2025

Whitepaper

Addressing AMR: Regulatory Challenges and Opportunities in Non-Traditional Antimicrobial Development

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Summary

Abstract

Antimicrobial resistance presents one of the most urgent global public health and development threats we face today. It is a phenomenon that has its origins in nature, but modern medical practices have transformed into a worldwide crisis as existing traditional antibiotics have become obsolete in the face of rapid resistance. As we risk running out of effective therapies to fight infection, we look into the new era of "non-traditional" antimicrobials in the development pipeline and summarise the development and regulatory challenges that put the practical application of these promising scientific developments in this field at risk.

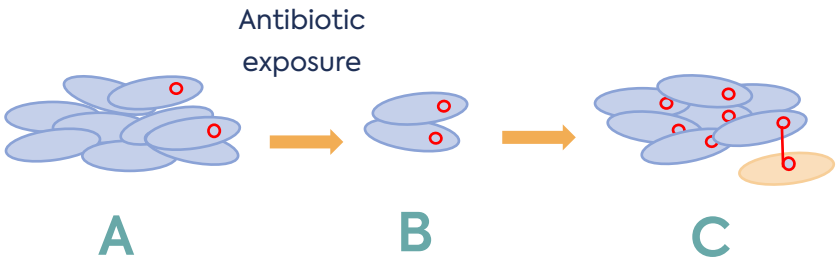
Introduction

Antimicrobial resistance (AMR) has been described as one of the century's most urgent global health challenges. Simply put, everybody will be affected by its spread, which is largely unchecked. This might be directly due to contracting a multi-drug-resistant (MDR) infection that might prove impossible to treat or indirectly as a result of the increased risks associated with even routine medical procedures considered low-risk today.

What is Antimicrobial Resistance?

Antimicrobial resistance is when bacteria, viruses, fungi and parasites no longer respond to antimicrobial medicines. This is a natural process whereby microbes evolved mechanisms to help them survive, initially against competition from other bacteria (WHO, 2023). Some bacteria evolved to produce their own antimicrobials that would inhibit or kill competitors. Eventually, this developed into an arms race between natural antimicrobials and methods of resistance against them. This was a relatively slow battle until humans discovered how to cultivate and use natural antimicrobials against pathogenic bacteria. At this point, widespread usage of natural and later chemically synthesised antimicrobials hugely increased exposure. In particular, exposure to sub-lethal doses within the so-called "mutant selection window" increased due to environmental contamination or inappropriate antibiotic usage. Inappropriate use has been prevalent from commercialisation onwards, with most recent studies reporting that between 45% to 66% of antibiotics prescribed at the primary care level are unnecessary and that the indicated drug, dosage, or treatment duration is unsuitable in approximately 50% of prescriptions (Dutescu and Hillier, 2021). The now near-constant selection pressure microbes face due to exposure to various antibiotics with different modes of action has accelerated their natural evolution. The end result of this provides novel mechanisms to survive and thrive in the presence of these antimicrobials (Davies and Davies, 2010).

Figure 1: Selection of Resistant Bacteria



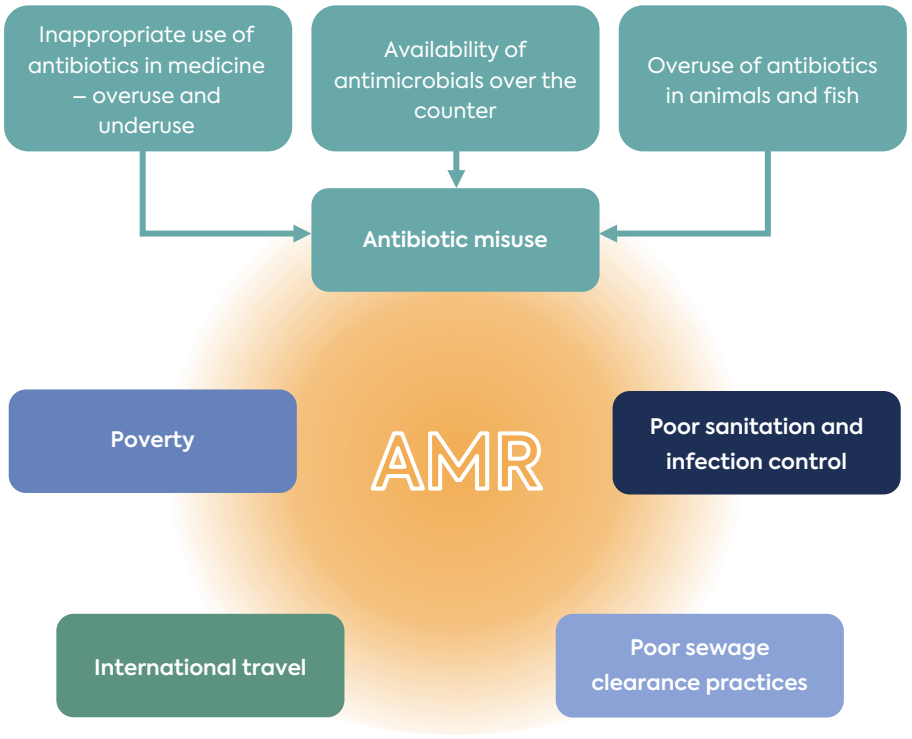
A. Bacterial colony containing wild type (susceptible) bacteria and some resistant isolates that have acquired an AMR plasmid
B. After the colony becomes exposed to antibiotics, through therapy or environmental contamination, the genes on the AMR plasmid confer a survival advantage to the resistant isolates, which survive while susceptible bacteria are killed
C. Resistant bacteria proliferate, and are able to further disseminate the plasmid to other bacteria via horizontal gene transfer. If this is in a patient, they would continue to get sick, and the infection would be more challenging to treat, requiring alternative therapy

Resistance can be intrinsic, naturally occurring in a species, or acquired through chromosomal genetic changes as well as through the acquisition of mobile genetic elements (Reygaert, 2018) such as plasmids. Mobile genetic elements allow resistance genes, once developed in a single bacterial species, to be mobilised and more widely disseminated (Partridge et al, 2018). This ability for bacteria to rapidly pick up and disseminate potentially useful resistance or other virulence genes means that previously susceptible bacteria of a completely different species can

become highly resistant to many clinically used antimicrobials instantly. This bacterial strain will have a survival advantage over other bacteria without resistance genes (Figure 1), allowing it to replace the susceptible bacterial strains.

Several factors accelerate resistance (Figure 2), including misuse of antimicrobials in clinical and veterinary practice. In addition, environmental contamination from the manufacture and use of antimicrobials has accelerated the process (Samreen et l, 2021). There are also local factors such as poor infection control and the poor antimicrobial prescribing and adherence practices seen in some areas of the world, global trade, travel and climate change (Castro-Sanchez et al, 2016).

Figure 2: Causes and contributing factors to the AMR problem



AMR's current and projected impact is profound; In 2019 alone, AMR is estimated to have contributed to almost 5M deaths, with 1.3M directly attributed to it. Without a global response to AMR, it is projected (O'Neill report, May 2016) that by 2050, 10M people will die annually due to drug-resistant infections. AMR deaths are projected to overtake both cancer and diabetes as the world's biggest killers. Additionally, it threatens medical procedures such as routine surgery and chemotherapy. Livestock health is also endangered, thereby disrupting the global food chain and bringing a socio-economic impact (World Bank Group, 2017) to the agricultural sector. If current trends continue, there will be an estimated 11% loss in livestock production by 2050. The World Bank estimates that AMR could cause annual GDP losses of 3.4 trillion and force 24 million more people into extreme poverty by 2030. Low-income countries will be the most affected by this.

Current Issues with Antimicrobial Development

No new classes of antibiotics have been discovered since the 1980s. All antibiotics brought to market in the last 30 years are variations of existing drugs (Ho, 2024). Larger pharmaceutical companies with the financial resources to develop new antimicrobials have, during the last decade, largely discontinued their antibiotic development programmes (Nature News Feature, 2020). Smaller entrepreneurial biotech companies now lead antibiotic research and development; in 2019, it was estimated that small and medium-sized companies accounted for 90% of new antibiotics in development.

With an estimated 10-15 years and over $1 billion in development costs per antibiotic brought to market (Wellcome, 2023), this can be too much of a resource-depleting exercise for many smaller companies. Although many of these smaller companies collaborate with larger pharmaceutical companies for later stages of development, prior to this, they must fund development alone. The high failure rate in bringing antimicrobial products to market, which is quoted as high as 95%, could make or

break a smaller company, so development in this area is a very large risk (Ardal et al, 2019).

If a product is brought to market, it is a struggle to recover the costs. Any effective new products are considered a "last resort" therapy, used sparingly to limit new resistances emerging that would compromise effectiveness (NICE, 2025). Furthermore, the nature of antibiotics and the course of a bacterial infection means that when antibiotics are used, usually only a short course is required. Many illnesses are long-term conditions requiring constant therapy sales, which might be a more tempting prospect for a pharmaceutical company.

These circumstances have resulted in very few approved antimicrobials in the last few years, and not many are currently in the pipeline. This contrasts with an increasingly desperate need for novel drugs to treat bacterial infections. This fact has been recognised by WHO and health authorities alike; Global Leaders approved a political declaration at the United Nations General Assembly High-level Meeting on Antimicrobial Resistance in September 2024 (UN General Assembly, 2024). The WHO also lists priority bacterial pathogens intending to guide investment into R&D of new antibiotics (WHO,2024a). Gram-negative organisms, responsible for 2/3 of multi-drug resistance, sit at the top of this list, posing the greatest threat to human health (Breijyeh et al, 2020). Very few products in the pipeline are targeting these pathogens (WHO, 2024b). Of these, very few are novel, which increases the risk of resistances already existing or easily being developed from existing resistance mechanisms to similar products (Bergkessel, 2023).

Undoubtedly, new classes of traditional agents are needed, with Multidrug resistance now commonplace amongst bacterial pathogens with antibiotic resistance now affecting all antibiotic classes (Jakson et al, 2018). However, given how hard it is to find new antibiotics with new modes of action and the relative ease and speed with which resistances to even novel classes have emerged, it is important that any plausible alternatives are vigorously pursued. Recent advances in several areas of science have given rise to the so-called "non-traditional" antimicrobials. These differ vastly from existing traditional options and are being developed with the problem of AMR in mind (Theuretzbacher and Piddock, 2019).

Non-Traditional Antimicrobials

Traditional agents are typically direct-acting small molecules which inhibit growth or kill pathogens. Non-traditional antimicrobial approaches are diverse and work through other means to influence the course of an infection. This includes prevention, and optimising host immunity, through to directly acting on the pathogen. Whilst many non-traditional agents in development directly act on the pathogen, others have no inherent effect on bacterial growth in vitro. They are considered a promising advance in the fight against AMR as they target microbes in novel ways that reduce the likelihood of sharing resistance mechanisms with existing traditional antibiotics. They also provide a greater challenge to microbes to develop resistance to something which often does not have a direct target of its action. Table 1 describes some of the non-traditional antimicrobials already in development.

Table 1: Summary of the categories of non-traditional antimicrobial therapies currently in development (WHO 2024b)

Category	Function
Bacteriophages	Are bacterial viruses that can cause direct lysis of target bacteria. 13 in clinical pipeline
Antibodies	These can be monoclonal antibodies designed to target virulence factors, or a toxin on the pathogen, and inactivate or neutralise the pathogen. Seven in clinical development
Immunomodulating agents	Change the body's immune response. Pathogen-specific immunomodulators include antibody reagents and vaccines.

	Non-specific examples include cytokines, antimicrobial peptides, certain antimicrobial drugs and Two in clinical development
Microbiome-modulating agents	Modify the microbiome to eliminate or prevent carriage of pathogenic bacteria. Includes live biotherapeutics. Nine in clinical development.
Miscellaneous agents	Do not fit any of the above categories Four are in clinical pipeline

Bacteriophages

The use of bacteriophages (Brives and Pourraz, 2020) to fight pathogenic bacteria has been practised in some areas of Eastern Europe anecdotally for at least the last century. However, research into this area has only taken off in the last 10-15 years due to the emergence of multi-drug-resistant organisms and advances in modern virology. At the time of writing, the Portuguese Health Authority (INFARMED, I.P.) has announced official approval has been granted to the use of phage therapy to combat antibiotic resistant infections alongside a new guidance released entitled 'Guiding Standard on the Use of Compounded Medications for Phage Therapy in the Hospital Context – Magistral Preparations of Bacteriophages' (Technophage, 2024). This decision is a groundbreaking achievement hoped to lead the way for other countries to follow suit.

Bacteriophages (also known as phages) are viruses that strictly infect bacteria (Sawa et al, 2024). As they are specifically targeting bacteria, they can be used to treat or interfere with bacterial infections without direct damage to healthy mammalian or commensal microbial cells. In addition to this, they are able to penetrate biofilms, something traditional antibiotics frequently fail at (Olawade et al, 2024). Recent research into phage therapy has focused on directly and indirectly utilising engineered bacteriophages in order to treat bacterial infections

Lytic phages are those that, in the course of an infectious cycle, destroy their bacterial cell host. This can lead to the possibility that mass bacterial lysis could cause the release of bacterial endo-toxins into the blood, which might result in sepsis, something already seen to occur with traditional bactericidal antimicrobial therapy. Usually, the phage attaches itself to the bacterial cell membrane in a process that is highly targeted (Ranveer et al, 2024). Often, a unique protein on the surface of the bacteria is targeted, a specificity that can be engineered to be more or less broad. Some phages might recognise a bacterial species, and others might only attach to some targeted genetic variants of that strain. This leads to the potential for targeting specific pathogens and leaving the microbiome intact, but also within those pathogens, perhaps even targeting those drug-resistant or other unique pathogenic variants (Olawade et al, 2019).

Table 2: Current approaches in phage therapy (Theuretzbacher and Piddock, 2019)

Approach	Composition
Fixed phage cocktails	Fixed composition of lytic phages to achieve a broad host range of a bacterial species
Individualised phage cocktail	The lytic phages are stored individually in a phage bank with established QC. Only the most active phages based on rapid diagnostic tests are selected for an individual patient
Genetically engineered phages	Engineered phages with improved or specific characteristics
Genetically engineered non-replicating phages as vehicles - phagemids	Engineered phages that express additional antimicrobial peptides or protein toxins leading to rapid, nonlytic bacterial death. May deliver CRISPR-CAas3 genes directly into bacteria

Phage products, eg endolysins	Natural or recombinant cell wall hydrolysing phage-based enzymes. Endolysins against *Staphylococcus aureus* are in clinical development

Phages must be active against >90% of strains within a bacterial species in order to treat an infection without the emergence of bacterial resistance, which might occur with the use of a single phage type. Cocktails of different phages are additionally therefore used for therapy both to increase the spectrum of activity, as well as making it extremely unlikely resistance can be developed against a variety of phages with different targets (Theuretzbacher and Piddock, 2019). The need to use multiple phages however, introduces the possibility of undesired interactions between phages within a mixture, and also with the host immune system (Molina et al, 2022). In addition, the use of a large cocktail of different phages introduces manufacturing and quality control issues, as interactions between different phages can be difficult to predict in terms of synergistic and antagonistic effects, as well as the unique pharmacokinetics (PKs) and pharmacodynamics (PDs) of phages making dose-finding for cocktails a challenge (Theuretzbacher and Piddock, 2019). As a result, developers are trying to reduce the number of phages in fixed cocktails, but this in turn will reduce the range of susceptible bacteria.

Patient-specific cocktails may help to address this issue. These would contain only the one or two most appropriate phages against the specific pathogen affecting one individual - essentially personalised phage therapy from a library of pre-approved phages. However, this approach also relies on the use of new, fast diagnostic tools that are not yet typically available in clinical practice. In addition, modern genetic engineering tools for patient-specific phages with improved and highly specific features would be necessary (Theuretzbacher and Piddock, 2019). Both of these requirements might make these therapies prohibitively expensive to many facilities providing healthcare.

Another indirect way in which phages are being considered for therapeutic use is in utilising non-lytic phages simply as vehicles, known as phagemids. These phagemids would infect bacterial target cells and deliver DNA, resulting in the target bacteria expressing antibacterial proteins or genes. These then go on to cause non-lytic bacterial death, thereby avoiding the risk of endo-toxin release that might accompany lytic phage use. These phagemids can be as targeted and engineered as lytic phages, while avoiding potential side effects caused by mass bacterial cell lysis within the body (Krom et al, 2023).

The final way phages are being researched as potential therapies in bacterial infections is indirectly using phage-derived products. This includes products such as endolysin enzymes, which are bacteriolytic on contact and can be highly specific. Lysins usually work from inside the cell, but recombinant lysins have been developed to be lytic from the outside of the cell, something that is far easier to achieve with Gram-positive bacteria. At the moment, this leaves a potential gap in much needed treatments for Gram-negative bacteria, although the area of phage therapy is still rapidly developing (Liu et al, 2023).

Monoclonal Antibodies

As of 2024, 14 human monoclonal antibody (MAb) products are in development for infections caused by the seven ESKAPEE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp* and *Escherichia coli*) and *Clostridioides difficile* (Ho et al, 2024). Monoclonal antibodies are specific immune cells that can be administered, usually via an infusion, during acute infection and can have an immediate effect in fighting infections. This is still a relatively new field when discussing the treatment of bacterial infections (Troisi et al, 2022), although there are some examples of recent use. Since 2016, a MAb has been available to treat anthrax in combination with traditional antibiotics (Zurawski and McLendon 2020) and MAbs were employed in the treatment of COVID-19 (Mornese Pinna et al, 2021).

Monoclonal antibody treatments are highly specific for their target, allowing them to act on pathogenic bacteria without targeting the normal human microbiome or

host cells during treatment. They have been shown to work rapidly to produce sustained antimicrobial activity and have a very small risk of resistance development. They utilise several naturally occurring immune mechanisms including enhanced opsonisation for phagocytosis, direct bactericidal activity, complement deposition, anti-virulence, and toxin neutralisation, with plenty of options clinically. A summary of the different targets of antibody therapy for bacteria can be seen in Table 3 below.

Table 3: Summary of current Mab targets for bacteria (Motley et al, 2020)

Target	Pros	Cons
Bacterial toxins	Virulence inhibition Structure conservation Easily accessible	No direct antibacterial action
Surface proteins	Easily accessible Direct antibacterial action	Extensive variability
Polysaccharides	Virulence inhibition Direct antibacterial action Structure conservation	Limited accessibility

This does however provide the possibility that there could be some immunogenicity associated with MAb use, which has been seen with monoclonal antibodies used for a number of indications. Molecular engineering technologies have helped to reduce immunogenicity and enhance MAb effects in existing licensed MAb therapies (Troisi et al, 2022). This will only improve as newer techniques emerge, and with more research into the immune system and how it interacts with its targets and host immune cells.

The administration of MAbs to patients diagnosed with specific infections should also limit selection pressures against these specific targets. This would ensure that the efficacy of the target is maintained long-term against resistance. Recent advances in the engineering of MAbs have allowed researchers to create immunologic molecules with improved tissue penetration, enhanced recruitment of a range of immune cells, multiple variable regions with different specificities, and even the ability to assist with the precise delivery of other drugs that would be toxic systemically (Motley and Fries, 2017).

A number of studies have found not only that monoclonal antibodies are effective in themselves, they also work well in combination with traditional antibiotics to increase their effectiveness. This fact is already being utilised with several antibody-antibiotic conjugate products in development. These are composed of monoclonal antibodies that are covalently linked to potent antibiotics. These conjugates facilitate selective binding to specific antigens and direct delivery of antibiotics to the infection site (Zurawski and McLendon 2020).

There are, however, some downsides and challenges to overcome (Ho et al, 2025). The practical difficulties lie in the need for rapid, highly accurate diagnostic technology to accompany MAb therapy. The kind of specificity MAbs allow mean that this is essential to the success of MAb therapy, or it risks the MAbs not working against their target. This then increases the cost in terms of equipment and the technical skill involved in staff preparing and administering these therapies. For many less developed countries, this would simply not be an option as a standard treatment, and indeed for many smaller facilities in developed countries too. Finally, the stability of MAb therapies can be poor (Basle et al, 2020). We have seen this with the stability of vaccines that are also proteinaceous in nature, and how difficult it can be to use these therapies when their ability to work requires fastidious care, storage, and temperature control (Dumpa et al, 2019). This is also not possible in some areas of the world, even if the cost allowed.

Immunomodulatory Agents

Immunomodulating agents help to treat infectious diseases by utilizing the antimicrobial effector mechanisms of the immune cells. They therefore act on the host rather than the pathogen, and are usually products of the immune system. The immune system is complex and multifactorial, which provides footholds for many possible types of immunomodulatory intervention, at different stages of the infection and can roughly be divided into those that are either pathogen-specific, or non-specific effectors (Pirofski and Casadevall, 2006). Potential immunomodulating agents may encompass a great diversity of drug classes, targeting a variety of biological processes that modify a range of host cell functions (Theuretzbacher and Piddock, 2019). The innate and adaptive immune responses can be harnessed, with a range of different cell mediators being researched as potential therapies. These include natural killer cells, macrophages, neutrophils, T-helper cells, cytotoxic T-cells, and mediators involved in the stimulation of the inflammatory response (Strzelec et al, 2023).

Immunomodulators are also not a new area of treatment; they have been used successfully over the last decade in areas such as the treatment of tumours and *Mycobacterium tuberculosis*. In many cases, drugs already approved and on the market for other indications will be able to be re-purposed to act as immunomodulators in combination with other therapies (Konwar et al, 2022). Some examples of where this has already occurred include NSAID's, statins, Linezolid, and Metformin. The properties and mechanisms that these drugs use to enable them to function well for their original indication may have beneficial effects on the site of an infection. For example, NSAIDS aid in pain relief and reduction of inflammation and fever by inhibiting the synthesis of prostaglandins, which mediate the inflammatory process. They have been successfully re-purposed for the treatment of TB by reducing the inflammation caused by the influx of monocytes, lymphocytes and neutrophils. NSAIDs have been shown to attenuate the disproportionate inflammatory response caused by migration of these cells in active TB, and contributed to an improvement in the disease outcome (Samreen et al, 2021).

It is intended that these drugs will be used in combination with traditional antibiotics by creating an environment that aids the body's natural immune response. This is achieved by exploiting natural mechanisms to enhance the therapeutic benefit of an adjuvant while limiting inflammation-induced tissue injury. A range of potential immune modulators have been proposed, including toll-like receptor (TLR) agonists to stimulate the innate immune responses against bacterial infections, NOD like receptor agonists, and innate defence regulator peptides (Hancock et al, 2012).

There are already some examples used in the treatment of bacterial infections; for the treatment of tuberculosis, antimycobacterial immunity in the body can be enhanced by many immunomodulatory agents such as arginine, active vitamin D3, 1,25-dihydroxyvitamin D3 (vit D), or histone deacetylase (HDAC) inhibitors such as sodium phenylbutyrate (PBA) (Konwar et al, 2022; Muvva et al, 2021).

However, one reason this strategy has not seen many drugs approved for bacterial indications is that the effects of immunomodulators can be inconsistent when used alone. They may also have different effects depending on which products they are used alongside. This has made them difficult to assess generally during clinical trials (Strzelec et al, 2023). There is also the fear that the use of immune-stimulating products may induce catastrophic effects, such as cytokine storms. More research needs to be undertaken to understand the immune system and how exactly it is stimulated to be able to use immunomodulators with confidence (Zhang et al, 2023). Often the mechanisms and effectors involved, and how they interact with each other, are not fully understood; just the resulting immune response itself.

Immunomodulating agents open up a large variety of cells and effectors that can be harnessed to fight infection. They have already been shown to make other therapies more effective when used in conjunction. This may help to turn the tide on the course of infections by optimising natural immune responses the body is already capable of. In addition, without directly targeting the pathogen, there is no specific mechanism.

Microbiome Modulating Agents

Microbiome-modulating agents also work on the host environment, in this case, the commensal organisms that comprise a healthy human microbiome. These treatments seek to provide the healthiest environment to prevent and help fight any bacterial pathogens. The overall aim is to eliminate or prevent the carriage of resistant or pathogenic bacteria in the first place (Montassier et al, 2021). The gut microbiome is a reservoir for the potential spread of resistance genes from commensals to pathogens, termed the gut resistome. Microbiome modulator approaches include probiotics, prebiotics, synbiotics, metaprobiotics, faecal microbiota transplantation (FMT), and live biotherapeutic products (LBP). Research in this area has been increasing in recent years with a range of diseases treated successfully by microbiome modulators including pneumonia, the common cold, influenza and new coronavirus infections (Wang et al, 2024).

With respect to AMR, faecal microbiota transplants have seen particular success in terms of products brought to market. The 2023 WHO report into Antibacterial agents in clinical and preclinical development lists three microbiome-modulating products for the treatment of recurrent *Clostridium difficile* infection (CDI) that have received marketing authorization (SER-109, BB128 and RBX2660 in the US, Australia, and the US respectively) since 2022. At the time of publishing the report, there were 9 products in clinical trials, eight of which were live biotherapeutics for the treatment of recurrent CDI (WHO, 2024b).

Faecal transplants have been shown to successfully restore a healthy gut microbiome to a sufferer of recurrent CDI, with one study suggesting a 90% cure rate, with no relapse within 10 weeks of therapy (Cammarota et al, 2017). After antibiotic treatment of an initial CDI infection, colonisation by *Clostridium difficile* often occurs. Treatment of CDI often involves the use of broad-spectrum antibiotics, and these can have a detrimental effect on the healthy bacteria comprising the microbiome. When the latter are killed off, the gut is re-colonised, often with the same *Clostridium difficile* bacteria, which leads to recurrent infections. This is also an extreme lesson in what can occur if the microbiome is disrupted (Song and Kim, 2019). This important component of the gut will contribute to healthy digestion while preventing colonisation by harmful pathogens.

In addition to preventing harmful colonisation, several commensal organisms, such as Lactobacillus and Bifidobacterium, have been shown to control inflammation by modulating immunity, thereby limiting tissue damage associated with infections (Wang et al, 2024). Microbiome modulating agents look to ensure the microbiome consists of these healthy bacteria. This, in turn, will aid digestion, modulate immune reactions, and prevent colonisation with harmful bacteria. It may, therefore, be a key factor in future prevention of or aiding recovery from AMR infections.

Miscellaneous Agents

This somewhat poorly defined group consists of other antimicrobials that inhibit the production or activity of pathogen virulence factors in various ways. The mechanisms of action of individual therapies within this group are various, and they include toxin production and virulence factor secretion, impeding bacterial adhesion to host cells and biofilm formation, interrupting or inhibiting bacterial communication, and downregulating virulence.

Four antibacterial non-traditional agents currently in the pipeline fall into this group. (Table 4). Two inhibit biofilm formation; one is being investigated in the treatment of *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis (CF), and the other is an adjunct treatment for joint infections following total knee arthroplasty. Another works by binding and neutralising bacterial toxins when used in association with antibiotics and is currently being investigated in severe bacterial pneumonia in a Phase 2 trial. The final product is an inhalable drug, which acts as an iron analogue to starve bacteria of iron and is being investigated for use in lung infections in CF patients (WHO, 2024b). If brought to market, these products consisting of a diverse range of drug types - and mechanisms of action - could add great value to the success of existing therapies without further exacerbating AMR.

Table 4: Summary of Miscellaneous Agent Non-Traditional Antimicrobials currently in the development Pipeline (WHO, 2024b)

Name	Phase	Class	Route	Indication
OligoG	2	Anti-biofilm	Inhalation	Chronic *P. aeruginosa* lung infection in CF
PLG0206	1b/2	Anti-biofilm	Irrigation	Prosthetic Joint infection
CAL02	2	Broad spectrum anti-toxin liposomal agent and nanoparticle	IV	*S. pneumoniae*
AR501 (Panaecin)	1/2a	Anti Iron	Inhalation	*P. aeruginosa*

Regulatory Implications

The novel nature of many of these approaches means there is a lack of evidence to support the development of regulatory guidance. The need for innovations in regulatory practice to match innovations in scientific research and development is clear to health authorities in the EU and UK.

In the UK, the MHRA is actively attempting to engage with innovators as early as possible to identify products in development and prepare appropriate guidance before a submission for authorisation is made.

The EMA is also clear that early interaction is key to optimal development and timely approval of antimicrobial medicines. AMR is addressed in the draft joint EU network strategy up to 2028, published by the EMA and the EU Heads of Medicines Agencies (HMA). Within the strategy, early support is offered to the developers of new antimicrobials via the Emergency Task Force (ETF) and the Innovation Task Force (ITF). These groups allow enhanced access to regulators and scientific support to facilitate development and licencing (EMA and HMA, 2024).

Conclusion

The emergence of antimicrobial resistance (AMR) presents an unprecedented global health emergency. Antimicrobials, since their discovery and widespread use, have become the cornerstone of modern medicine – something now threatened by the ongoing battle with AMR., and that with our current arsenal of approved traditional antimicrobials, we appear to be losing.

Political leaders have recognised the severity of the problem with policy changes designed to incentivise development. However, the discovery of new classes of antibiotics is notoriously challenging, and few have made it to market in recent years. Those that do will always be vulnerable to the development of resistance by target organisms. It can be hoped that improved incentives will support the continued development of antibiotics, but novel approaches are also required. More widespread vaccination and the availability of rapid diagnostic and antibiotic sensitivity tests are a crucial part of the picture, as are the numerous non-traditional treatment approaches described above.

The pace of scientific innovation in this field is rapid and has outstripped the development of regulatory guidance. Recognising this, regulators in the EU and the UK are clear that they do not want to contribute to a delay in getting these much-needed medicines to patients and strongly encourage developers to engage with them early. In this way, it is hoped that regulatory and scientific development will move hand in hand to bring new medicines to market as quickly as possible. With a whole new range of potential therapies in the development pipeline and the issue finally becoming a priority for world leaders and Health Authorities alike, it is hoped

we can begin to get a grip on the spread of the multi-resistance bacterial infections which threaten to pull us back into the dark ages of medicine.

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We develop and execute innovative phase-appropriate regulatory strategies, providing comprehensive support from early development to post-licensing activities for medicinal products and medical devices. Our team comprises nonclinical, CMC, clinical and MedTech consultant experts from pharmaceutical, medical device and regulatory agency backgrounds. We have proudly served companies of all sizes and backgrounds in various regulatory jurisdictions.

At DLRC, we have a long track record of successful interactions with regulators and are experienced in early dialogue. We can help you plan your approach and get the most out of these interactions. Contact us at hello@dlrcgroup.com to discover how.

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