 149]

Macrolides bind (as with many other antibiotics) to the 50S subunit of the bacterial ribosome, but not to the PTC, instead blocking the exit tunnel, preventing peptides from leaving the ribosome. Macrolides, however, tend to have larger molecular weights than other antibiotic classes (730-860 Da as opposed to 300-630 Da for others) and to be less polar[150], which makes them less generally bioavailable to cells and thus less effective.[151] Mutations in the 23S rRNA sequence, acquisition of a methyltransferase to modify the rRNA, generation of a peptide to displace macrolides from the ribosome, phosphorylation or lactone hydrolysis, and efflux pumps can confer resistance to macrolides. Macrolides are generated either directly from *Streptomyces* species or by semisynthesis from erythromycin or other macrolide isolates.[152] The Myers group (among others) developed modular syntheses of macrolides, allowing variation in substituents, ring size, and polarity that are not possible for semisynthetic macrolides; the complexity of macrolides, their polarity, metabolic stability (to lactone cleavage), and effective charge can be readily varied, yielding amine-substituted macrocycles with improved activity against drug-resistant bacteria and to broaden antibacterial scope.[150] Macrolide Pharmaceuticals was established in 2015 to use the Myers group's methodology to develop novel antibiotics.[153]

Rifamycins : First discovered in 1957 by Sensi at the Dow-Lepetit Research Laboratory in Milan, Italy, from the fermentation of *Streptomyces mediterranei*[154], rifamycins are polyketides that are

part of the ansamycin class of natural products, contain a naphthalene aromatic moiety, and demonstrate antibiotic properties against gram-positive and some gram-negative bacteria.[155] Their antibacterial properties come from interfering with RNA synthesis by targeting RNA polymerase; they inhibit transcription and block the elongations path by binding to the B subunit of RNA polymerases.[43, 156] There are currently 4 FDA approved antibiotics in this family: rifampicin, rifabutin, rifapentine, and rifaximin. Rifampicin, rifabutin, and rifapentine are used to treat, among other things, tuberculosis and *Mycobacterium avium*[157], while rifaximin is used to treat gastrointestinal and liver diseases.[158] The high frequency of endogenous resistance development, via the mutation of rpoB encoding the B subunit of the RNA polymerase[155, 156, 159], is of great concern. Further literature on the resistance mechanisms[156, 159] ,on new analogs, and on combination strategies to improve efficiency can be found.[155, 160-162]

Pyrimidines: A variety of pyrimidines with antibiotic activity have been prepared because of the relative facility of assembling the pyrimidine ring and pyrimidine-containing antibiotics such as sulfadiazine (an N-2-pyrimidinyl p-aminobenzenesulfonamide) are in clinical use.[163] However, two antibiotics with pyrimidine cores are used clinically. Pyrimethamine is used as an antimalarial and antitoxoplasmic agent; at low doses, it is used to suppress non-*Falciparum* malaria while at high doses, it is used to treat toxoplasmosis. Trimethoprim is a pyrimidine-containing antibacterial used most often in a fixed combination with the sulfonamide sulfamethoxazole.[164] Trimethoprim inhibits dihydrofolate reductase, which helps bacteria to synthesize folates, necessary cofactors for DNA synthesis.[165] Sulfamethoxazole is a mimic of p-aminobenzoic acid, a building block for folate synthesis; thus, Daraprim (pyrimethamine) attacks two steps in bacterial folate synthesis simultaneously, reducing the rate of resistance. As a result, it inhibits most strains of *Streptococcus pneumoniae, Escherichia coli* (including susceptible enterotoxigenic strains implicated in traveler's diarrhea), *Klebsiella* and *Enterobacter* species, *Haemophilus influenzae*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Shigella flexneri*, *Shigella sonnei*, and *Pneumocystis jiroveci.* Daraprim (pyrimethamine) is used to treat bacterial ear infections, UTIs, bacterial complications of bronchitis, *Pneumocystis jiroveci* pneumonia, and traveler's diarrhea.

There are some liabilities to Daraprim (pyrimethamine), however. Trimethoprim is a substrate for bacterial P/gp drug transporters.[166] *Klebsiella pneumoniae* and *Serratia marscens* show resistance to Daraprim (pyrimethamine) because they alter their cell membranes to inhibit passive transport, preventing drugs from exerting their effects. In addition, sulfa drugs may have severe hypersensitivity reactions.[164]

To avoid sulfonamide-induced hypersensitivity reactions, researchers have sought trimethoprim analogs that can be used as monotherapies. One such compound is iclaprim, which has been tested as a monotherapy against acute bacterial skin and skin structure infections and community-acquired pneumonia. Two different companies, Arpida AG and Motif BioSciences, have attempted to gain approval for iclaprim. Arpida's application to the US FDA was rejected because it was not sufficiently non-inferior to the standard of care.[167, 168] Motif performed multiple Phase 3 studies on iclaprim[169-172]; however, its approval would have required additional studies to address potential liver toxicity.[173, 174]

Quinolones: Quinolones are a family of synthetic broad-spectrum antibiotics whose basic structure is an N-1 alkylated 3-carboxypyrid-4-one ring fused to another aromatic ring, i.e. a bicyclic core structure related to a 4-quinolone.[175] Usually included with the quinolone family is the 1,8-naphthyridone core (X=N). The first publication of quinolone structures having antibacterial activity was a patent by Imperial Chemical Industries (ICI) published in 1960[176], this

was followed by Sterling disclosing the antibacterial properties of 1,8-naphthyridones[177] and nalidixic acid.[178, 179] Modifications to the base structure can enhance activity, control potency, and influence pharmacokinetics, though positions 3 and 4 are crucial for enzyme binding and should not be altered.[180] Most common modifications are substitutions on carbon 5,6,7, and 8. The addition of fluoro to the C-6 position is the key characteristic of a large subset of quinolones called fluoroquinolones. This includes ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin, delafloxacin, trovafloxacin, and many others.

This family of antibiotics, depending on the member, can target gram-positive and gram-negative bacteria by inhibiting bacterial topoisomerase II, DNA gyrase, and DNA topoisomerase IV enzymes; this mechanism of action interferes with DNA synthesis and preventing the replication process.[44, 175, 180] Still, growing bacterial resistance is raising concerns in the use of this class of antibiotics. Three main mechanisms of resistance have been documented: target-mediated resistance, plasmid-mediated resistance, and chromosome-mediated resistance. More information on these mechanisms can be found in recent reviews by Maxwell *et al*.[180], Tang and Zhao[181], and Ruiz.[182]
Apart from increasing antimicrobial resistance, debilitating side effects of quinolones and fluoroquinolones are a concern that is restricting their use.[183-186] Monga *et al*., Mittal *et al.*, and Nikolić and Radić *et al.*, on the topic of quinolones, thoroughly discuss synthetic advances,[187] emerging antibiotics,[188] and the application of metal complexes in the context of quinolones.[189]

Lincosamides: Lincosamides (or lincosamines) are (alkylpyrrolidinecarbonylamino)trideoxyoctopyranoside antibiotics. Of the lincosamides, lincomycin (R = H) and clindamycin (R = Cl) (**Supplementary Table 1**) are the only two lincosamides in clinical use.[190] Lincosamides are bacteriostatic against Gram-positive cocci, *Staphylococcus*, group A and B *Streptococcus*, *Clostridium* species*, Corynebacterium diphtheriae*, *Bacillus anthracis*, and Gram-positive anaerobes but are not effective against *Neisseria* species, enterococci, *Haemophilus influenzae*, or *Moraxella catarrhalis*. Clindamycin also inhibits the growth of *Plasmodium berghei* and *Toxoplasma gondii*. Lincomycin is thus used for Gram-positive skin, skin structure, and bone infections, while clindamycin is used for anaerobic bacterial infections, particularly intestinal and vaginal infections. The lincosamides are administered intravenously but are incompatible with ampicillin, magnesium sulfate, calcium gluconate, phenytoin, B vitamins, and barbiturates. Lincosamides bind to the peptidyltransferase center of the 50S subunit of the bacterial ribosome to prevent peptide transfer and thus inhibit bacterial protein synthesis (a mechanism common to multiple antibiotic classes because of its conservation).[138] However, bacteria have multiple pathways to resist lincosamide-mediated toxicity. The cell walls of Gram-negative bacteria reduce passive diffusion of antibiotics, which can be further reduced if efflux pumps are also present (a mechanism also available to Gram-positive bacteria). Methylation of the 23S rRNA by the methyltransferase produced by the CFR gene reduces the ability of lincosamides to bind to the ribosome, as it does for streptogramins and macrolides. In *Staphylococcus aureus*, an O-nucleotidyltransferase mediates the adenosine monophosphorylation of the 4'-hydroxyl group of lincosamides to ablate binding. Finally, alterations of membrane permeability in Gram-positive bacteria can reduce the cellular concentrations of lincosamides and thus their effectiveness.

Streptogramins: Streptogramin antibiotics are produced by *Streptococcus* species.[191] A-class streptogramins such as virginiamycin M2 and the semisynthetic dalfopristin contain 23-membered

macrocycles with fragments derived from both polyketides and amino acids. B-class streptogramins contain 19-membered depsipeptide (peptides with ester linkages) lactones; one example is quinupristin. Dalfopristin and quinupristin together comprise the antibiotic Synercid which was approved by the US FDA in 1999 for treating multidrug-resistant (MDR) skin infections, including those caused by vancomycin-resistant enterococci (VRE). Class A streptogramins bind to the 50S subunit of the bacterial ribosome at its peptidyltransferase center (PTC), while the class B streptogramins bind to the 50S subunit of 70S ribosome at the exit tunnel;[192] the binding of class B streptogramins to the bacterial ribosome is increased in the presence of the class streptogramins so that the combination of class A and B streptogramins is bactericidal while class A or B streptogramins alone are bacteriostatic. Inhibition of the bacterial ribosome prevents protein synthesis and thus kills bacteria. Streptogramins are useful against aerobic Gram-negative and Gram-positive bacteria such as vancomycin- or multidrug-resistant *Enterococcus faecium* (not *faecalis*), *Staphylococcus aureus*, and *Streptococcus pyogenes*.[193]

Resistance to the streptogramins class of antibiotics is difficult, as the PTC is highly conserved and tolerates minimal alterations.[194] Export of streptogramin antibiotics from bacterial cells occurs through transporters encoded by genes such as *lsa(E).*[195] In addition, O-methylation of A2503 in the bacterial ribosome blocks the binding of antibiotics to the PTC and thus reduces or negates inhibition. In addition, acetylation of A2503 with virginiamycin acetyltransferases also reduces streptogramin antibiotic activity. Other mechanisms include the presence of efflux pumps.[196] While the use of streptogramins is limited, the development of synthetic methods and the modularity of their structures makes them accessible to chemical synthesis which allows significant modification of the cores not available through semisynthesis. The Li and Seiple groups have developed analogs of streptogramins and the related lankacidins as potential antibiotic agents with expanded scope[191], with the synthesis of streptogramins on up to 10g scale. For example, the replacement of the methyl group β to the ester oxygen in virginiamycin M2 with an allyl group and of the right-hand ketone with a fluoromethylene moiety yields a highly active analog with improved activity against drug-resistant strains of *Staphylococcus aureus.*[191]

Oxazolidinones: It is the class of antibiotics that inhibit protein synthesis. Two aryl-substituted oxazolidinones have been approved as antibacterial agents. Linezolid (R = MeCONH; R^1 = 4-morpholinyl) was approved by the US FDA in 2000 for treating vancomycin-resistant *Enterococcus faecium*, drug-resistant and -susceptible *Staphylococcus aureus* and *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*.[197] Tedizolid [R = HO; R^1 = 2-(5-tetrazolyl)-5-pyridinyl] phosphate ester (**Supplementary Table 1**) was approved by the US FDA in 2014 for bacterial skin and skin-structure infections by *Enterococcus faecalis*, drug-resistant and -susceptible *Staphylococcus aureus* and *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and the *Streptococcus anginosus* group.[198] Oxazolidinones bind to the bacterial 50S ribosome subunit at the PTC, inhibiting protein synthesis by hindering the formation of initiation complex.[199] Resistance to oxazolidinones is slow to develop but has been observed – O-methylation of A2503 in the 50S subunit of the bacterial ribosome (mediated by the methyltransferase Cfr) abrogates binding, as does the G2576T mutation in domain V of the 23S rRNA. Mutations in the genes rplC and rplD for the ribosomal proteins L3 and L4 also yield resistant bacterial phenotypes. The simplicity of oxazolidinones and the availability of aryl-nitrogen coupling reactions such as Buchwald-Hartwig coupling enables drug developers to rapidly generate analogs to circumvent bacterial resistance. Linezolid, however, has limited aqueous solubility, making its administration more difficult. In addition, reversible myelosuppression and irreversible optic and peripheral neuropathies are observed on long-term

administration (six months or more) of linezolid, and it acts as an inhibitor of monoamine oxidases, making it incompatible with a variety of foods and drugs.

Pleuromutilins: Pleuromutilin (R = HO) (**Supplementary Table 1**) is an antibiotic natural product isolated from *Clitopilus scyphoides* and *Clitopilus passeckerianus* (originally *Pleurotus mutilis*).[132, 194] Four analogs of pleuromutilin are used as antimicrobial agents. Tiamulin and valnemulin are both used as veterinary drugs. Retapamulin (Altabax) was approved by the US FDA in 2007 for treating impetigo caused by methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*.[200] Lefamulin (Xenleta) was approved by the US FDA in 2019 as a treatment for community-acquired bacteria pneumonia.[201] Pleuromutilins are effective against a variety of Gram-positive pathogens, including *Streptococcus* and *Staphylococcus* species and *Enterococcus faecalis* and *faecium*; they also are effective against Gram-negative bacteria including *Haemophilus* and *Neisseria* species, *Moraxella catarrhalis*, *Legionella pneumoniae, Mycobacterium tuberculosis*. Mycoplasmas, ureaplasmas, and Chlamydia species are inhibited by pleuromutilins. Lefamulin can potentially cause QT prolongation and thus severe or fatal arrhythmia.[132, 194, 201]

Pleuromutilins bind to the 50S subunit of the bacterial ribosome[194] at the PTC, preventing protein synthesis; bacteria can evade resistance to them by methylating the rRNA at A2503 or mutating the L3 ribosomal protein to block the binding of pleuromutilins, resistance can also be due to presence of efflux pumps.[202] In addition, *Enterobacteriaceae* possesses the AcrAB/TolC efflux pump to export pleuromutilins from the cell and avoid their effects. Finally, the lipophilicity of pleuromutilins can reduce their bioavailabilities; prodrugs, however, can improve the permeability of pleuromutilins into cells and thus their antibacterial activities. Analogs of pleuromutilin have been prepared to expand the antibacterial scope of pleuromutilins, mostly by modification of the acyl moiety on the C14 alcohol.[203-212] Some recent work has disclosed methods for modification of the pleuromutilin skeleton in addition to the pendant ester.[213]

3.2. Alternatives to conventional antibiotics

The continued and growing threat from antibiotic resistance coupled with a lack of newer antibiotics has necessitated the use of alternatives to combat these formidable bacterial infections. **Figure 2** shows a Trend Landscape Map representing number of documents, including journal and patent publications, from 2012 onwards for data retrieved from the CAS Content Collection, associated with emerging antibacterial strategies. The number of documents directly correlate with the interest of researchers in any particular antibacterial strategy or the form of antibacterial being used in the last decade**.** Based on the numbers in the map**,** a selected few of which we are discussed briefly in this section.

Stringent response inhibitors: Persistent infections affect many; while they are often asymptomatic, the persisting bacteria may be reactivated at any time to cause renewed infection. The quiescent pathogens are termed "persister bacteria".[58] Many different mechanisms by which persistent infection is thought to be achieved have been proposed and include stringent response,[58] SOS response,[214] toxin-antitoxin response,[215] and oxidative stress response.[216] Stringent response is a mechanism by which bacteria counter extreme nutritional starvation (amino acids, fatty acids, iron) and other stresses that allow for survival.[217, 218] Classified as a stress response, the expression and accumulation of guanosine 5'-diphosphate 3'-diphosphate (ppGpp) and guanosine 5'-triphosphate 3'-diphosphate (pppGpp) are the hallmarks of the

stringent response.[219] Both ppGpp and pppGpp, often collectively referred to as (p)ppGpp, are produced by (p)ppGpp synthetase which includes the RelA/SpoT homolog and small alarmone synthetase proteins.[220] The exact mechanism by which these molecules achieve stringent response is thought to be varied, one of which includes binding directly to RNA polymerase leading to decreased transcription.[219, 221] While initially discovered in *E. coli*,[222] subsequently stringent response has also been identified in many other bacterial species including *Mycobacterium*[223] and *Bacillus*.[224] It is now increasingly believed that activation of stringent response might be an important determinant of antibiotic efficacy and might contribute to antibiotic resistance.[225, 226] One avenue that has been explored in recent years, is the use of structurally similar compounds such as 2'-deoxyguanosine-3',5'-di(methylene bisphosphonate), and analogs leading to competitive inhibition of (p)ppGpp synthetase and decreased production of (p)ppGpp[227] putting a halt to further downstream signaling. Other examples of structurally similar analogs of (p)ppGPpp explored as stringent inhibitors include relacin[228] and its derivatives.[229] Peptide-based derivatives that bind to and trigger degradation of (p)ppGpp have also been developed[230] and were shown to be effective against multidrug-resistant ESKAPEE pathogens.[231] In recent years, similar efforts have been made for *Mycobacterium tuberculosis*[223, 232] by designing small molecule (p)ppGpp synthetase inhibitors based on ppGpp and relacin[233] and identification of novel/new leads by screening a 2 million compound library.[234] Other bacterial strains for whom this avenue is being explored include *Neisseria*[235] and *Bacillus*.[236]

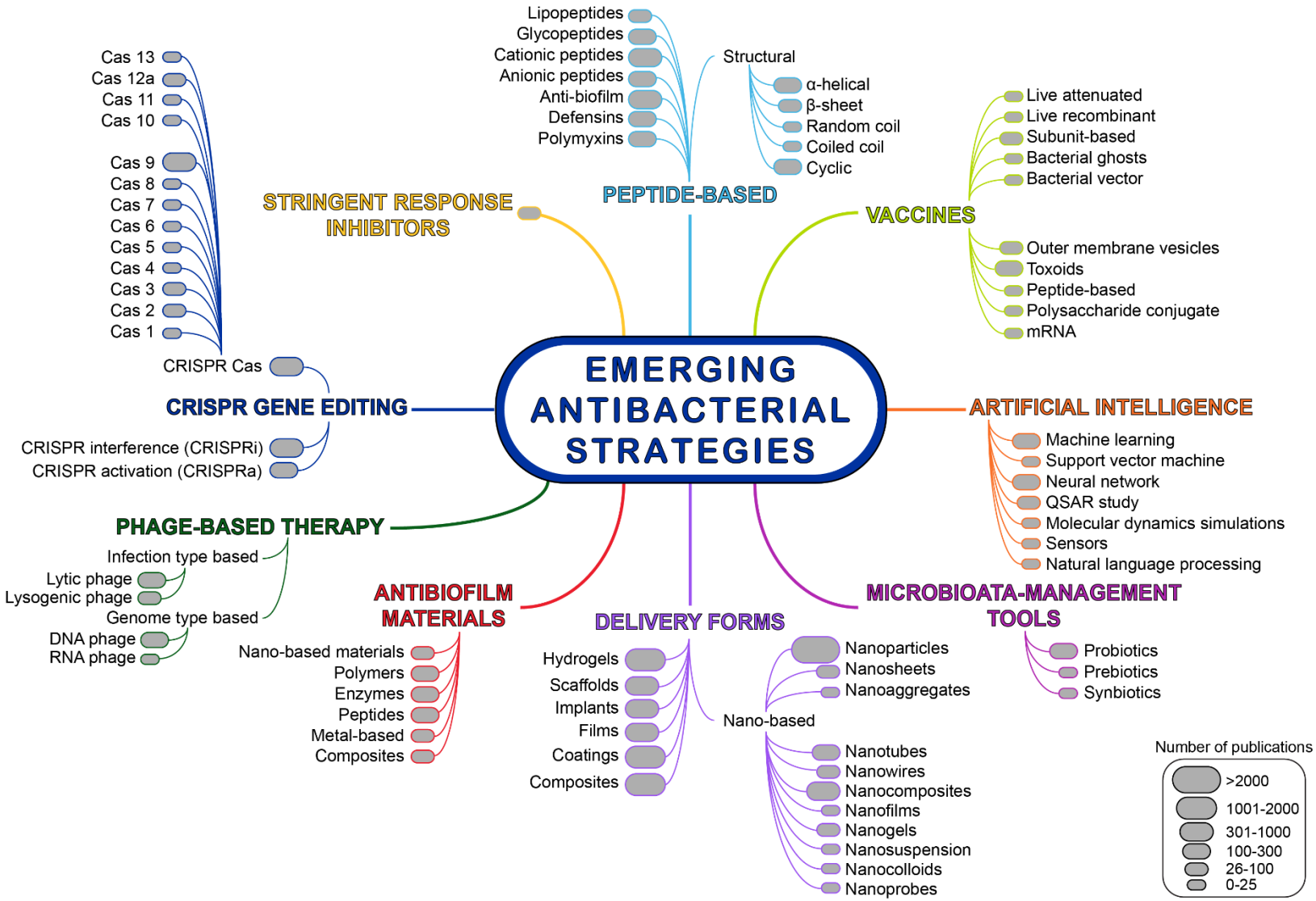


Figure 2: Trend Landscape Map representing number of documents (journal and patent publications) from 2012 onwards for data retrieved from the CAS Content Collection, associated with emerging antibacterial strategies (including emerging forms and newer methodologies used in developing antibacterials).

Bacterial vaccines: In lieu of the development of novel antibiotics, prevention of bacterial infections via the use of vaccines might be a key alternative strategy available. Additionally, the use of vaccines and prevention or minimization of bacterial infections leads to decreased antibiotic consumption and is therefore likely to help with antibiotic resistance.[237] Finally, by reducing or eliminating drug-resistant strains, vaccines could aid in decreasing antibiotic resistance.[237] Vaccines designed could either be prophylactic or therapeutic, the latter being useful for preventing the infection from relapsing again and appearing to be more common in the context of tuberculosis.[238] Vaccine can be composed of (i) live-attenuated bacterial cells, (ii) inactivated bacterial cells and, (iii) subunit vaccine which contains just enough material from bacterial cells to elicit an immune response and might include specific proteins or polysaccharides.[239] Finally, inactivated toxins isolated from bacterial cells can also be used to design "toxoid" vaccines[239] examples include the DPT vaccine and tetanus vaccine among others.[240]

A report released by the WHO in 2021 provided details of >60 and >90 vaccines in clinical and preclinical development.[241, 242] The report was focused on identifying vaccines that have been designed for the bacterial strains that are listed in the 2017 WHO Bacterial Priority Pathogens List.[242, 243] The report indicates a lack of vaccines in development for *E. faecium* and *Enterobacter* spp. both of which are classified as high and critical priority in terms of requirement of new/novel antibiotics by the WHO.

Despite obvious benefits, the development of vaccines against multidrug-resistant strains has been slow. In recent years, bacterial vaccine-related research has branched out into the incorporation of nanoparticles for improved delivery[244] as well as increased/improved antigenicity.[245] Another avenue of interest is the development of vaccines against multiple bacterial strains.[246] The critical role of vaccinations in helping to deal with the COVID-19 pandemic is bound to help generate interest in and accelerate the development of bacterial vaccines, especially mRNA-based vaccines. Indeed, in early 2023, Kon *et al.* reported an mRNA-based lipid nanoparticle vaccine for the deadly bacteria *Yersinia pestis* responsible for plague.[247]

Antimicrobial peptides: Antimicrobial peptides (AMPs) are gaining popularity in the treatment of drug-resistant bacteria as alternatives for more traditional small molecule antibiotics. They are mostly bioactive proteins naturally produced by all types of living organisms as host defense system[248], though some artificial AMPs have also been synthesized.[249] AMPs are typically short (<100 amino acids) amphiphilic cationic peptides with a broad spectrum of antimicrobial activity, an overall net charge of +2 to +11, with around 50% of hydrophobic residues, many positive residues (arginine, lysine, histidine), and a molecular weight of <10kD.[248, 250-252] They can be divided into many ways: ribosomally synthesized peptides and non-ribosomally synthesized peptides,[253, 254] linear and cyclic peptides,[255] or based on their secondary structure.[256, 257] In general, antimicrobial peptides target the cell membranes of pathogens; more details on their mechanisms of actions can be found in reviews by Moretta *et al.*,[248] Zhu *et al.*,[258] and Zhang *et al.*[250] There are over 3000 natural AMPs as of November 2022 according to the Antimicrobial Peptide Database,[259] some examples of them are glycopeptides, lipopeptides, lipoglycopeptides, lantibiotics,[260-267] defensins,[268] and thiopeptides.[269-271] We will be briefly discussing the first 3 categories, but for more general information on emerging antibiotic peptides, structure-activity-relationships (SAR) studies, strategies to improve AMP activity and biocompatibility, AMP applications, resistance, AMPs in clinical trials, etc. please refer to previous reviews cited in this paragraph. **Figure 3** suggests that antimicrobial peptides show a steady growth till 2020 in both journal and patent publications. Interestingly, the growth in patent publications is faster as compared to journal publications, indicating commercial interest in this area. Notable categories of antimicrobial peptides are:

Glycopeptides: Glycopeptides are glycosylated non-ribosomal peptides that are composed of tricyclic or tetracyclic polypeptide scaffold, typically a heptapeptide scaffold made by proteogenic and nonproteogenic amino acids alongside sugar residues, chlorine atoms, methyl groups, or lipid chains.[272, 273] They display antibacterial activity against Gram-positive bacteria typically by inhibiting cell wall biosynthesis due to binding to the C-terminal D-Ala-D-Ala moiety of the peptidoglycan precursor Lipid II, preventing transglycosylation and transpeptidation for cell wall synthesis.[273-277] They are effective against *Staphylococcus aureus* (including MRSA), *Enterococcus* spp., *Clostridium difficile,* and healthcare-associated infections that are resistant to other antibiotics like *Enterococcus faecalis* and *Enterococcus faecium*. Some members of approved drugs of this group are Vancomycin (1958),[278] teicoplanin (1988),[279] telavancin (2009),[280] dalbavancin (2014),[281] oritavancin (2014).[282] Many novel derivatives and new glycopeptides are also being developed, studied, and optimized.[272-274, 283] Known resistance mechanisms include target site modification, cell wall thickening, enzymatic modification of vancomycin and efflux pumps.[284]

Lipopeptides and lipoglycopeptides: As the name suggests, lipopeptides consist of a lipid moiety attached to peptide molecules. Daptomycin, which gained US FDA approval in 2003,[285] remains the only lipopeptide that is currently in use against Gram-positive bacteria.[286] Structurally, daptomycin is a cyclic lipopeptide consisting of 13 amino acids out of which 10 amino acids form a macrolide ring.[287] Over the years, structure-activity relationship (SAR) efforts have been made to identify structural features required for daptomycin's antibacterial effect and to try and improve them.[287, 288] Daptomycin functions by disrupting the bacterial cell membrane directly by binding to phosphatidylglycerol[289] and in an indirect manner by tampering with the synthesis of peptidoglycans[290, 291] with the antibacterial effect observed appearing to be dependent on the presence of and binding with calcium.[292, 293] Other examples of calcium-dependent antibiotics[294] include lipopeptides isolated and purified from natural sources such as octapeptins, [295] friulimicin B[296] and amphomycin among others. Octapeptins-which are cyclic lipopeptides, function by inserting into bacterial cell membrane, they have shown an increase in interest, especially in the last 5 years or so[297-300] with efforts being made to systematically study them in order to design newer and more efficacious analogs.[301-303]

Lipoglycocpeptides consist of carbohydrate and lipid moieties attached to peptide molecules. Examples of US FDA-approved lipoglycopeptides include telavancin,[304] dalbavancin,[305, 306] and oritavancin.[307, 308] The lipoglycopeptide class of antibiotics tends to act via bacterial cell wall disruption by interfering in the synthesis of peptidoglycans[309] similar to glycopeptides such as vancomycin. Most likely as a result of the large size, lipoglycopeptides tend to be absorbed poorly upon oral administration and have to be administered intravenously.[310] They tend to be long-acting with half-lives in the range of several hours.[305, 311] A recent study highlighted lower healthcare costs associated with the treatment of recurrent and serious bacterial infections in individuals with substance use disorder with long acting lipoglycopeptide[312] and a 2020 review described similar outcomes/findings.[313]

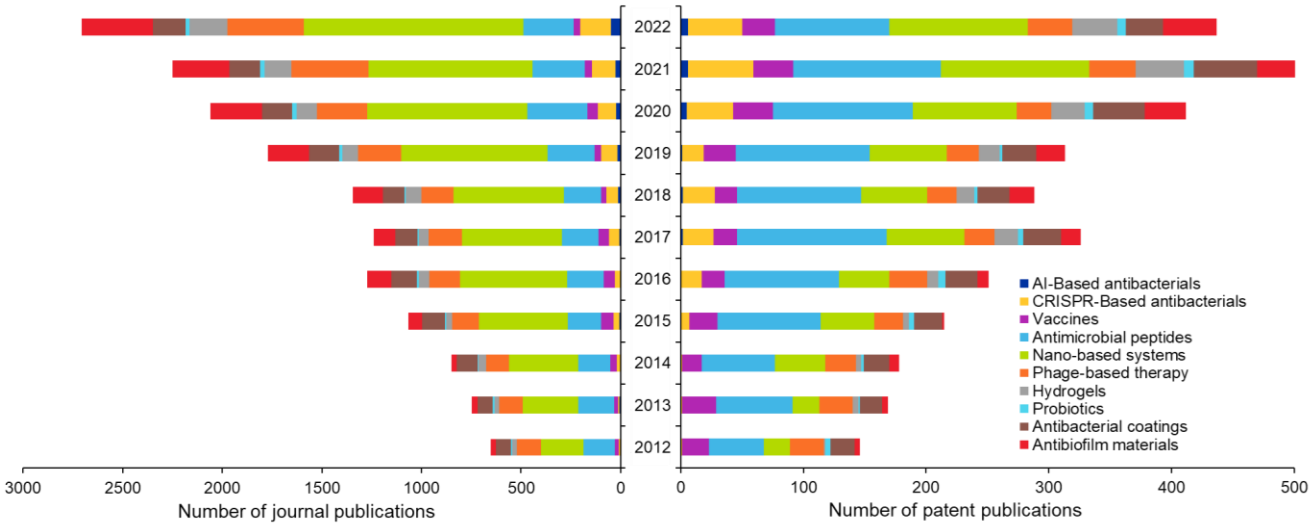


Figure 3: Number of journal and patent publications per year mentioning the use of emerging strategies in antibacterial research over the last decade (2012-2022).

Bacteriophages: Bacteriophages are viruses capable of targeting and destroying bacterial cells selectively.[314] While the discovery of bacteriophages can be traced back to the late 1800s, their subsequent development was overshadowed by the discovery and popularization of antibiotics.[314] Broadly speaking the lytic cycle of bacteriophages involves the following major steps: (i) attachment to bacterial cells via receptors, (ii) injection of viral DNA into bacterial cells, (iii) replication of viral proteins and components within bacterial cells, (iv) packing and release of replicated viruses after bacterial cell lysis.[314] The exact series and mechanism of events may differ depending on the bacteriophage and the host bacterial cell. In contrast in a lysogenic cycle, incorporation of viral DNA into host DNA occurs.[315] Bacteriophages tend to be specific in terms of the receptors they interact with and the species they can affect/target.[316, 317] Advantages associated with bacteriophage therapy include: effectiveness against MDR bacteria[316, 317], specificity in terms of species and/or strains, and leaving the patient's gut microbiome largely unaltered.[318, 319] Furthermore, bacteriophage therapy has been shown to have an excellent safety profile in human beings.[318, 320-322] All of these features mean that as the threat of MDR strains becomes more imminent, bacteriophage therapy has seen a promising resurgence in interest.[323-326] In a recent study, a group of researchers designed and administered personalized bacteriophage therapy to an individual suffering from lung infection caused by MDR *Pseudomonas aeruginosa* and appeared to be successful in stopping antibiotic therapy completely.[326] Other instances of successful personalized bacteriophage therapy against MDR strains have also been reported.[327] However, there are still challenges that need to be addressed in order to make bacteriophage therapy more viable – poor in vivo efficacy in terms of targeting bacterial species in the gut upon oral administration is an important one.[328, 329] There are also noted instances of resistance against bacteriophages though their prevalence is far lower than antibiotic resistance.[330, 331]

Microbiota Interventions/Probiotics: The use of antibiotics kills not only disease-causing bacterial species but other beneficial bacterial species prevalent in the human gut. Alteration of the complex and dynamic gut microbiota has been increasingly linked to several diseases[332, 333] including mental health disorders. Furthermore, evidence suggests that disruptions/alterations of the gut microbiome following antibiotic therapy can be long-lasting from anywhere between weeks to up to several months.[334] It has been shown that co-administration of probiotics along with

antibiotics could be beneficial to counter the negative impact of antibiotics on the gut microbiome.[335] Consequently, this practice is becoming more prevalent and popular; however, there have been concerns raised about the actual benefit of consuming probiotics in rebalancing the gut microbiome.[336]

3.3. The importance of anti-biofilm materials

Biofilms are a complex community of mono-species or multispecies microbes that are attached to a surface and to each other and are embedded in a self-produced extracellular matrix that consists of proteins, polysaccharides, and environmental DNA.[337-339] This allows bacteria to withstand hostile environments, and starvation desiccation, and is protected from fluctuations in humidity, temperature, pH, etc. Bacteria in biofilms can evade the host defense systems and can cause local tissue damage and acute infection.[338] These biofilms can develop in catheters, pacemakers, joint prostheses, dentures, contact lenses, prosthetic heart valves, and implants.[337] Biofilms also protect bacteria and increase bacterial resistance against conventional antibiotics. Dry surface biofilms, which might contribute to healthcare-acquired infections, can be difficult to remove and allow bacteria to tolerate or resist attacks by other pathogens, disinfectants, antiseptics, heavy metals, and other antimicrobial agents.[340] This means that the development of new anti-microbial materials that also have anti-biofilm properties is of utmost importance in the healthcare industry.

3.4. Emerging antibacterial forms

A variety of purposes require prolonged antimicrobial activity or repulsion of microorganisms for which conventional antibacterial administration is less likely to be effective. The use of materials to deliver antibiotics rather than conventional drug delivery methods requires more invasive methods but can provide localized, prolonged, and stimulus-dependent antibacterial activity. Various forms such as hydrogels, films, coatings, scaffolds, implants, and nano-based forms such as nanoparticles are being used to design antibacterial strategies. Medical devices such as catheters and intravenous lines can be sources of microbial infection which can potentially be prevented with antimicrobial materials; in addition, the formation of biofilms can impede their functions, making antimicrobial or antibiofilm materials necessary for their continued function. Similarly, implants for bone may be necessary to induce bone regeneration but can also act as sources of infection which impedes their effectiveness. Surfaces that are touched by many people can act as vectors of infection; antimicrobial coatings on such surfaces can reduce the transmission of microbes. Antimicrobial films can be useful in preventing food spoilage and reducing food waste and food-borne illness. Fabrics with antimicrobial coatings can reduce disease spread and the energy costs and need for cleaning. The forms of materials are important for their activities. Some commonly used examples are:

Hydrogels: They are moldable and injectable materials, and their low density and degradability make them useful for drug delivery and wound healing. Their solvent accessibility also makes them effective at stimuli-sensitive materials. As with many of the materials noted, hydrogels are not inherently antibacterial and require antibiotics or other antimicrobial components to exert antibacterial activity. The surface area of hydrogels can allow them to act in place while being exposed to cells or bodily fluids, which allows either diffusible antibiotics or gel-bound antibiotic agents such as antimicrobial peptides to be used.[341] The hydrogel material can also protect the antibiotic agents against degradation, allowing them to be more effective at the same dosage or to be equally effective at a lower dosage. Hydrogels are impermanent, and their low densities and solvent accessibility make them useful as stimulus-responsive materials. Antimicrobial hydrogels

may respond to acidity, either reversibly (through conformational shifts) or irreversibly (by chemical reactions such as hydrazone cleavage). They can also be degraded by enzymes such as hyaluronidase which are specific to pathogenic bacteria or by toxins secreted by bacteria, enabling selective antimicrobial activity.

Biologically derived polymers can also be used for antimicrobial hydrogels. Lignin, in particular, has been used because of its broad availability and tunable stiffness, making a variety of forms accessible.[342] For example, lignin-containing hydrogels containing silver nanoparticles have been used as antibacterial agents.[343] A copolymer of lignin with poly(ethylene glycol) and poly(*co*-vinyl methyl ether-maleic acid) containing curcumin has been shown to be active against *Staphylococcus aureus* and *Proteus mirabilis* biofilms.[344] Lignin-based nanoparticles combined with a poly(oxazoline) triazole have been used as anti-inflammatory agents.[345]

Nanoparticles: The small size of nanoparticles makes them easy to deliver, while their high surface area-to-volume ratio allows them to deliver drugs effectively. Surface modification of nanoparticles can be used to tailor them for specific targets and locations, and the surface chemistry and composition control the timing of activity, drug release, and of duration of action. In addition, alteration of the morphologies of nanoparticles also alters their aggregation, movement, and persistence. All of these properties increase the attractiveness of nanoparticles as antimicrobial agents.[346] Changes in composition can allow nanoparticle-bound drugs to evade or reduce drug resistance mechanisms; for example, poly(*co*-lactic acid-glycolic acid) (PLGA) nanoparticles containing metronidazole were as effective against juvenile periodontitis as tetracycline, though metronidazole was previously found to be ineffective against the contributing bacterium *Aggregibacter actinomycetecomitans.*[347, 348] LGA or polyamide (PAMAM) nanoparticles containing platensimycin were more effective against *S. aureus* in mice than free platensimycin and were even effective against MRSA in mice.[349] PLGA nanoparticles containing azithromycin showed improved activity against MRSA and *Enterococcus faecalis*, but not *Pseudomonas aeruginosa*; improvement corresponded to the presence of efflux pump-derived resistance as nanoparticle encapsulated antibiotics are reported to bypass the efflux activity in bacteria .[350] Metal or alloy nanoparticles can also be effective antibacterial agents. Silver nanoparticles have been used to prevent bacterial growth and treat infections, but their toxicity may limit their use.[351] Copper nanoparticles also show antimicrobial activity as well.[352]

Films or coatings: Films occlude microbial access to surfaces, preventing their adherence, preventing biofilm formation, and killing bacteria. Hospitals are high traffic areas with objects and surfaces being handled/touched by many people, making them foci of disease spread. Antibacterial copper nanoparticle-containing coatings have been suggested for application to surfaces in hospitals such as bed rails and chairs to reduce the viability of bacteria and viruses on those surfaces.[353] For example, poly(ethylene glycol diacrylate) films containing copper nanoparticles were prepared as antibacterial films.[354]

Catheters and intravenous lines are also common sources of infection; they carry bacteria from the environment into patients, bypassing the defenses of the skin and mucous membranes, and increasing the population of microbes in people of special concern in immuno-compromised individuals who have reduced energy or resources to fight off infection. Reducing the ability of medical devices to transmit infection would be an effective way to improve the health and survival of hospital patients. To this end, polycationic polymers (including quaternary ammonium salt-containing polymers), zwitterions, poly(ethylene glycols), and antibacterial peptides are promising materials to be used as antibacterial coatings for preventing medical device associated infections.[355-357] Flat surfaces can be used to harvest UV and visible light and use it to generate reactive species such as singlet oxygen. While ultraviolet light is lethal to many microbes, it is

also harmful to human and animal cells, and so materials that can use visible light to generate reactive species are preferable. A photoactive polymer was prepared and shown to generate singlet oxygen, killing nearby cells.[358] The anatase form of titanium dioxide generates reactive oxygen species upon irradiation which are toxic to microbial cells;[359] this activity also underlies the use of TiO_2 in self-cleaning window coatings.[360]

Antimicrobial films may also serve other purposes. Antifouling coatings can be formed without the use of antimicrobial agents by the generation of superhydrophobic surfaces in which the feature sizes (on a micron or nanometer scale) and shapes prevent both water and other solvents from binding effectively to the surface. Surfaces that can repel water and other solvents can also prevent dirt and microorganisms from adhering to a surface.[361-363] Superhydrophobic films can also be used on fabrics to repel water and dirt, to reduce their need for laundering, but previous coatings have used fluorinated polymers whose degradation products, intermediates, and precursors are persistent pollutants with unknown toxicities, deprecating their use. Antibacterial films can also be used to reduce bacterial degradation of food, reducing food waste. Edible films using chitosan, starches modified to improve their durability in the presence of water, carboxymethylcellulose and cyclodextrins, pectin, zein, whey protein, and the Maillard adducts of soy protein and carbohydrates have been tested for food preservation to preserve food while reducing fossil fuel use.[364]

Scaffolds and implants: Networks also have a high surface area-to-volume ratio but are localized to specific sites and generally are more persistent than hydrogels. They are useful as substrates for cell growth and thus are useful for wound and bone healing. For wound healing, networks of chitosan,[365] and sodium alginate with poly(vinyl alcohol)[366] can both facilitate healing and inhibit infection. Bone matrixes require yet more persistence to allow the growth of new bone and greater rigidity because of the stiffness of bone. Antibacterial agents are important because bone infections are likely less accessible to antimicrobial agents and thus are more difficult to treat; preventing them would be more efficient than treating them. One example is a gentamicin-containing porous implant for bone healing;[367] a quaternized chitosan/polyester/hydroxyapatite scaffold was also implanted in rats and rabbits and had antibacterial and bone-healing activities.[368] Implants using cationic polymers[369] or copper nanoparticles were effective at preventing infections, with the copper/polyetheretherketone implant being effective against MRSA.[370] An alternative antibacterial method is the use of nitric oxide-releasing agents in concert with bone matrixes to kill microbes.[371]

Composites: Composites use multiple materials in concert. One example of an antibacterial composite is the combination of copper compounds with an anion-exchange resin to kill bacteria in water for purification.[372] The addition of tetrachlorocuprate(II) salts to an anion exchange resin and reduction with ascorbic acid yielded a composite resin containing Cu_2O; exposure of Gram-positive *Enterococcus faecalis* to the material reduced bacterial load by 10^5 while the resin did not affect Gram-negative *Escherichia coli*. Antimicrobial composite materials are useful for medical devices such as dental implants where infections may be difficult to treat or may cause secondary structural damage. For example, silver and zinc oxide nanoparticle-containing composite resins for dental use were tested and inhibited *Streptococcus mutans* and *Lactobacillus* species.[373] Polylysine was incorporated into a dental composite to prevent caries-induced demineralization and repair failure[374], and noncovalent assemblies of N-Fmoc-pentafluorophenylalanine bound to a dental resin reduced bacterial growth of *Streptococcus mutans* at 0.25-1% concentrations and nearly abolished it at 2% concentration.

The variety of materials capable of exerting antimicrobial activity provides options not only for treating microbial infection but also for preventing microbial transmission and infection. They are

also capable of reducing some of the other effects of bacterial and microbial growth such as fouling and food spoilage. While materials are subject to evolutionary strains in microbes and thus require monitoring, they provide broader and longer-term means to deal with a variety of problems related to microbial growth and infection.

4. Landscape view of antibacterial research – insights from CAS Content Collection

The CAS Content Collection[15] is the largest human-compiled collection of published scientific information representing a valuable resource to access and keep up to date on scientific literature with over 59 million records across disciplines including chemistry, biomedical sciences, engineering, materials science, agricultural science, and many more, from all over the world. Comprehensive data from the CAS Content Collection allows quantitative analysis of global research publications across various parameters including time, geography, scientific area, medical application, disease, and chemical composition. To apprehend the research landscape for antibacterials in the last decade, a search query was developed to extract the dataset and analyzed extensively giving insights into publication trends, patent activities, CAS-indexed concepts, and substances.

In the last decade, there have been over 35,000 scientific publications (mainly journal articles and patent publications) related to antibacterial research in the CAS Content Collection indicating continual research, development, and commercialization efforts being made in this field. Journal publications dominate the field while patent publications amount to 1/5th of the journal publications. This trend suggests that vast amounts of academic research in the last decade has not yet resulted in commercialization. There has been an overall growth in journal publications over the last 5 years with a >15% increase in the last year **(Figure 4A)** correlating well with the post-COVID19 increase in nosocomial infections.[7] China, India, the United States, Iran, and the Republic of Korea are the world leaders with respect to the number of journal publications **(Figure 4B)** with China having nearly twice as many publications than India. Noteworthy, Iran, India, and Italy have a much higher number of published journal articles as compared to patent publications while China has ~3-fold greater number of journal and patent publications, respectively, as compared to the United States, indicating differential allocation of research funds in each country or region.

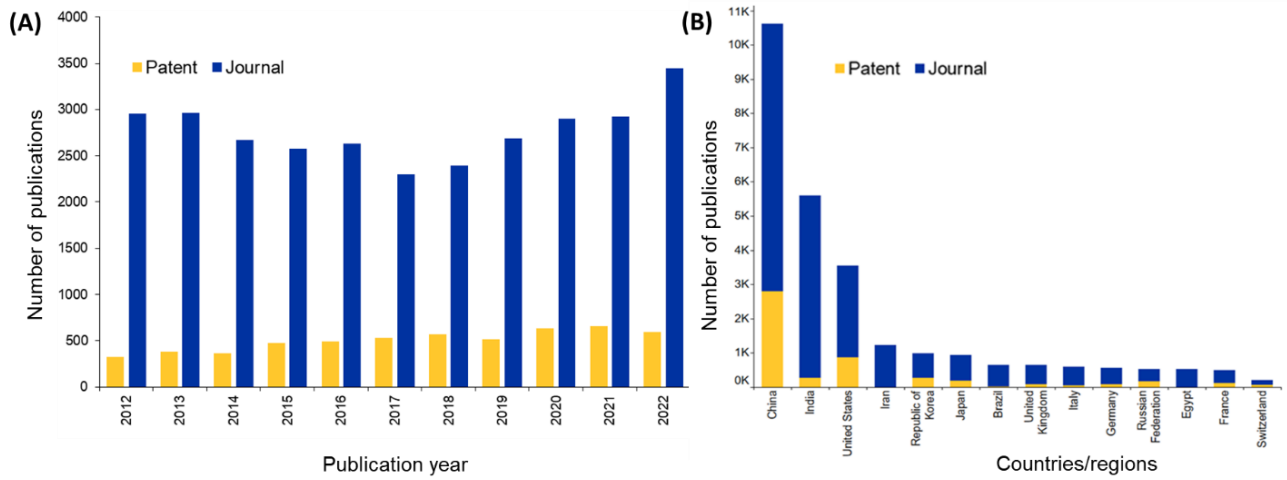


Figure 4. **(A)** Number of journal and patent publications per year in the field of antibacterial research (shown as blue and yellow bars, respectively) over the last decade (2012-2022). **(B)** Top countries/regions for the numbers of antibacterial-related journal articles (blue bars) and patents (yellow bars) over the last decade (2012-2022).

We identified leading organizations for journal publications in research related to antibacterials (**Figure 5A**) with respect to both the number of journal publications as well as the average number of citations per publication (an indicator of the influence of that publication in the field). Unsurprisingly, research institutes from the United States and China account for nearly half of the top journal publications and is followed closely by Canada. One institute each from India, Israel, Portugal, the Republic of Korea, and Australia features in the list of top institutes. The journal Antimicrobial Agents and Chemotherapy appears to publish the highest number of articles related to antibacterial research **(Figure 5B)** and is the most-cited journal in the field **(Figure 5C).**

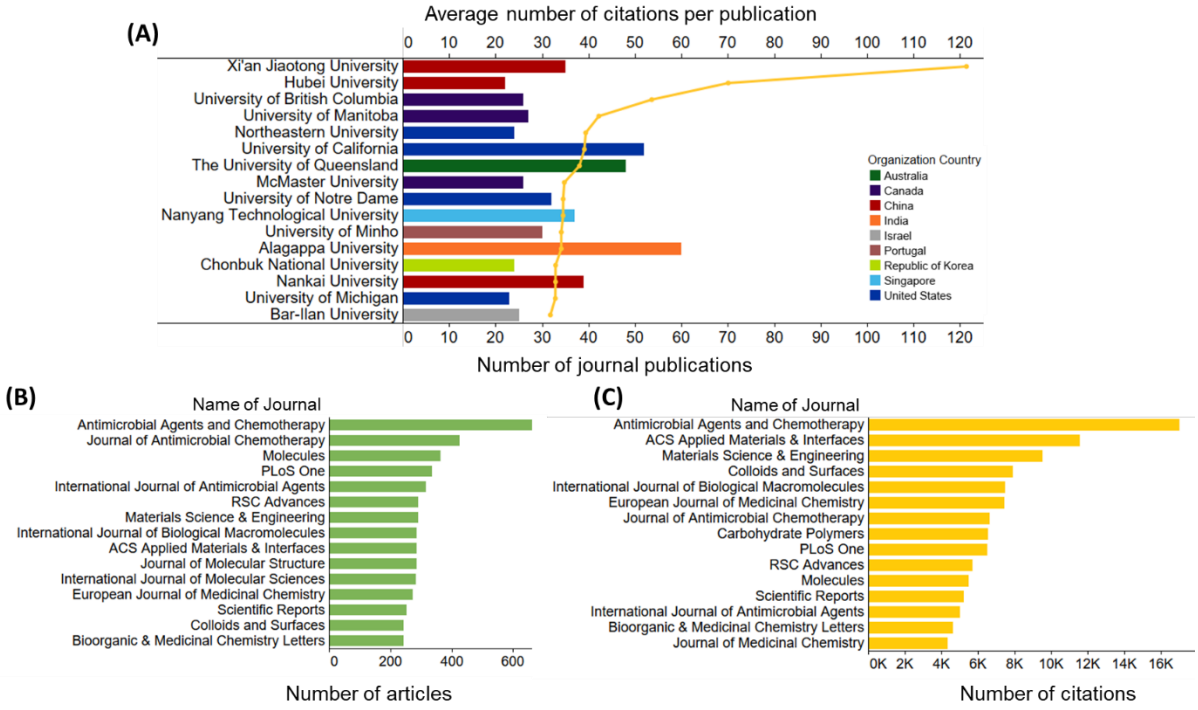


Figure 5. **(A)** Top research institutions in terms of average citation numbers per journal publication between 2012-2022. Colors of the bars represent the institution's country/region: red (China), blue (USA), Indigo (Canada), green (Australia), light blue (Singapore), brown (Portugal), orange (India), light green (Republic of Korea), grey (Israel); the yellow line represents the average number of citations per publication. Top scientific journals with respect to **(B)** the number of antibacterial research-related articles published and **(C)** the number of citations they received for the period 2012-2022.

Patent publications were analyzed to identify leading patent assignees and their geographical distribution. In terms of the number of patent publications, patents by non-commercial assignees outnumber commercial ones indicating that non-commercial organizations are engaged in more antibacterial research and are trying to find ways to patent and commercialize them. Interestingly, the number of patents by non-commercial assignees has shown a steady increase in the past decade while the number remains more or less steady for commercial assignees **(Figure 6A).** China dominates patents in the field of antibacterials as it has the highest number of commercial and non-commercial patent assignees (**Figure 7).** Chinese universities account for all the top

fifteen spots in the top non-commercial assignees. Unsurprisingly, the number of patents by non-commercial assignees from China is ~4 times higher than the USA, and ~3 times higher than that of Korea. China, the USA, Japan, Korea, India, the UK, and Italy are the top assignees for commercial patents. Patents from Wockhardt Limited, the leading commercial organization in the field of antibacterials, has notable patents on the use of nitrogen-containing compounds as antibacterials.[375, 376] Other companies such as F.Hoffmann-La Roche have patents related to sequence-specific antibacterial testing,[377] peptide macrocycles against drug-resistant strains of *Acinetobacter baumannii,*[378] among many others.

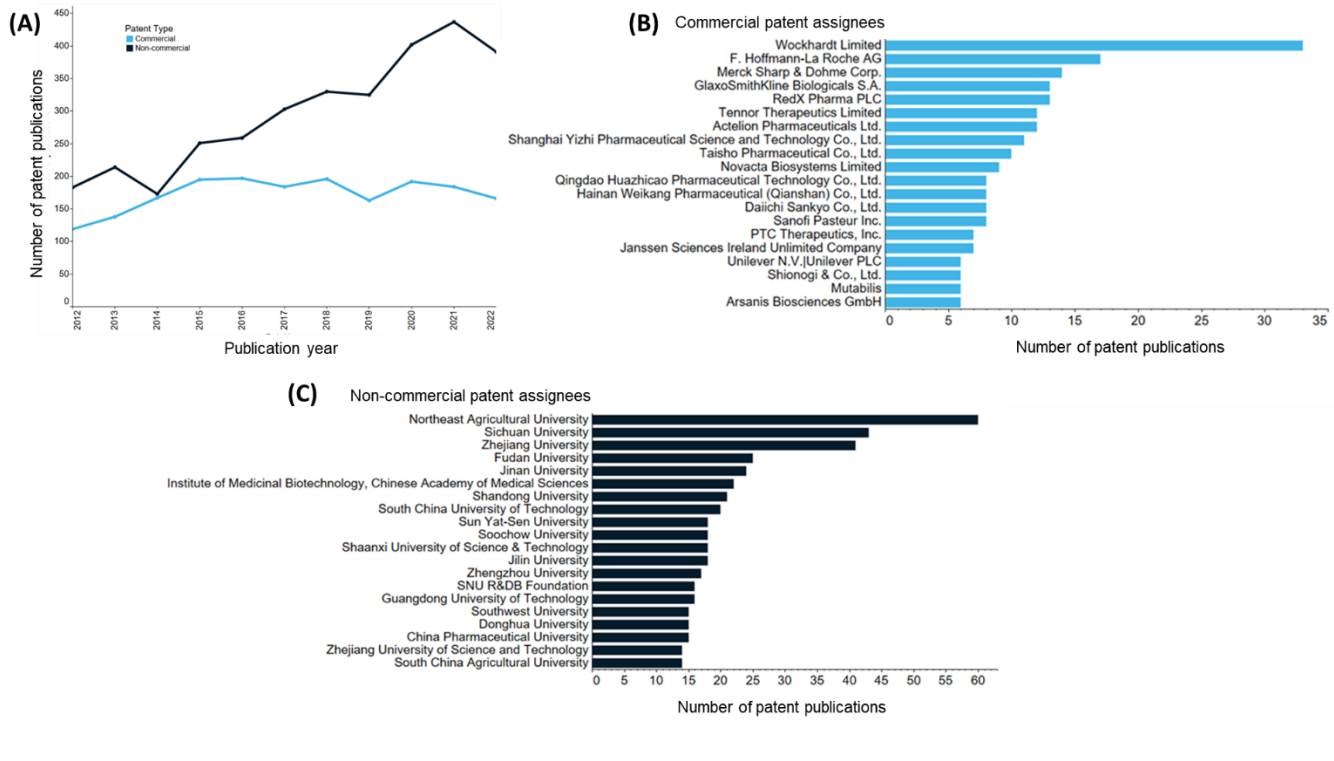


Figure 6. **(A)** Number of patent publications per year between 2012-2022 by commercial (blue) and non-commercial (black) assignees. Top twenty **(B)** commercial assignees and **(C)** non-commercial assignees with respect to the number of antibacterial research-related patents published from 2012-2022.

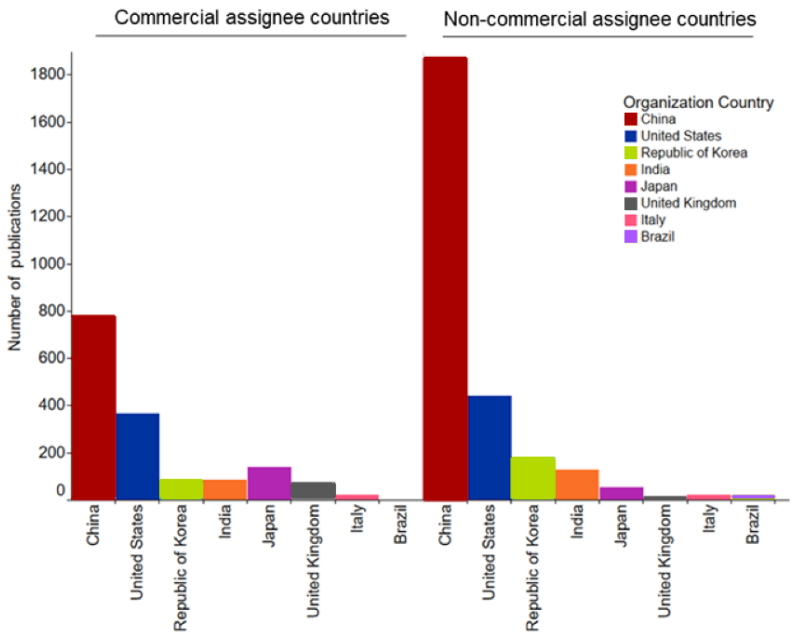


Figure 7. Country-wise distribution of patent publications for commercial assignees (left panel) and non-commercial assignees (right panel). Colors of the bars represent the organization's country/region: yellow (China), blue (USA), light blue (Republic of Korea), orange (India), magenta (Japan), grey (United Kingdom) and pink (Israel).

Patent protection is influenced by the country/region of the applicant, consequently the same invention can be filed for patent protection in several jurisdictions, or it can be filed through the World Intellectual Property Organization (WO) and later filed to patent offices in different countries. This accounts for certain patent families being counted more than once, which represents them being filed at multiple patent offices. **Figure 8** represents a chronological flow of filing individual patent applications within patent families in various national patent offices, the World Intellectual Property Organization, and the European Patent Office (EP). The left column shows the top ten patent assignee countries/regions in terms of the number of patent activities (here, an activity is defined as an event where a patent document, either an application or a granted patent, is published). The extreme right column shows the patent office where the patent activity took place. The center column, connecting the two, indicates the office where the first patent in the family was filed. Unsurprisingly, China and USA have the highest patent flow activity which correlates well with their high patent numbers. Interestingly, most countries tend to have a higher number of patent filings at their home country's patent office followed by their initial filings at the World Intellectual Property Organization.

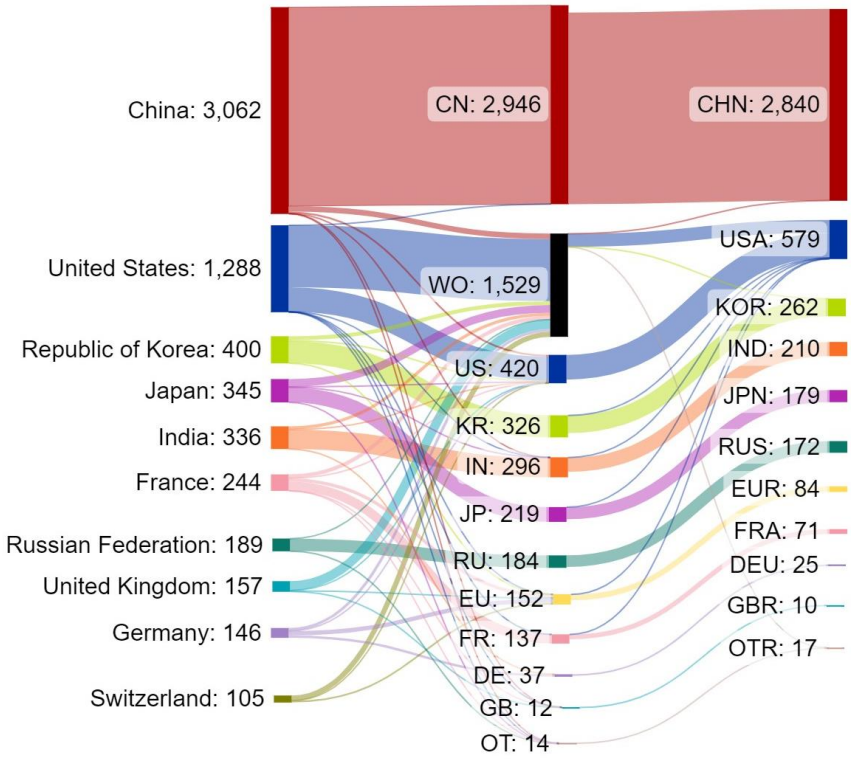


Figure 8. Patent flow of antibacterial-related patent filings from different assignee countries/regions to various patent filing offices (center) and final destination patent office (right). The abbreviations in the center and right indicate the patent offices. Standard two- and three-letter codes are used to denote country names corresponding to their patent offices.

We further explored distribution and trends in the published documents (journals and patents) dealing with various antibacterial-related concepts. **Figure 9A** shows the number of publications corresponding to the most prominently occurring bacteria in the field of antimicrobials. *Staphylococcus aureus* shows the maximum number of publications followed by *Escherichia coli;* this is unsurprising as these microorganisms are the most common causes of hospital-associated infections and bacteremia (the presence of bacterial infection in blood) in predisposed populations.[379] MRSA remains a prominent cause of bacteria-related deaths worldwide.[336] Interestingly, all the bacteria from the 'ESKAPEE' list including *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp.*, Escherichia coli* feature in this list indicating that significant research efforts are being directed towards combatting these bacteria.[380] In terms of the number of publications mentioning specific bacterial diseases or conditions, tuberculosis was the most common bacterial disease found (**Figure 9B**). This is consistent with the frequency of indexing of bacterial species, in which *Mycobacterium tuberculosis* is the most often seen in publications. (**Figure 9A**). Urinary tract infections, nosocomial, and respiratory infections have also been frequent subjects of published research (**Figure 9B**). Quinolones and fluoroquinolones appear to head the top antibiotic classes, followed closely by tetracyclines and aminoglycosides **(Figure 9C)**.[381]

(A)

Bacteria	Number of publications
Staphylococcus aureus	17,255
Escherichia coli	13,688
Pseudomonas aeruginosa	7,490
Klebsiella pneumoniae	4,242
Bacillus subtilis	2,729
Acinetobacter baumannii	2,449
Staphylococcus epidermidis	2,256
Enterococcus faecalis	2,198
Streptococcus pneumoniae	1,280
Enterococcus faecium	1,150
Enterobacter cloacae	989
Bacillus cereus	872
Mycobacterium tuberculosis	863
Proteus mirabilis	860
Streptococcus mutans	812

(B)

Disease/condition	Number of publications
Tuberculosis	1,055
Neoplasm	978
Urinary tract infection	648
Pneumonia	648
Nosocomial infection	644
Bacteremia	486
Wound infection	422
Sepsis	379
Skin infection	315
Respiratory infection	264
Diarrhea	248
Cystic fibrosis	234
Endocarditis	200
Osteomyelitis	193
Dental caries	165

(C)

Antibiotic class	Number of publications
Quinolones/Fluroquinolones	1,639
Tetracyclines	1,057
Aminoglycosides	646
Phenicols	507
Macrolides	490
Polymyxins	418
β-lactam antibiotics	403
Glycopeptides	351
Sulfonamides	330
Lipopolypeptides	202
Pyrimidines	184
Oxazolidinones	91
Rifamycins	70
Lincosamides	63
Streptogramins	24

Figure 9. Heat map table indicating number of publications for top **(A)** bacterial species, **(B)** diseases/conditions caused by bacteria and **(C)** antibiotic classes used in the field of antibacterials.

To understand the co-occurrence of major classes of antibiotics and various bacterial species, we generated a heat map as shown in **Figure 10.** Here, relative frequencies of each bacterial species have been calculated within each class of antibiotics and is indicative of the relationship between each antibiotic class and the top species of bacteria. Overall, *Staphylococcus aureus* and *Escherichia coli* have the highest relative frequencies for each major antibiotic class indicating a higher amount of research documents present for these bacteria. Certain classes of antibiotics are selectively effective against Gram-positive or Gram-negative species. For instance, aminoglycosides are documented to be more effective against gram Gram-negative bacteria, particularly *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* comprising more than 50% of co-occurrences. Similarly, a higher use of polymyxins against Gram-negative bacteria , especially *Acinetobacter baumannii* and *Klebsiella pneumoniae* correlates with the literature.[382] On the other hand, lipopeptides and glycopeptide-based antibiotics have higher document frequencies with Gram-positive bacteria such as *Staphylococcus aureus*.[381]

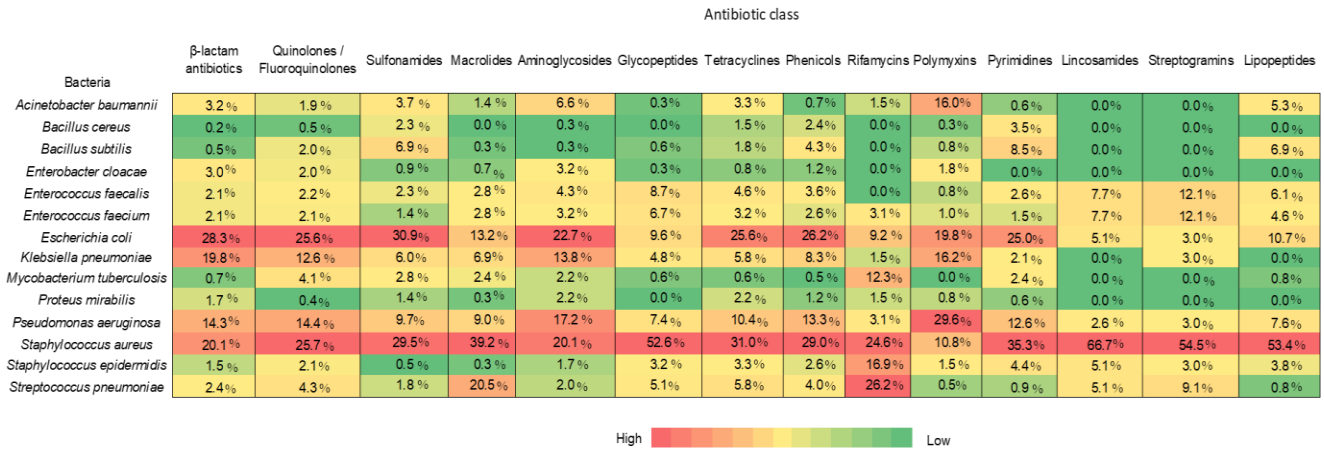


Figure 10. Heat map of the relationship between the most used classes of antibiotics (top) and prevalent bacterial species (left) in the field of antibacterial. Data comprises of journal and patent publications obtained from the CAS Content Collection for the period 2012 to 2022. Relative frequencies of each bacterial species have been calculated within each class of antibiotics.

Data analysis for substances in the field of antibacterials for the last decade depicts a steady number over the years. Substance analysis was confined to relevant roles including therapeutic (THU) and pharmacological activity (PAC). **Figure 11** represents the growth of substances associated with the antibacterial field in the last decade. In the initial years, the number of substances reported in journal publications was higher than the number reported in patent publications, but the trend reversed between 2018-2020. Interestingly, the number of substances reported in journals and patents is nearly identical in 2022.

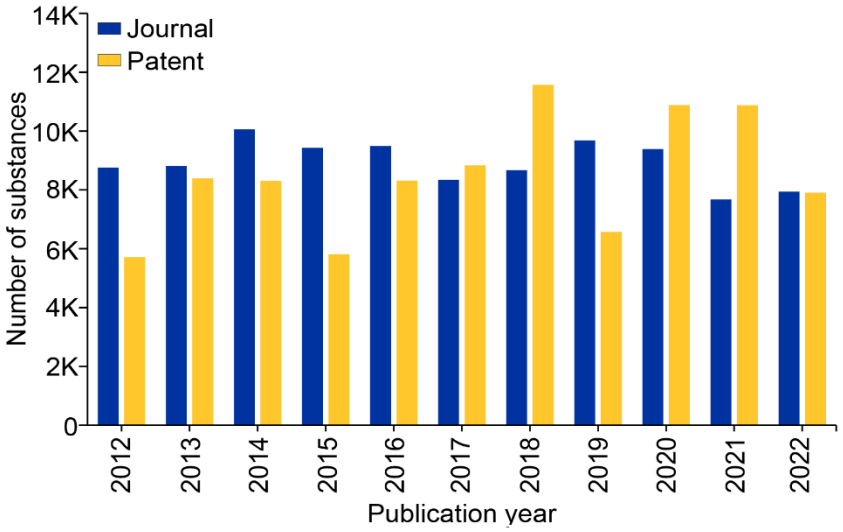


Figure 11. Growth in substances associated with antibacterials over 2012-2022 from the CAS Content Collection. Only substances indexed with a therapeutic (THU) or pharmacological activity (PAC) role was included for the analysis.

Further investigation into the classes of substances suggests that organic and inorganic small molecules, protein/peptide sequences, polymers, elements, and alloys are the major classes of importance in the field of antibacterials. **Figure 12** represents the growth of various substance classes in the last decade. The number of substances classified as organic and inorganic small molecules is 40-50 times higher than the next class of substances - protein/peptide sequences. Other classes such as polymers, elements, and alloys, while important, still account for a much smaller fraction of substances being used in the field of antibacterials. Amongst the major classes, organic/inorganic small molecules show a marginal decrease post-2020 indicating the shift in interest from small molecules towards more novel/alternative forms of antibiotics such as materials and forms. **Figures 13** depicts the distribution of substances from journal and patent publications, respectively. Overall, the distribution varies slightly between journals and patents where the percentage of small molecule substances is slightly lesser in patents when compared to journal publications whereas peptide-based substances are reported more in patent publications.

As seen in **Figure 13**, there are over 216,000 small molecule substances associated with publications in our dataset. Amongst the small molecule category, ciprofloxacin, and levofloxacin (both belonging to the quinolone class of antibiotics) have the highest number of occurrences, and this agrees with **Figure 9C** wherein the number of publications for quinolones and fluoroquinolones were the highest. Other antibiotics featured in the list belong to various classes such as ß-lactam antibiotics (imipenem, ceftazidime, ampicillin, meropenem, cefepime, penicillin, etc.), aminoglycosides (amikacin), macrolides (erythromycin) among others. Among the proteins/peptides found in the field of antibacterials, a total of ~26k substances have been

reported. Unsurprisingly, peptide-based antibiotics such as vancomycin - a glycopeptide antibacterial[383] exhibit the highest number of occurrences followed by the lipopeptide antimicrobial, daptomycin.[384] Antimicrobial peptides such as cathelicidin LL-37,[385] nisin,[386] magainin 2 (MG2a) ,[387] and Streptogramin B[388] among others also feature in top protein/peptide substances. Polymers with antibacterial properties have various advantages over their small molecule counterparts such as higher efficacy, reduced toxicity, lesser environmental problems, and lesser susceptibility to antimicrobial resistance.[389] Natural polymers such as chitosan, cellulose, and starch and synthetic polymers such as polyethylene glycol (PEG), poly (vinyl alcohol) (PVA) and polycaprolactone (PCL) are among the top-ranking polymer-based substances in this field. Metals such as silver, gold, titanium, gold, etc. feature among the top element-based substances. Substances from other categories such as ceramics, plastics, and mxenes are also used in the antibacterial field indicating substance diversity.

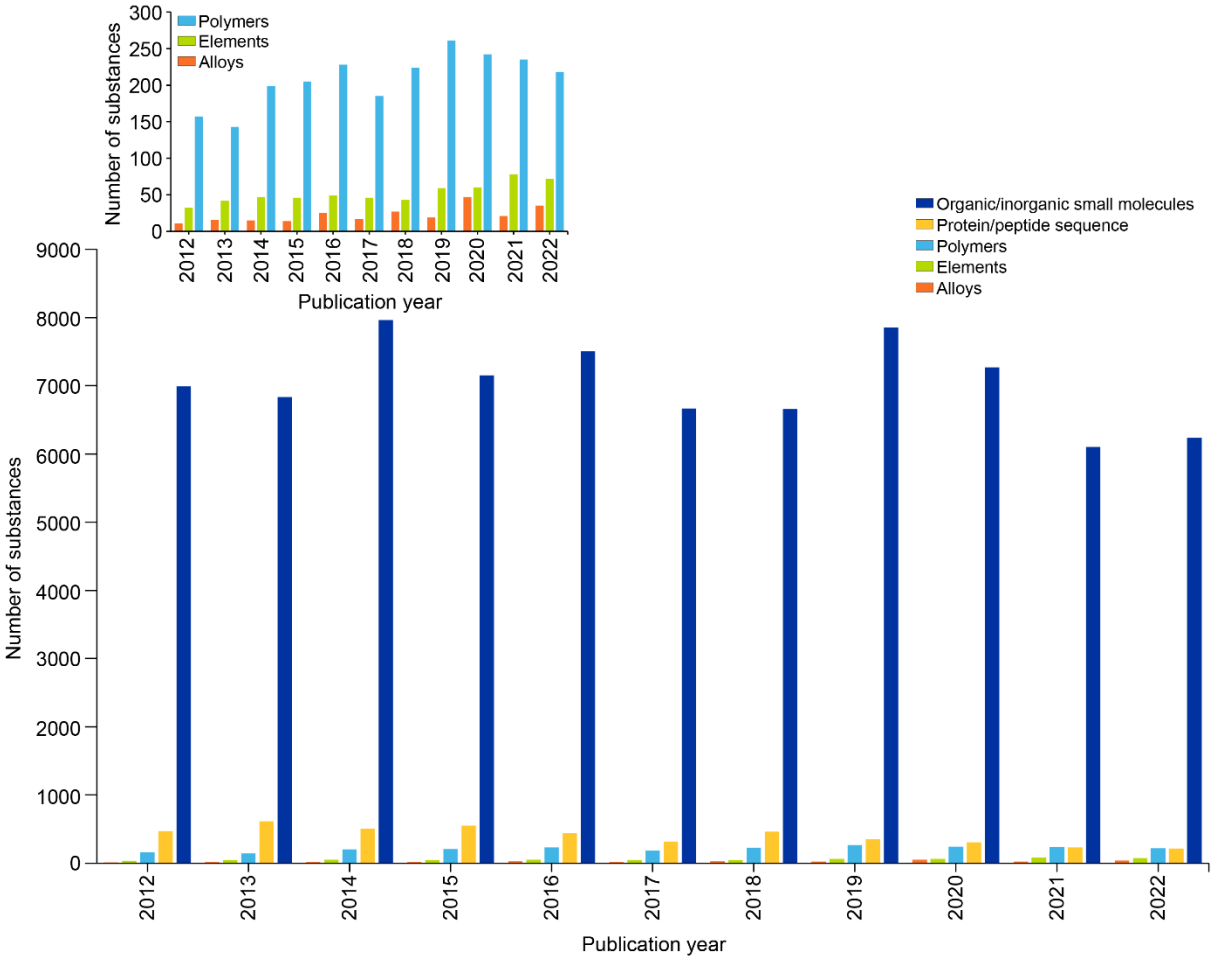


Figure 12. Number of substances of different classes associated with antibiotics over 2012-2022 from the CAS Content Collection. Only substances indexed with a therapeutic (THU) or pharmacological activity (PAC) role was included for the analysis. Inset graph shows a zoomed in view with an emphasis on polymers, elements, and alloys to better reflect growth over the last decade.

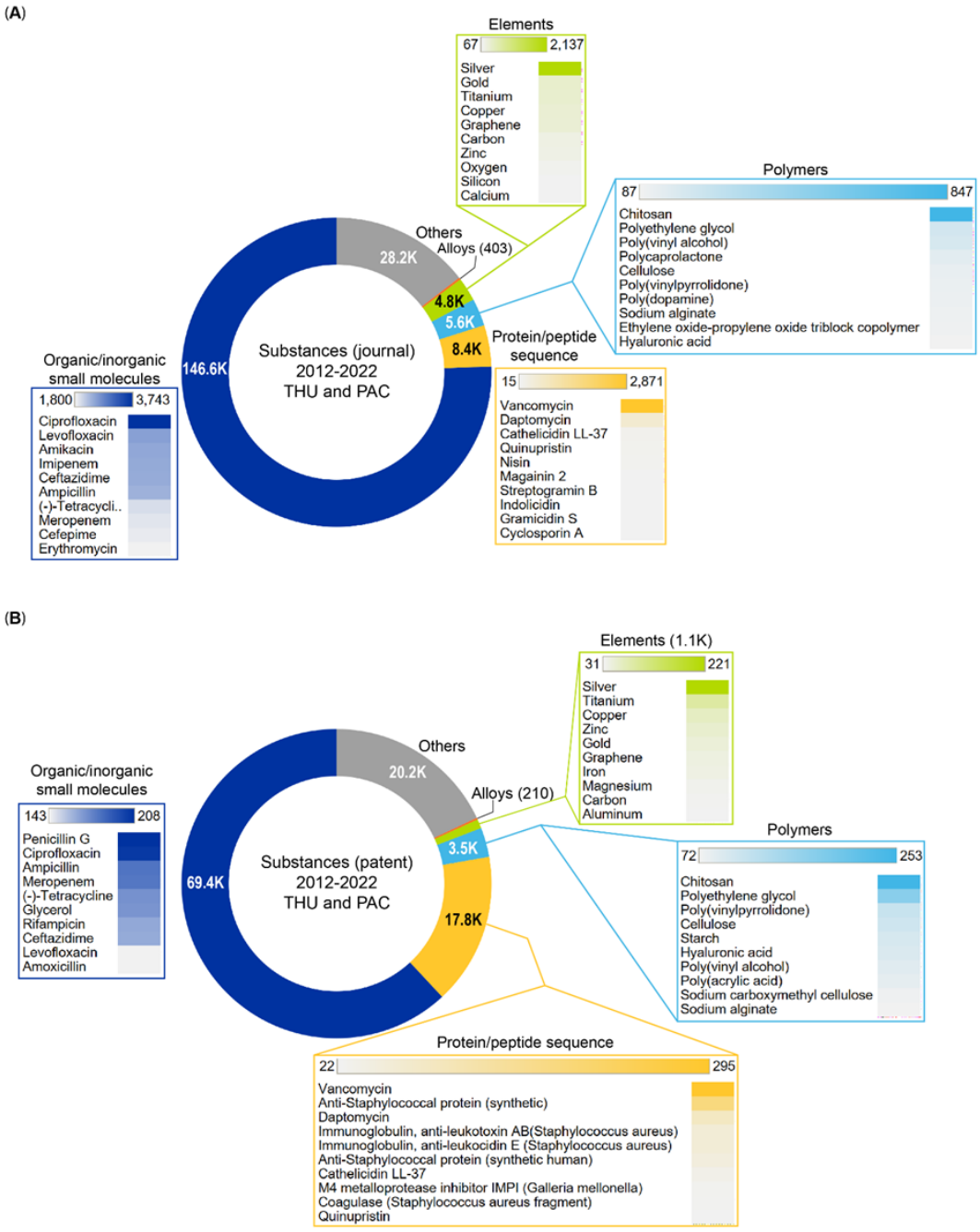


Figure 13. Distribution of substances associated with antibiotics over 2012-2022 from the CAS Content Collection. Only substances indexed with a therapeutic (THU) or pharmacological activity (PAC) role were included for the analysis. Heat map tables list the top 10 substances co-occurring in those specific classes.

Correlation between various substance classes and different bacterial genera is shown as a Sankey graph for journal and patent publications (**Figure 14**). *Staphylococcus, Escherichia, Pseudomonas, Klebsiella,* and *Bacillus* have the highest number of reported substances associated with both journal and patent publications. Interestingly, greater number of protein/peptide-based substances associated with journal publications appear to be focused on *Acinetobacter* and *Actinobacteria* while for patent publications, *Staphylococcus, Escherichia,* and *Pseudomonas* are the top bacterial genera.

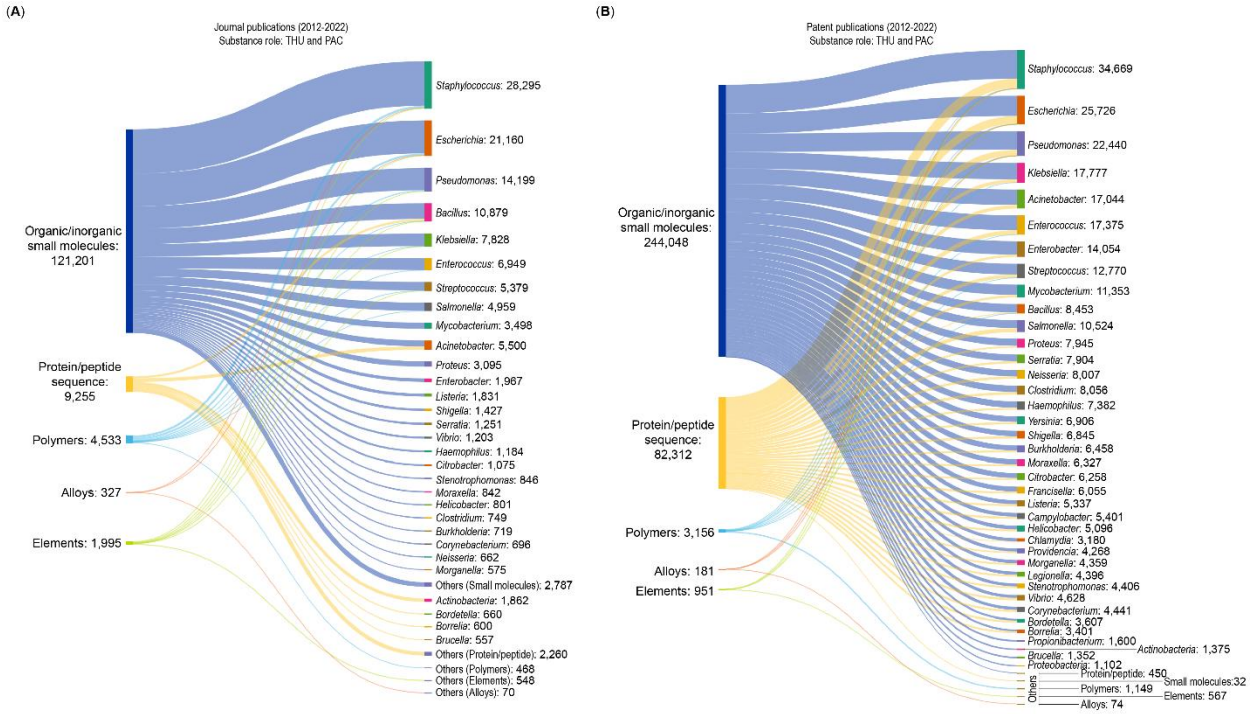


Figure 14. Sankey graphs indicating co-occurrences between different classes of substances and various bacterial genera in (**A**) journal and (**B**) patent publications from the CAS Content Collection for the period 2012-2022. Only substances indexed with a therapeutic (THU) or pharmacological activity (PAC) role were included for the analysis.

Since antimicrobial resistance is a growing threat, the CDC has maintained a list of microbes that could be urgent antimicrobial resistance (AMR) threats, serious AMR threats, or AMR watchlist (microbes which could become serious threats in future due to their propensity of becoming multidrug resistant) in 2019.[30, 390] These lists serve as strategic tools to prioritize and address the most pressing antimicrobial threats. **Figure 15** represents the growth of substances associated with bacteria belonging to each of these lists, from journal and patent publications in last decade. **Figure 15A** which shows growth for bacteria from the CDC's urgent threat list comprising drug-resistant *Acinetobacter, Neisseria gonorrhoeae, Clostridioides difficile, and* Enterobacterales. *Acinetobacter* has the highest number of reported substances. Substances for *Neisseria gonorrhoeae* have shown a more or less steady growth in the past 3 years. **Figure 15B** represents substance growth over the years for bacteria in the CDC's serious threat list. The highest number of substances are reported for *Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus, and Mycobacterium tuberculosis.* Almost all bacterial species show sustained interest with the number of substances associated with them being steady. *Salmonella typhi* in particular appears to show a modest and steady increase in the number of substances for the last three years. **Figure 15C** depicts substance growth over the years for bacteria in the CDC's watchlist. Interestingly, *Mycoplasma genitalium* shows a spike in the number of substances in 2022. *Mycoplasma genitalium is* the causative agent for urethritis in men (urethral inflammation) and cervicitis in women (cervical inflammation) and is resistant to azithromycin. *Bordetella pertussis* on the other hand is responsible for whooping cough and shows a steady increase in substances over the last 3 years nearly doubling in 2022 indicative of interest in this direction. Finally, **Figure 15D** represents substance growth in the last 10 years for ESKAPEE pathogens - *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii,*

Pseudomonas aeruginosa, Enterobacter spp., *Escherichia coli* showing that overall number of reported substances show a slight decrease in last few years.

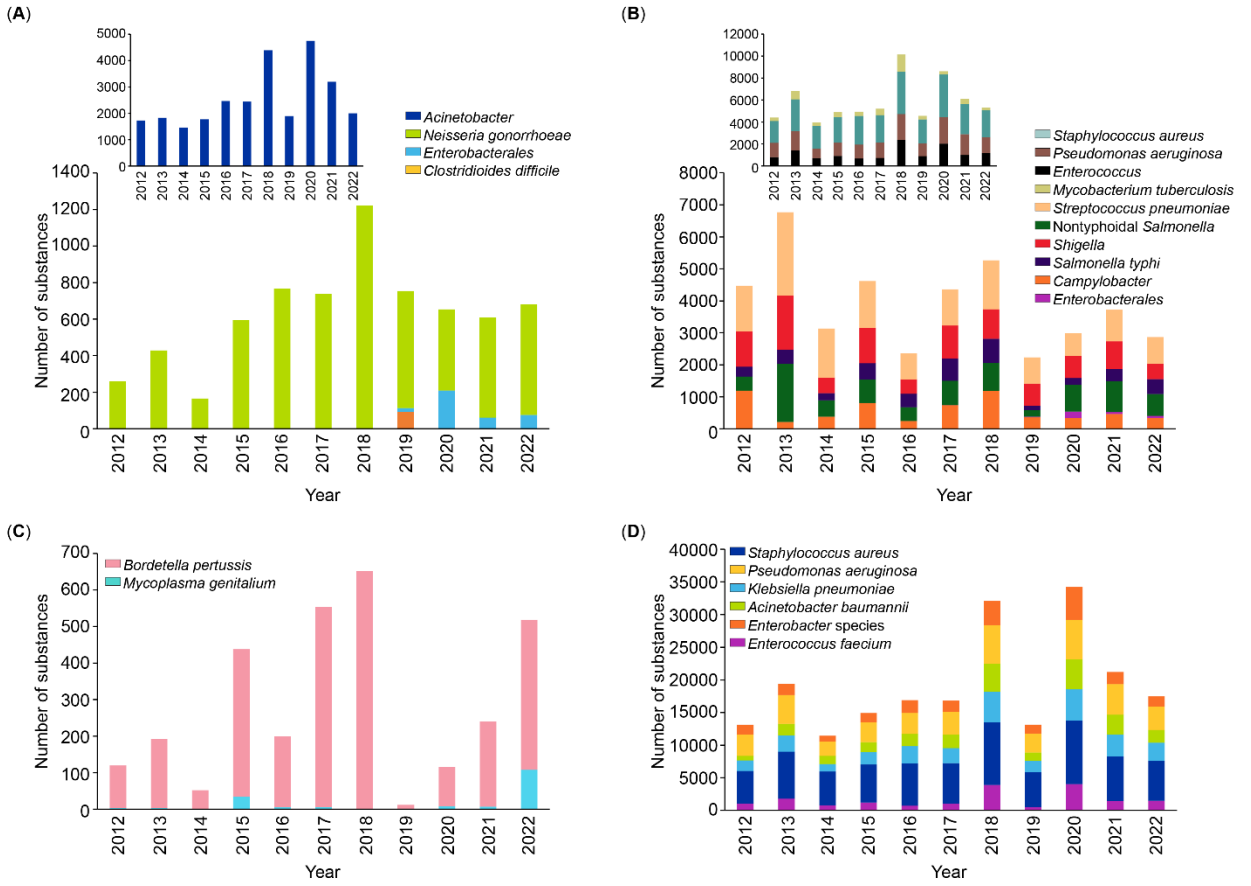


Figure 15. Growth in substances for bacterial strains recognized as (**A**) CDC's urgent AMR threat, (**B**) CDC's serious AMR threat and (**C**) CDC's AMR watchlist, and (**D**) ESKAPEE pathogens from the CAS Content Collection for the period 2012-2022. Only substances indexed with a therapeutic (THU) or pharmacological activity (PAC) role were included for the analysis.

5. Capital Investment

Data from Pitchbook[391], an online platform for investment data, reveals a steady increase in invested capital over the last decade (**Figure 16A**)**.** The exceptions appear to be 2017, 2019, and 2022 which show a curious dip in the amount of invested capital (**Figure 16A**), the exact reason for which remains unspecified. Similar dips, especially around 2016 and 2019, are also observed in our substance data (with a far less noticeable dip in publications) from the CAS Content Collection. In terms of geographical distribution, the US continues to lead in terms of capital invested in 2022-2023, followed closely by Europe and Asia (**Figure 16B**). Among the leading countries or regions, the United Kingdom (GBR) and India (IND) are the only two that show an increase in capital investments in 2022-2023 as compared to the previous years, 2020-2021 (**Figure 16C**). Despite this, USA leads in terms of the sheer volume of capital invested being ~5X that of China (CHN) in 2022-2023 (**Figure 16C**)**.** Growth in capital invested over the last decade for a few of the leading countries or regions indicates a curious periodic trend showcased most notably by the USA, Germany (DEU), and China and to a smaller extent by India and Korea (KOR). This trend appears to be characterized by spikes in capital invested between 2013-2016 and 2017-2021 (**Figure 16D**) led by Germany, a country with a strong pharmaceutical research and development initiative/presence/sector. Overall, investments in 2022-2023 in the field of

antibiotics appear to be lower for most countries or regions except for Italy (ITA) (**Figure 16D**) and could be a sign of waning interest. In terms of industry type, unsurprisingly the healthcare sector accounts for most of the capital invested over the last decade (**Figure 16E**). This is followed by the business-to-business and business-to-consumer sectors. The materials and resources sector also shows a decent volume of investment, perhaps indicative of increasing commercial interest **(Figure 16E)**. Finally, the information technology sector accounts for a very small portion of capital invested (**Figure 16E**).

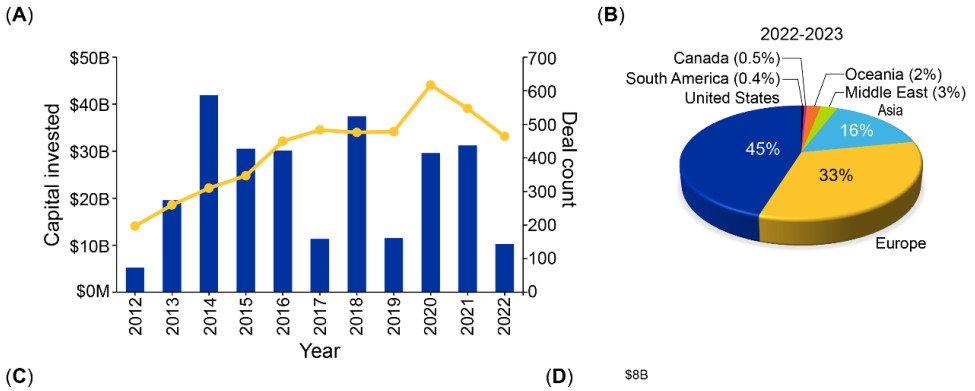


Figure 16. Commercial interest in antibiotics (data from PitchBook). (**A**) Capital invested and deals related to antibiotics for the last decade (2012 to 2022). (**B**) Geographical distribution of capital invested in 2022-2023 in the field of antibiotics. (**C**) Leading countries or regions in terms of capital invested over 2020-2023. (**D**) Growth in capital invested over time for a few key countries or regions. Standard three-letter codes are used to represent countries or regions. (**E**) Distribution of capital invested across different industry types over the last decade.

6. Role of CRISPR based gene editing in antibacterials

Clustered regularly interspaced short palindromic repeats (CRISPR) based gene editing system originated in bacteria as a defense mechanism against bacteriophages. However, CRISPR- Cas nucleases, especially CRISPR-Cas9 systems can be used to produce antimicrobials **(Figures 2,3).**[392] They are used for designing antibacterial therapies by using engineered CRISPR-Cas systems for gene-editing to destroy specific bacterial DNA, thereby offering alternative for traditional antibiotics. It can be used for 'phage therapy enhancement' where bacteriophages can be engineered to offer specific treatment against bacterial infections. CRISPR systems can also be used to understand bacterial pathogenesis and resistance mechanisms which can help in designing targeted therapies. In addition, it can also be used for developing diagnostic tools, such as specific high sensitivity enzymatic reporter (SHERLOCK) for rapid and accurate identification

of pathogenic bacterial strains. CRISPR based system has been used for targeting biofilm formation genes in *Pseudomonas aeruginosa.*

7. Role of AI in antibacterials

The development of any antibiotic is a tedious and time-intensive process. Low success rates of most candidate drug molecules in combination with lesser return of investments to companies are major challenges in the field of antibacterial development. The advent of artificial intelligence (AI) has led to an acceleration in drug development with algorithms being developed to identify viable hit molecules. With the rapid advancements in this field, algorithms that are being created using machine learning (ML) and neural networks (NN), are being leveraged for larger in-silico exploration and identification of newer antibacterials. **(Figure 3)** depicts a clear accelerated growth in journal publications related to the use of AI in antibacterial research in the last decade. However, the increase in the number of patent publications remains relatively low indicating nascency in this field and that most research is still in the academic stage yet to reach commercialization. **(Figure 16)** represents a VOSviewer analysis[393] for various concepts in the field of artificial intelligence in antibacterial research. In the network visualization, items are represented by their label and by default also by a circle. The size of the label and the circle are directly correlated to the weight of the item. Distance between two items indicates the relatedness of the concepts, the closer the stronger they are related. VOSviewer, by default, also assigns the nodes in a network to clusters (each indicated by a different color). A cluster is a set of closely related nodes. Each node in a network is assigned to exactly one cluster. It shows that in the last decade, use of AI in antibacterial research is being carried out to a larger extent for bacteria such as *E. coli, S. aureus, M. tuberculosis, P. aeruginosa,* etc. AI-related concept terms such as 'machine learning', 'simulation and modeling', 'algorithm' form more and intense connections with various bacteria indicating the increased interest and applicability of AI in this field (**Figure 2)**.

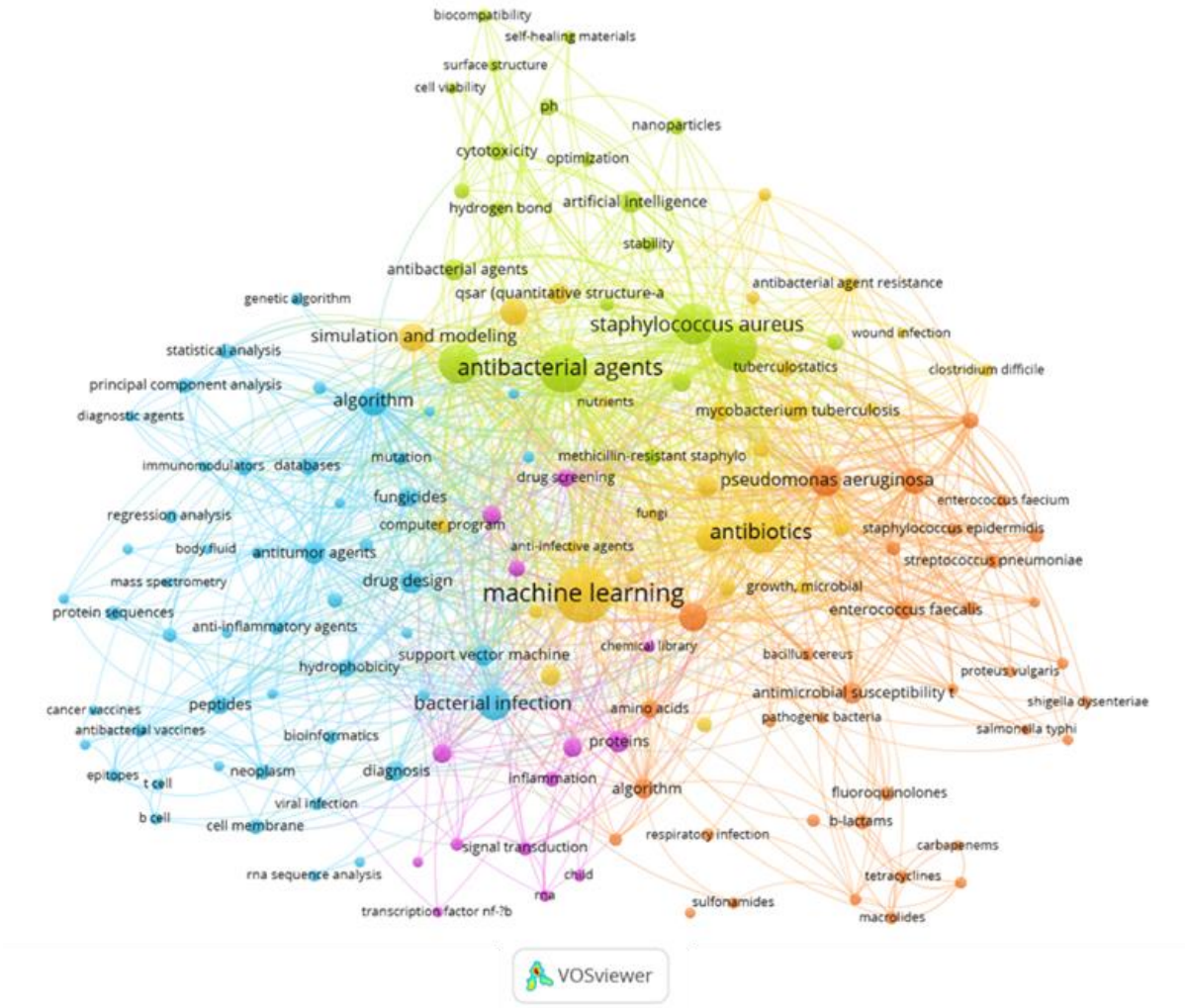


Figure 16. VOSviewer graph indicating networks of various co-occurring concepts related to the use of AI in the field of antibacterials in the last decade.

7. Perspectives and future scope

The global spread of multi-drug resistant bacteria is an alarming problem causing a threat to human health. The statistics from reputable sources such as WHO, CDC and World Bank have revealed the severity of treat that resistant bacteria can cause. They regularly publish reports which provide insights into the impact of resistant bacterial infections on public health domain. In line with the aim of preventing and addressing bacterial infections, CDC's lists of urgent treats, serious threats and watchlist species is periodically updates suggesting the dynamic nature of challenge and ever-evolving resistance among bacterial species. Various research endeavors are being made toward the development of novel antibiotics, but it comes with its own challenges.

Development of novel antibiotics requires a deeper understanding of the host-immune system and individual-level differences in the host immune system are responsible for differential results of the same antibiotic treatment in any population. While traditional antibiotic approaches continue to be utilized for treatment of bacterial infections, the biggest challenge remains the development and persistence of antimicrobial resistance. Bacteria are either naturally resistant to some

antibiotics, or they develop antibiotic resistance through gene transfer. The problem is compounded by the fact, that the development of antimicrobial resistance in bacterial species is much faster than the pace of development of any novel antibiotic.[34, 36] Moreover, the development of antibiotics is more challenging for Gram-negative bacteria as they have an outer membrane which prevents the entry of various drugs. Another major challenge is the treatment of bacterial infections if the bacteria form biofilms as biofilms prevent the entry of antibiotics and the lowest concentration of antibiotics entering the biofilm can promote the development of antimicrobial resistance.[394] Therefore, there is a dire need for novel antibacterial materials such as peptides, bacteriophages, enzymes, biopolymeric materials, and hydrogels that can help mitigate the issues with currently available antibacterial drugs. Another major advancement is the use of artificial intelligence (AI) and machine learning (ML) based approaches, CRISPR-based gene editing methodologies, that have slowly started entering the field of antibiotics which can significantly reduce the timeline for the development of any new antibiotic. The widespread use of AI is still in the nascent stages, and it requires more research efforts in the future. A better understanding of resistance in bacteria can help in the development of novel antibiotics and treatment strategies to manage bacterial infection.

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