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A call for action to the biomaterial community to tackle antimicrobial resistance

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The global surge of antimicrobial resistance (AMR) is a major concern for public health and proving to be a key challenge in modern disease treatment, requiring action plans at all levels. Microorganisms regularly and rapidly acquire resistance to antibiotic treatments and new drugs are continuously required. However, the inherent cost and risk to develop such molecules has resulted in a drying of the pipeline with very few compounds currently in development. Over the last two decades, efforts have been made to tackle the main sources of AMR. Nevertheless, these require the involvement of large governmental bodies, further increasing the complexity of the problem. As a group with a long innovation history, the biomaterials community is perfectly situated to push forward novel antimicrobial technologies to combat AMR. Although this involvement has been felt, it is necessary to ensure that the field offers a united front with special focus in areas that will facilitate the development and implementation of such systems. This paper reviews state of the art biomaterials strategies striving to limit AMR. Promising broad-spectrum antimicrobials and device modifications are showcased through two case studies for different applications, namely topical and implantables, demonstrating the potential for a highly efficacious physical and chemical approach. Finally, a critical review on barriers and limitations of these methods has been developed to provide a list of short and long-term focus areas in order to ensure the full potential of the biomaterials community is directed to helping tackle the AMR pandemic.

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Introduction

Antibiotics are a precious resource capable of specifically targeting microbial infections with little impact on endogenous human cells. Since the discovery of penicillin, antibiotics have been coined 'wonder drugs', helping to save hundreds of millions of people.[1,2] Today the use of antibiotics is broad and encompasses almost every aspect of our society, including healthcare, the food industry and agriculture. This makes it difficult to imagine a world devoid of such fundamental substances. Nevertheless, as microorganisms continue to develop resistance mechanisms to the use of antibiotics, termed antimicrobial resistance (AMR), this future may become a reality. This includes a rise in the spread of resistance to widely used antibiotics such as vancomycin in *Enterococci* and an increasing number of pan-drug resistant pathogens.[3–5]

Predictions of the global socioeconomic impact caused by AMR have been estimated as $100 trillion per annum with a potential loss of 10 million lives annually by 2050.[6] Although these predictions have been labelled as uncertain and pessimistic,[7] AMR is certainly one of the great challenges of our era. The hazard posed by AMR has led to global action since 2001,[8] however, it was not until the Global Action Plan on

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Antimicrobial Resistance was adopted at the 68th World Health Assembly in Geneva (2015) that positive developments have been felt.[4,9] It is clear, that if we are to prevent a 'post-antibiotic' era then action must be taken at all levels and across multiple disciplines. This review focuses on steps that the biomaterials community, as a key field of innovation for antimicrobial substances, may take to help tackle AMR.

Bacteria have been present on this planet for 3.5 billion years, capable of resisting and flourishing in extreme conditions where more complex life is not able to prosper.[10] This adaptability stems from their large populations, rapid division cycles, and the ability to transfer genetic information between species.[11] As a consequence, bacteria have evolved a series of complex resistance mechanisms against toxic substances (Fig. 1a).[12,13] These tools provide a natural resilience that can overcome antibiotic therapies, a problem noticed by Alexander Flemming shortly after the discovery of penicillin, which led to a warning on handling antibiotic dosages and treatment periods.[14] Whilst the mechanisms of AMR demonstrate the adaptability of bacterial species, human overuse and misuse of antibiotics has been largely at fault for selection of resistance mutants and their expansion to high prevalence.

Antimicrobials work by inhibiting various essential cellular processes and pathways. Specifically, antibiotics have class dependant modes of action that precisely target an aspect of a bacterial cell's ability to survive (Table 1).[15] Most antibiotic classes were discovery between 1928 and 1987 with no new categories reaching the market since (Fig. 1b). In recent years, handling of antibiotics has been poorly managed, with these substances rapidly entering mass production in multiple industries and little control over availability, indications and dosage regimes. Due to this extensive availability and lack of oversight or control on application there has been a great deal of drug overuse which has exacerbated the global AMR problem.[16] Understanding of the evolution of resistance in relation to selective pressures has improved since antibiotics were first employed. Specifically, the critical importance of delivering sufficient and lasting antibiotic concentrations to completely eradicate an infection and limiting resistance is today well appreciated. Now more than ever it is clear that the development of novel antimicrobial substances and delivery systems is vital to the containment and prevention of AMR, an area in which the biomaterials field is well placed to have a massive impact.

Table 1 The mechanism of action of common antibiotic classes[19]

Mechanism of action	Antibiotic classes
Inhibition of cell wall synthesis	Beta-lactams Glycopeptides Cyclic lipopeptides
Inhibition of protein synthesis	Tetracyclines Aminoglycosides Oxazolidinones Streptogramins Ketolides Macrolides Lincosamides
Inhibition of DNA housekeeping	Fluoroquinolones
Inhibition of RNA synthesis	Rifampin
Inhibition of folic acid synthesis	Sulphonamides Trimethoprim
Disorganisation of the cell membrane	Polymyxins

Once novel antimicrobial technologies are discovered, it is necessary to begin the long and risky endeavour of gaining regulatory approval. The prospective damage that potentially hazardous antibiotics could cause to human health has led to a policy of safety first from the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). As a result, the process of taking a newly discovered drug from the laboratory to the market requires extensive preclinical data and three phases of clinical trials before registration of the new product.[20–22] Analysis of these pipelines shows that navigating these policies and obtaining regulatory approval can take more than a decade and cost up to $1 billion,[20,21,23] generally making it unfeasible for small and medium R&D companies. Thus, antibiotic research has historically been driven by large medical corporations, however, today few incentives are

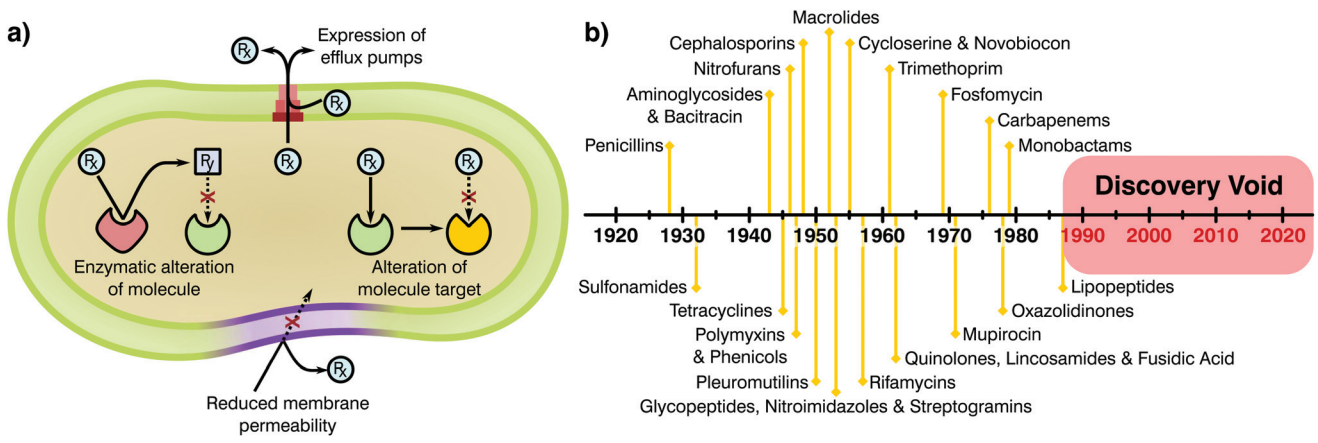

Fig. 1 (a) Mechanisms attributed to antibiotic resistance, adapted from ReAct[17] and (b) timeline of antibiotic class discovery showing the discovery void of marketed classes.[17,18]

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in place to encourage their involvement.[21] The main groups of novel antimicrobials were found early after the discovery of penicillin, with most antibiotic classes obtained by empirical screening more than 50 years ago[24–26] for which oxazolidinones and cyclic polypeptides were discovered last in the late 70s and 80s, respectively (Fig. 1b).[25,27] Thus, all "low hanging fruit" in the production of antimicrobial derivations and combinations may have been tapped. Since the discovery of new classes has slowed, progress has often been made by modifying existing ones to escape class-related resistances[28] and the combination of several marketed drugs (*i.e.* "protecting drugs")[29] to prevent AMR while minimising the risks involved with the development of novel drugs. Although this approach has led to many new antibiotics entering the market, typically the 'arms race' continues with resistance emerging to each new derivative necessitating further development and refinement.[29,30]

The relatively low price and treatment period associated with antibiotics requires a significant, immediate demand of a new drug for a company to invest in its development. Although the number of patients requiring novel drugs for AMR is on the rise, currently the 5% increase in Health Acquired Infections (HAI) is not sufficient to make such an endeavour economically attractive.[21] To put this into perspective, a study by the London School of Economics has indicated that the typical net present value (NPV) of an antibiotic is in the region of −$50 million compared, for example, to the development and marketing of drugs for musculoskeletal conditions, which have an NPV of $1.15 billion.[31] These factors and statistics reveal that only 1 of 5 infectious disease products that start clinical trials will obtain regulatory approval.[26,32,33] Thus, leading to a paradox where new antibiotic drugs are critically needed, while the antibiotic pipeline continues to run dry. As new antimicrobials are found, experts should be aware of the chasm between laboratory discovery and marketing to ensure that promising technologies are pushed forward. This requires building up a strong case to capture investors and relevant stakeholders, for which it is necessary to perform relevant tests to governmental approval and the correlation between *in vitro* and *in vivo* models.

The number of R&D teams experienced in discovery of antibiotics has been diminishing over the years as a direct consequence of mergers in large pharmaceutical companies.[26,33] Currently only 4 large pharmaceutical companies (Merck & Co., Roche, GlaxoSmithKline and Pfizer) still have active antibiotic programmes with a limited presence of small-medium sized enterprises (SMEs).[34] Consequently, there has been a slow and steady loss of knowledge and capacity in antimicrobial development that, coupled with the difficulties inherent to the development of novel antimicrobial substances, has pushed forward translation over innovation.

Sadly, this change in paradigm is not restricted to the antibiotic pipeline and has further been encouraged through modifications in the regulatory approval pipeline. Medical device regulations have changed over the years, leading to the appearance of simpler approval guidelines, such as the premarket notification (PMN) or 510k by the FDA.[23] These regulatory pathways rely on the existence of predicate devices that are legally marketed, with similar intended uses, documented proof of substantial equivalences and no detrimental safety and effectiveness differences with the novel product. These normally require an investment between $1–5 million over 3–6 years,[23] contrasting with the $45 to $150 million of capital spent over 5–8 years[35] for the more complex Premarket Approval (PMA) where no predicate can be found. This reduction in economic investment coupled with the risk of obtaining PMA approval (only 1% finally enter the market)[23] has led the research community to focus their efforts on developing novel delivery systems of already approved substances or reworks of marketed products. This prevalence of translation has restricted innovation primarily to SMEs and universities, enhancing the need for collaboration between the biomaterials community and industrial partners.

Over the last two decades, the danger posed by AMR in society has been realised, making regulatory bodies take approaches to contain and control AMR drivers.[16,36–39] Nevertheless, most changes are slow or must still deal with bureaucratic loops, which limits their application and contributes to the increasingly pressing hazard brought by antibiotic resistant bacteria.[23] This slow pace of governance from international regulatory bodies further strengthens the importance of tackling AMR at all levels of the pipeline, including fields that may change the state of play such as biomaterials science. As the main source of innovation, the research community has taken a lead in understanding AMR, their mechanisms and developing novel therapies.

More than 70 000 publications linked to AMR have been issued globally, with 8575 made available solely in 2019.[40] More interestingly, roughly 8% of these can be correlated with the analysis and advancement of better antimicrobials and therapies by the biomaterials community, showcasing an increasing involvement (Fig. 2). Since the dissemination of the "Global strategy for containment of antimicrobial resistance" by the World Health Organization (WHO) in 2001,[8] the number of research publications developed by the biomaterials science field on AMR has risen from 23 to 676 in the 2001 to 2019 period (Fig. 2a). Alongside this the diversity of fields that biomaterials science contributes to has evolved, with microbiology being the largest sector showcasing a willingness to support AMR solutions (Fig. 2b).

The aim of this review is to detail the current state of technologies developed by the biomaterials research community to tackle AMR. Two case studies are presented to highlight innovation that is being driven to improve topical and local delivery of antimicrobials. Finally, this work provides a concise list of recommendations to ensure that progress of novel technologies in the AMR field continues and that these game-changing approaches may effectively infiltrate the marketplace.

Novel antibiotics

Since the void of class discovery, numerous analogues of existing antibiotics have successfully been marketed, which has pro-

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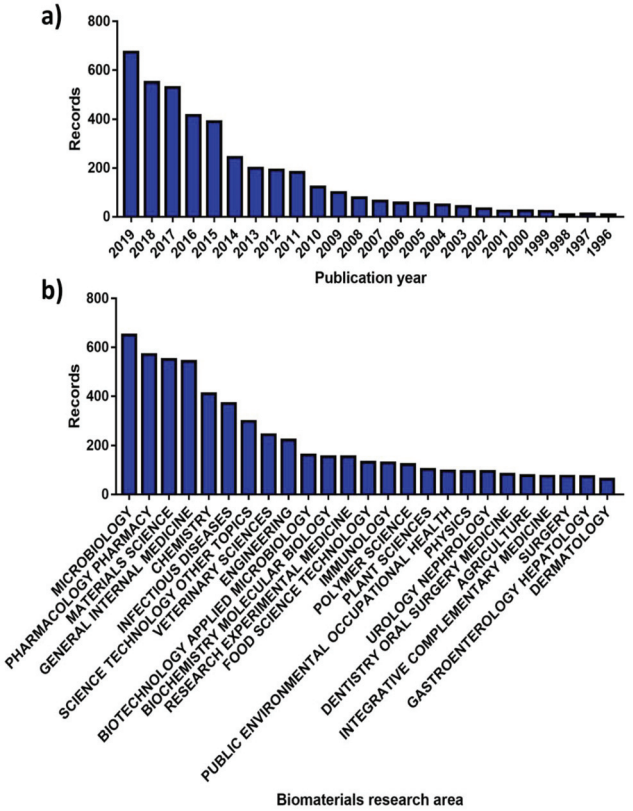

Fig. 2 Number of publications for AMR materials ordered by (a) year and (b) research area. Source "Web of Science".

vided a short-term solution to the development of drug resistant bacteria.[41] The limited effect of such strategies has already been highlighted by Watson,[42] who found that 50% of European deaths associated with infection in 2008, may have been due to resistant bacteria. More recent studies suggest that this trend is on the rise with Cassini *et al.*[43] stating that the burden of resistant infections is now closer to 75% of the total deaths caused by infection in Europe. There is also further concern surrounding the rise of last-line antibiotic resistant bacteria, with 35% of total deaths related to infection in 2019 caused by these species.[42] Thus, it is clear that new antimicrobials are needed.

Further study within medical services has shown that only 17 different microorganisms, including *Enterococcus faecium, Staphylococcus aureus*, *Klebsiella pneumonaie, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Escherichia coli* (ESKAPE pathogens) account for up to 87% of all HAI.[44,45] With AMR increasing and the development of new antibiotics grinding to a halt, to help drive and guide development the WHO published a list of 12 priority pathogens in 2017 (Table 2).[46] These are the species most likely to cause a significant impact on human health if resistance continues to develop on its present trajectory. The pathogens are graded from critical to medium with those in the critical category resistant to multiple antimicrobials, including carbapenem (a 'last resort' antibiotic), posing an imminent threat to health.[46,47] In addition to the organisms prioritised by the WHO, the Centre for Disease Control and Prevention (CDC) also identifies *Candida auris* and *Clostridioides difficile* (*C. difficile*) as urgent threats to healthcare.

Table 2 World Health Organisation priority pathogens[46]

Critical
Acinetobacter baumannii – carbapenem resistant
Pseudomonas aeruginosa – carbapenem resistant
Enterobacteriaceae – carbapenem resistant, extended-spectrum beta-lactamase producing (ESBL)

High
Enterococcus faecium – vancomycin resistant
Staphylococcus aureus – methicillin resistant, vancomycin intermediate and resistant
Helicobacter pylori – clarithromycin resistant
Campylobacter spp. – fluoroquinolone resistant
Salmonellae – fluoroquinolone resistant
Neisseria gonorrhoeae – cephalosporin resistant, fluoroquinolone resistant

Medium
Streptococcus pneumoniae – penicillin non susceptible
Haemophilus influenzae – ampicillin resistant
Shigella spp. – fluoroquinolone resistant

According to The Pew Trust, as of December 2019 approximately 41 new antibiotics are in Phases 1–3 of development.[48] This suggests that the drug development pipeline has been reinvigorated, although the number of substances that gain approval may of course be much lower. Historic data suggests only 20% of these new antibiotics will make it to market[49] with only 11 of these being a novel class or targeting a new mechanism. Furthermore, only 6 of those have expected activity against WHO or CDC priority pathogens (Table 3),[48] limiting the prospects of novel antibiotics available to tackle AMR.

The discovery of penicillin later led to the creation of many derivatives, built with the intention of circumventing the issue of penicillin-resistant bacteria.[50] Further advances were also made in the development of antibiotics delivered in conjunction with anti-bacterial resistance factors. Such an approach was taken by adding clavulanic acid, which inhibits beta-lactamase resistance, to amoxicillin.[51] However, there is a limit to the number of different analogues that can be synthesised from a single chemical core and even more so on those that can counteract bacterial resistance mechanisms. Many other antibiotics have undergone analogue development, with some more amenable than others.[52] Beta lactams have been the most successfully derived antibiotics with many analogues containing penicillin or cephalosporin cores, although the quinolone and aminoglycoside classes have also provided numerous alternatives.[19] Unfortunately, rapid evolution and development of bacterial resistance has been shown in all cases, negating the effects of even the most ingenious medicinal chemistry solutions.[19,52]

Biomaterials strategies

As previously highlighted, there has been a global culture of misuse and overreliance on antibiotics, surrounded by a

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Table 3 Novel antibiotic classes currently in global clinical development phases[48]

Drug name	Drug class	Target	Activity against ESKAPE pathogens?	Activity against WHO or CDC priority pathogens
Gepotidacin	Triazaacenaphthylene	Type II topoisomerase (novel A subunit site)	Yes: *S. aureus*	Yes: Drug-resistant *N. gonorrhoeae* Possibly: ESBL
Ridinilazole	Bis-benzimidazole	Inhibition of cell division and reduction of toxin production	No	Yes: *C. difficile*
Zoliflodacin	Spiropyrimidinetrione	Type II topoisomerase (GyrB)	Yes: *S. aureus*	Yes: Drug-resistant *N. gonorrhoeae*
MGB-BP-3	Distamycin	DNA minor groove binder	Possibly: *E. faecium, S. aureus*	Yes: *C. difficile*
CRS3123	Diaryldiamine	Methionyl-tRNA synthetase	Yes: *E. faecium*, *S. aureus* Yes: *C. difficile*	
Ibezapolstat (ACX-362E)	Dichlorobenzyl guanine (DCBG)	*C. difficile* DNA polymerase IIIC	No	Yes: *C. difficile*

'*magic bullet*' ethos where these compounds were viewed as the only solution to microbial infections. Nonetheless, the pipeline for novel classes of antibiotics is very poorly populated, limited by regulatory processes and the complex mechanisms behind antibiotic resistance. The development of next generation antibiotics is vital to the future of medicine; however, other alternatives and methodologies must be employed in order to both reduce the use of antibiotics and slow the development of resistance. In this regard, the biomaterial community has a long history of developing and innovating solutions to healthcare challenges. Current ongoing research is focused in various different areas including the development of alternative antimicrobials, modification of device surfaces and the improvement of delivery systems (Fig. 3), posing a prime example of game-changing research that this community has to offer against AMR emergence.

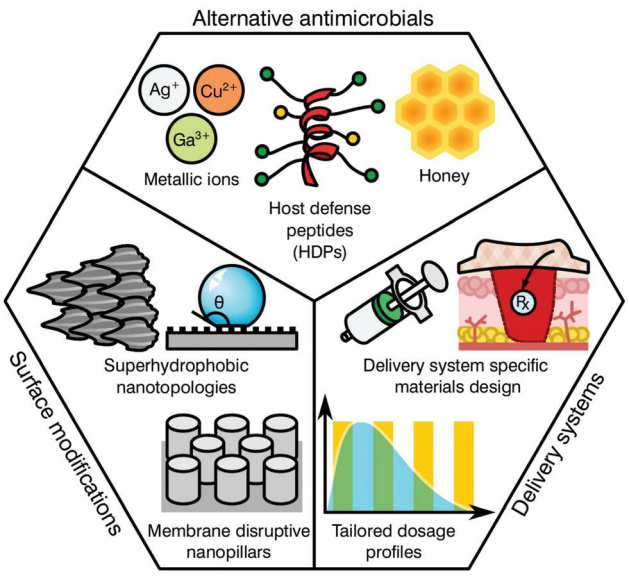

Fig. 3 Biomaterial driven strategies for reduction of antimicrobial burden and AMR acquisition.

Alternative antimicrobials

The goal of developing antimicrobial materials is to produce a biocompatible product adept at inhibiting or killing microorganisms that may colonise the surface of a material or the surrounding area without the development of resistance. Before the discovery and introduction of antibiotics in medicine, natural antimicrobials such as metallic ions and honey were routinely used for the treatment and prevention of infection, with use dating back millennia.[53–55] During the upcoming of the antibiotic era these substances where rapidly substituted, however, renewed interest in such materials is motivated by a hope to reduce the current burden of AMR on global healthcare.

Unlike traditional antibiotics that have specific modes of action and provide an ease of progressive resistance, both antimicrobial metallic ions and honey target multiple cellular processes and lead to pleiotropic effects within the target organism.[56–58] In the case of metallic ions, it has been shown that these certain elements, including silver, copper or arsenic, are capable of interfering with enzyme activities, disrupting membrane functions or damaging DNA, complicating resistance development.[59,60] For most transition metals, this is further enhanced by involvement in reactive oxygen species (ROS) generation, which elicit its antimicrobial action through reactions with thiol groups, oxidation of cell walls and membranes, inhibition of protein synthesis and disruption of electron transport.[61–65] These mechanisms have encouraged research on transition metals of the d-block, (*i.e.* Cu, Zn, Ag, Cd) and other metals and metalloids from groups 13–16 (*i.e.* Al, Ga, Ge, As).[60] Nonetheless, the potential toxicity of such elements to human tissue has limited the applicability of most metals. This is the case for copper, with surfaces of the pure element capable of killing bacteria in mere minutes.[66] However, its prospective cytotoxicity has reduced its wider implementation, limiting it to niche uses like touch surfaces.[55] Other antimicrobial metals with high potency that are safer to the human body have been historically preferred, silver being the most prominently used in healthcare applications.[67]

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More recent developments have seen the formulation of other antimicrobial compounds for which polymers and peptides have awakened the interest of the biomaterial community. Antimicrobial polymers are emerging within the biomedical field as a direct consequence of their wide applications in the treatment and prevention of infection, either alone or in conjunction with other active substances.[68] The mechanism of action is dependent on formulation; however the majority of polymers interact with the charge on the surface of the microbial cell, disrupting transport, inhibiting protein synthesis and in some cases stripping the membrane completely causing contents leakage.[69] Common antimicrobial polymers include chitosan, heparin, ε-polylysine, polyacrylamides, polyacrylates, polysiloxanes, polyionenes and polyoxazolines for which thorough reviews are available in the literature.[70,71]

Similar to the mechanisms of action for antimicrobial polymers, antimicrobial peptides (AMPs) tend to target the cell membrane of microbes, however, they may also disrupt cellular metabolism and target components within the cytoplasm.[72] AMP's are usually amphiphilic consisting of both hydrophilic and hydrophobic groups. This grants the molecule solubility in aqueous environments and allows passage through lipophilic membranes[73] with different formulations available (Table 4).

The attractiveness of AMP's as versatile antimicrobial agents has been further increased by their influence in various biological processes, including immune and anti-inflammatory responses, causing a recent shift in terminology to host defence peptides (HDPs) to recognise their multi-functional nature.[74] As a consequence, the development of HDPs has progressed from simple contact killing or biocide releasing materials common in first generation polycations derived from quaternary ammonium compounds (QACs)[75] to more complex multifunctional antimicrobials such as multifunctional hyperbranched polyaminoglycoside for improved antibacterial activity, biocompatibility, and gene delivery.[76] A specific notable example of the flexibility of more modern HDPs can be seen in the nylon-3 polymers development by Liu *et al.*[77] These multifunctional polymers are capable of fine tuning the hydrophobicity, charge density, and conformational propensity of the material to selectively target specific bacteria while providing low hemolysis and minimal cytotoxicity. Further broad advancements in HDPs may be found in reviews by Ding *et al.*,[68] Haney *et al.*[74] and Ge *et al.*[78] Albeit promising, historically these types of antimicrobials have had significant disadvantages, such as short or limited periods of activity, tissue toxicity, high manufacturing costs and a poor ability to function in an ever changing healthcare environment.[73] However, given the current global AMR problem, these technologies are re-emerging within the biomaterials community with hope that they offer a new generation of antimicrobials and antimicrobial devices.

To overcome the inherent issues of HDPs, recent advances have been made in synthetic forms that are able to emulate specific amino acid sidechains, overall charge, molecular weight and three dimensional structures, retaining the properties of their natural counterparts.[91] Of particular utility is the ability to modify the properties of these synthetic HDPs to enhance therapeutic outcomes. Some examples are the helical, cationic polypeptides developed by Xiong *et al.*[92] or the structurally nanoengineered antimicrobial peptide polymers (SNAPPs) reported by Lam *et al.*[93] and Shirbin *et al.*,[94] capable of selectively eliminating bacteria while reducing side effects to mammalian cells. Further research in this area has also demonstrated the ability of polypeptides to include alternative killing mechanisms to conventional HDP structures. Such is the case of poly(2-oxazoline) (POX) a mimicking peptide that enacts its antimicrobial effect by promoting reactive oxygen species (ROS), limiting the prospects of AMR development.[95] These examples clearly highlight the novelty and growing potential of HDPs, for which more detailed information can be found in the literature.[68,96,97]

Table 4 Common antimicrobial peptides and their antimicrobial activity

Antimicrobial peptide	Antimicrobial activity	Ref.
Magainin	Bacteria, fungi, viruses	79–81
Cecropin	Bacteria, fungi, viruses	82–84
Brevinin-1	Fungi, and viruses	85 and 86
PMAP-23	Fungi	79 and 87
Protegrin	Bacteria and viruses	80 and 81
Dermaseptin	Viruses	82 and 83
Tachyplesin	Viruses	84 and 85
Polyphemusin	Viruses	86 and 88
Tenecin-3	Fungi	89
PR-39	Bacteria	90

Surface modifications

Biomedical devices are a crucial part of modern medicine and the global use of for example stents, valves, artificial joints and other implantables is increasing yearly.[98] However implanted device surfaces are susceptible to bacterial adhesion and biofilm growth, potentially compromising the materials effectiveness.[99] Such infections frequently fail to respond to systemic antibiotics and require invasive revision surgeries consisting of debridement in conjunction with long-term antibiotic treatment. These revision procedures have a success rate between 30 to 50%[100,101] with detrimental effects on the patient's recovery prospects alongside a heavy economic impact to the healthcare system. It has been found that the surface topography and degree of implant roughness has a significant effect on the attachment of micro-organisms, and therefore on biofilm formation.[102,103] Other factors that further dictate colonisation may include electrostatic interaction, wettability, van der Waals forces and steric hindrance.[104,105] Thus, the development of surfaces capable of preventing bacterial attachment and proliferation has become a relevant niche for biomaterial scientists.

Several studies have attempted to mimic the nano-textured topologies present in nature that demonstrate inherent anti-attachment properties leading to anti-biofouling or bacteri-

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cidal surfaces.[105] Some examples of plant and animal species exhibiting these characteristics can be found on the leaves of taro and lotus plants as well as shark skin.[106,107] These surfaces prevent bacterial colonization through superhydrophobic structures and anisotropic flow patterns at both micro and nano scales, which allow for the repulsion of microbes on the surface.[108,109] Consequently, these topologies confer a "self-cleaning" ability, reducing further proliferation of bacterial species. In contrast to antifouling, other natural topologies can interact with the cell membrane of the deposited bacteria, leading to its disruption and cell death. This is the case for the cicada wings and the skin of geckos[110–113] that exhibit nanoscale pillar structures capable of piercing the cell walls of microorganisms.[114,115] Interestingly, both antifouling and antibacterial properties can be present on the same surface. Some species of dragonfly combine both mechanisms on their wings for high anti-attachment and bactericidal effects.[116] Nevertheless, microbial attachment is a complex process dependent on numerous physicochemical properties and differs between bacterial species with limited knowledge available in the literature. Research by Ginestra *et al.*[117] and Villapún *et al.*[118] both discuss the necessity of combining physical and chemical approaches to effectively prevent and treat medical device infections. The current research on metallic implants is pointing out the possibility of fine tuning the topology and chemistry of biomaterials with natural antimicrobial properties to increase effectiveness.[118,119] Thus, surface alteration of inert and antibacterial surfaces is becoming more prominent in the biomaterial community.

Antimicrobial delivery systems

The complex problem of AMR is likely to require a multifaceted approach from the biomaterials community with considerations taken at many different levels.[120] One area of concern is the delivery of antimicrobials and how dose and material release kinetics are optimised to minimise resistance (Fig. 4). The mutant selection hypothesis[121,122] theorises that antimicrobial resistant subpopulations present before the start of a treatment regime are enriched and amplified when dosing commences if the concentration falls within a specific range (Fig. 4a), known as the mutant selection window. The upper limit of this range is determined by the mutant prevention concentration (MPC), which represents the minimum inhibitory concentration (MIC) of the test antimicrobial against the least susceptible mutant present within the population.[123] The lower limit of the mutant selection window is determined by the lowest concentration that is still able to exert selective pressure on the microorganism.[124]

From the mutant selection hypothesis, the biomaterials community can take two main principles. Firstly, traditional antimicrobial dosing strategies that aim to stop the development of resistance by killing susceptible cells still allow for the enrichment of resistant pathogens when the concentration of the treatment falls within that window.[125] Secondly, if the maximum concentration (C_{max}) of the antimicrobial exceeds and maintains above the mutant selection window, it should restrict the development of AMR for the treatment regime.[124] These two principles are critical to the design of biomaterials and the dosing strategies they permit in order to treat infections not already resistant to the antimicrobial being used.

Although seemingly straightforward, application of the mutant selection hypothesis is not so simple due to the large doses required (>MPC). It is necessary to consider that the concentrations required to minimise resistance development are often far higher than what is needed to treat the infection. At these high doses, antimicrobials may also present a number of side effects to the patient with a trade-off between an increased risk of toxicity in exchange for the reduced likelihood of developing a resistant infection.[124] Moreover, if the antimicrobial is dosed infrequently or the components are long lasting the concentration may end up falling within the mutant selection window. It is expected that AMR will develop faster in these instances than those microorganisms treated more regularly with concentrations maintained above the mutant selection window.[126,127] As such, the selection of an optimal dosing profile for the biomaterial is crucial in AMR prevention.

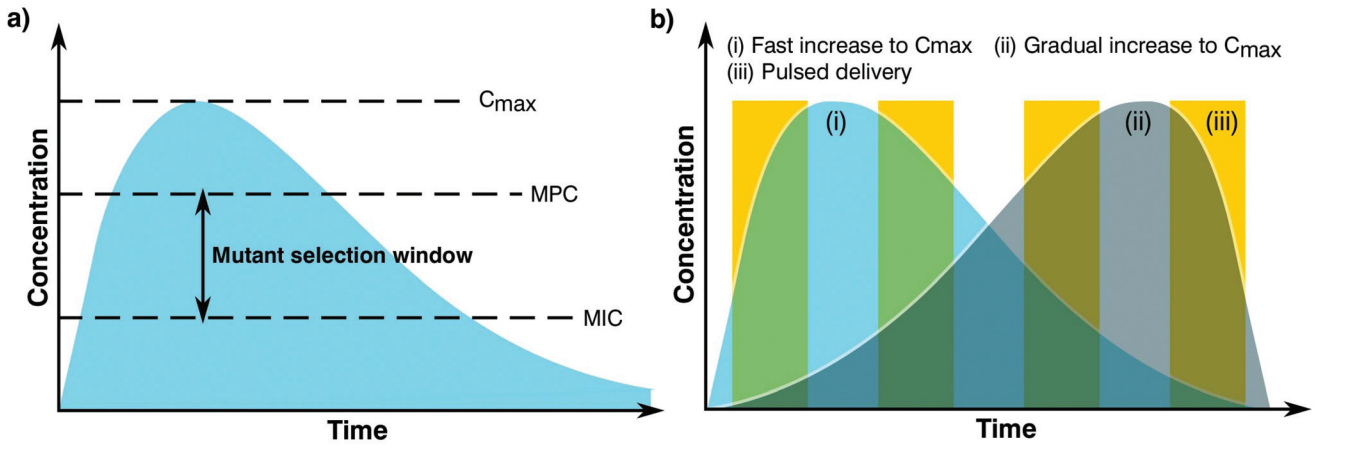

Fig. 4 Graphs showing (a) definition of the mutant selection window for an antimicrobial dosage and (b) dosage regimes.

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Generally, there are two prevalent pharmacokinetic dosing profiles (Fig. 4b), those which begin at a high concentration and gradually decrease (Fig. 4b(i)) and those that start at a low concentration and gradually increase (Fig. 4b(ii)). The first profile is often preferred since it minimises the chance of developing microbial resistance, however as the concentration of the dose gradually begins to fall, the time spent close to or within the mutant selection window increases.[125] An alternative solution of a short pulse kinetic profile has been proposed by Baker *et al.*,[128] aiming to minimise the time that the organism has to select for resistance while simultaneously reducing pathogen abundance due to the high antimicrobial concentration (Fig. 4b(iii)). To further add to these dosing profiles, it may also be beneficial to use combination therapies involving two or more antimicrobials.[129] This would allow high levels of protection to be maintained since when one concentration of antimicrobial falls below that of the MPC, another takes its place, providing good pharmacodynamic overlap. It is also worth noting that AMR can be selected during treatment, therefore this type of therapy may also be useful when antimicrobial-resistant genes are transmissible and can be gained by an infecting bacterial population.[130–132] However, difficulties in joint dosing, toxicology monitoring and pharmacokinetics make combined administration complicated.

Based on the impact of AMR and the limited prospects of future antibiotics being marketed, it is critical to develop novel antimicrobial substances and remodel current delivery systems to prevent resistance acquisition. To showcase the promising solutions identified by the biomaterials field, two case studies have been prepared. The first highlights research into dermal systems, while the second focuses on bone cement, revealing differences in approach linked to specific body areas. At the same time, limitations in current methods and attitudes will be introduced to propose recommendations for the development of a united front within the biomaterials field against AMR.

Case study I: topical applications

Topical wound care has improved and evolved over many years with a shift in practise from drying the wound site using absorbent gauze to strategies that focus on maintaining a moist healing environment.[133] This change in therapeutic process was brought about by observations made in 1962 by Winter[134] and later supported by Cho *et al.*[135] in 1998, where studies found that occluded wounds required less time for reepithelialisation than those allowed to air dry. By using a closed dressing, the wound is continuously exposed to growth factors, proteinases and chemotactic factors.[136] This type of environment also preserves the electrical gradient across the wound site, allowing for the stimulation of fibroblasts and permitting epithelial cell migration.[133]

Over the last decades, these[134,135] findings have pushed forward the development of different biomaterials for wound healing. Today, dressings are often divided into two categories passive and interactive. Passive dressings, such as a gauze, deliver no clinically recognised effect on the wound itself other than providing protection from the environment.[137] Interactive dressings are designed to actively stimulate the wound bed to support optimal healing conditions.[133] The added functionality of interactive dressing have made it a focus point for the biomaterials community with different strategies being developed to manipulate the wound environment, which now extends beyond speeding up re-epithelialisation. Other promising functionalities that have been engineered include stimulation of collagen synthesis, formation of a hypoxic environment to promote angiogenesis and strategies to decrease topical pH, which may reduce infection incidence.[138,139] In addition, modern dressing designs also factor in patient comfort, convenience of application and cosmetic outcomes, such as the reduction of scarring.[140–142]

With the realisation that maintaining a moist environment is beneficial for wound healing, some products have been designed to be moisture retentive, which may be quantified using the moisture vapour transmissions rate (MVTR). Dressings that have a MVTR of <840 g m^{-2} over a 24 hours period are described as moisture retentive.[143,144] This has led to a multitude of products on the market; however, it is noted that none can be described as ideal for all wounds (Table 5).

Although modern occlusive dressings aim to reduce microbial colonisation of the wound by employing mechanisms to reduce pH and create unfavourable conditions for microbial growth, topical infection is still a huge clinical problem. Infections have historically, in the pre-antibiotic era, been one of the leading causes of death globally with dermal

Table 5 Commercially available wound dressings[145]

Dressing type	Commercially available products	Characteristics
Gauze	Curity, Vaseline Gause, Xeroform	Can dry wounds
Films	Bioclusive, Blisterfilm, Cutifilm, Flecigrid, OpSite, Tegaderm	Retains moisture
Hydrocolloids	Aquacel, Comfeel, DuoDERM, Granuflex, Tegasorb	Traps fluid
Hydrogels	Carrasyn, Curagel, Nu-gel, Purilon, Restore, SAF-gel, XCell	Rehydrates wound
Foams	3 M Adhesive Foam, Allevyn, Lyofoam, Tielle	Moderately absorbent
Alginates	Algisite, Kaltostat, Sorbsan, Tegagen	Highly absorbent, acts as a haemostatic agent
Fibre mat	Aquacel Hydrofibre	Highly absorbent
Skin substitutes	Alloderm, Apligraf, Biobrane, Bioseed, Dermagraft, Epicel, EZ Derm, Hyalograft, Integra omnigraft, Laserskin, Myskin, TransCyte	Provides growth factors and cytokines

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trauma (*i.e.* burns, insect bite, surgical wounds or even a simple scratch) often proving fatal if infected.[146,147] After the discovery of penicillin, the number of individuals dying from topical infections significantly reduced, with current estimates suggesting that only 7–10% of hospitalised patients are affected with dermal infections.[148] Within a healthcare environment one of the leading causes of topical infections can be found at a surgical site (surgical site infection – SSI). This can occur in up to 5% of patients undergoing 'clean' surgeries and up to 20% in those undergoing intra-abdominal surgeries, affecting upwards of 300 000 people annually in the United States alone.[149,150] Among the increased morbidity associated with an SSI, it also delays healing, which may prolong hospital stays and return to normal activities causing further knock on negative effects to healthcare resources, the economy and patient well-being.

One of the most common pathogens associated with SSIs is *S. aureus*, which can colonise and be carried by healthy individuals, often in the nasal cavities without detrimental effect.[151,152] These bacteria can be found relatively easily, with 20% of healthy people designated as chronic carriers, 30% intermitted carriers and 50% not susceptible.[152] More distressing is that carriers are up to 12 times more likely to contract an infection than non-carriers.[148] To prevent and treat such infections, the biomaterials community have sought to functionalise topical dressing with various antibiotics, including ciprofloxacin (CIP), tetracycline, mupirocin, fusidic acid and gentamicin are commonly used[153,154] (Table 6). This is exemplified by the work of García *et al.*[155] whereby 1% chitosan films were modified using weisocyanate to provide a carrier for CIP. These films were found to inhibit bacterial growth with activity levels proportional to antibiotic content. Similar therapeutic responses had been reported by Li *et al.*[156] who developed CIP loaded electrospun fibre mats using thermo-responsive polymers poly(*N*-isopropylacrylamide) and poly(l-lactic acid-*co*-ε-caprolactone)(PCL). Alternative approaches include cellulose scaffolds loaded with tetracycline hydrochloride with the ability to inhibit and reduce the growth of bacteria as tested by disc diffusion and plate count methodologies.[157] Furthermore, hydrogel dressings have also been investigated for their ability to be functionalised to deliver tetracycline, as demonstrated by Chen *et al.*[158] In this work, it was shown that alginate-chitosan hydrogel dressings with incorporated gelatin microspheres containing tetracycline hydrochloride provide a more sustained controlled release, fundamental for AMR prevention. Interestingly, a semi-derivative of tetracycline (tigecycline) was developed to treat skin and soft tissue infections, which avoids the efflux-mediated resistance mechanism exhibited by both Gram positive and Gram negative bacteria.[159,160] Dhanalakshmi *et al.*[161] formulated chitosan nanoparticles loaded with tigecycline and coated with lectin to provide a more sustained antimicrobial release profile. More recently Nimal *et al.*[162] further developed this formulation by incorporating tigecycline-chitosan nano particles into a platelet rich plasma hydrogel. This system demonstrated improved antibacterial efficacy in comparison to other wound dressings. Thus, it is clear that wound dressings have been a particular medium used by the biomaterials community to deliver antimicrobial molecules.

Delivering antibiotics locally to wound sites could be preferential to systemic deliver for a number of reasons. Antibiotics need to be dosed to achieve a sufficient level of systemic efficiency, which can often lead to toxic reactions such as that of cumulative organ and cell toxicity. Topical delivery can provide better tissue compatibility, a lower occurrence of resistance and less wound healing interference.[153] In addition, the use of lower doses reduces the risks associated with systemic toxicity and can overcome problems related to poor blood cir-

Table 6 Antibiotic functionalised wound dressings

Antibiotic	Dressing type	Materials	Ref.
Ampicillin	Electrospun fibre mat	PCL	163
	Hydrogel	PVA/alginate	164
Cefazolin	Electrospun fibre mat	Gelatin	165
Ceftazidime	Electrospun fibre mat	Silk fibroin/gelatin	166
	Film	Guar gum/ethylenediamine/collagen	167
Ciprofloxacin	Electrospun fibre mat	Polyvinylpyrrolidone	168
		Polyurethane/dextran	169
Doxycycline	Film	Collagen/gelatin	170
Gentamicin	Electrospun fibre mat	Chitosan	171
Moxifloxacin	Electrospun fibre mat	PVA/alginate	172
Neomycin	Electrospun fibre mat	Poly(styrene sulfonic acid-*co*-maleic acid)/PVA	173
Norfloxacin	Film	Chitosan	174
Streptomycin	Electrospun fibre mat	Polyurethane/cellulose acetate/zein	175
	Hydrogel	PVA/cellulose	176
Sulfadiazine	Film	Alginate/cellulose	177
	Electrospun fibre mat	PCL/PVA	178
	Film	Alginate/cellulose	177
Sulfanilamide	Fibre mat	Alginate	179
Tetracycline hydrochloride	Film	Cellulose	157
	Hydrogel	Alginate/chitosan/gelatin	158
Vancomycin	Hydrogel	Silk fibroin/gelatin	180
	Film	Alginate/gelatin/halloysite nanotubes	181

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culation such as that found in wounds located in the body's extremities.[182] However, there is increasing concern around the development and subsequent threat caused by AMR. As such the healthcare industry has seen a revived interest in promising natural topical wound care agents, such as silver and honey, for both prophylactic and therapeutic use.[183]

For millennia honey has been used to treat topical wound infections with AMR not reported in the available literature.[184–187] The antimicrobial effects of honey are often attributed to a low pH (pH 3.2–4.5), high osmolarity and more notably the presence of peroxide or non-peroxide components.[57,58] Non-peroxide honeys, such as Manuka are monofloral and dependant on one source of nectar, in this case from the Manuka tree.[188] Increased levels of methylglyoxal (MGO), methylsyringate and bee defensin-1 are found within this type of honey, which results in a strong antimicrobial effect.[189–191]

Alternatively, there are other honey systems that instead of MGO utilise hydrogen peroxide (H_2O_2) and other ROS to produce an antimicrobial response. This compound arguably provides honey with its most potent antimicrobial mechanism.[192] Similar to MGO in Manuka honey, ROS has also been found to support wound healing, specifically the process of angiogenesis, and to act as an anti-inflammatory.[193–196] However, ROS is produced in the presence of water and therefore as a product makes it water sensitive and less stable than Manuka, further introducing batch to batch variation and limiting clinical adoption.

The bactericidal behaviour of Manuka and ROS producing honey, both *in vitro* and *in vivo*, has been extensively researched and against a diverse range of pathogenic organisms. This includes WHO priority pathogens such as MRSA and vancomycin-resistant *Enterococcus faecium*,[197–203] increasing the interest in its application to tackle AMR. Further to testing efficacy, attempts were made to generate strains of bacteria resistant to Manuka honey, however it was unsuccessful with no reports of clinical isolates that acquired resistance by both Blair *et al.*[204] and Cooper *et al.*[187] In addition to inhibiting planktonic cells, Manuka and ROS honey was also found to disperse, disrupt and kill bacteria within forming and established biofilms. This included preventing the formation of biofilms of *Staphylococcus* and *Streptococcus* species, *Pseudomonas aeruginosa*, *Escherichia coli*, *Acinetobacter baumannii* and *Klebsiella pneumonia*, clearly indicating strong clinical potential.[200,205–208]

Albeit their antimicrobial properties, the advent of highly efficacious antibiotics in the 20th century led to a diminished interest in applying honey in wound care. A key explanation for the reduced use of honey as a wound care treatment, like most naturally occurring antimicrobials, is its physical properties and characteristics, which are not compatible with modern day medicine or suitable for delivery in a clinical setting. With the rapid emergence of AMR the biomaterials community has taken a step forward to formulate delivery systems for natural antimicrobials that exist in undesirable forms. Medical grade Manuka honeys, such as Activon and Medihoney, are commonly used to impregnate or coat wound dressings. This is exemplified through the work of Taher *et al.*[209] and Kamaratos *et al.*,[210] which utilise nanocellulose and tulle dressing respectively as a carrier for honey products. On the other hand, research such as that by Mancuso *et al.*,[211] has taken this a step further through the development of biomimetic meshes containing Manuka honey. This work demonstrated the potential to develop a layer-by-layer assembly of nanocoated poly(ε-caprolactone) mesh, which elicited biocompatibility and antimicrobial behaviour.

Despite the water sensitivity of ROS producing honey biomaterial scientists have pushed forward the development of novel strategies to increase the presence of this type of honey in wound care. Research by Febriyenti *et al.*[212] and Khounganian *et al.*[213] explored formulating honey gels in order to ease delivery and stimulate wound healing. In both cases ROS producing honey gel shortened the wound healing time significantly and produced no negative side effects when compared with untreated and nondisclosed commercial products. However, the antimicrobial capacity of the formulation was not addressed. In order to realise the potential of ROS producing honey as a viable topical antimicrobial treatment, it must be capable of delivering specific and controlled amounts of the antimicrobial agent over a clinically relevant period. Surgihoney™ (SHRO), a bioengineered honey has been formulated to enable delivery of consistent antimicrobial doses.[214]

The antimicrobial effect of SHRO has also been demonstrated with clinical tests highlights its ability to prevent and treat SSIs as well as Hickman and Vascular line infections without the need for antibiotic administration.[215,216] As aforementioned, SHRO is an engineered honey, allowing the potency to be tailored as required. This 'dialling' enabled SHRO to be modified such that it outperformed other medical grade honeys, including Activon and Medihoney, and two of the most commonly used antimicrobials dressings, silver and iodine.[197] Although SHRO addresses the need to provide a medical grade honey product that can deliver a consistent dose of antimicrobial activity, its uptake clinically, much like Manuka honey, is hindered by its viscous and adherent properties. Therefore, in order for honey to become a more viable clinical treatment new delivery systems must be developed where the biomaterials community has significant expertise. To date research by Hall *et al.*,[202] has demonstrated a clinically efficacious emulsion system capable of easing the delivery of SHRO using an inversion trigger. This showcases that by engineering biomaterial delivery systems with appropriate physicochemical properties we may be able to better harness the antimicrobial efficacy of honey.

Furthermore, as well as using honey as a sole antimicrobial agent, its interactions with conventional antibiotics has revealed some promising results. Particular value may be sought in the topical application of honey to a wound alongside systemic delivery of an antibiotic. Jenkins *et al.*[217] noted synergistic effects between Manuka honey and a range of antibiotics, including oxacillin, tetracycline, imipenem and mupirocin against strains of meticillin-resistant *Staphylococcus*

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aureus (MRSA). Interestingly, it was found that the addition of honey caused the down regulation of mecR1, a gene that encodes for an MRSA specific penicillin binding protein (PBP2A) and in combination with oxacillin made MRSA once more susceptible to the antibiotic. Furthermore, Müller *et al.*[218] discovered strong synergistic activity of Manuka honey and rifampicin against numerous *Staphylococcus aureus* strains, including clinical isolates of MRSA. It was also found that the presence of Manuka honey prevented the development of rifampicin resistance *in vitro*. However, despite displaying a strong clinical potential, inconsistency in efficacy due to the natural origin of Manuka honey and its physical characteristics make consistent application difficult and appear to limit healthcare adoption.

It is clear that the biomaterials community plays a critical role in developing more clinically useful systems that maintain the efficacy of natural antimicrobials, such as honey. Future considerations should focus on developing biomaterials reflecting on how dosage may be controlled to maintain concentrations above the MPC. With the aid of the biomaterial's community further development of efficacious treatments can be achieved while also endearing to learn from our previous use of antibiotics.

Case study II: bone cements

The prospect of an infected device caused by an antibiotic resistance species is of great relevance to implantable technologies. In topical applications, changes of antimicrobial agent can be easily performed. However, access to an implantable for modification of ongoing therapeutics is complex and costly. Alongside the biological and mechanical requirements of these systems, implantable devices require special considerations from the biomaterials community.

Since the first successful long bone reconstructions performed in the 19th century, the field of orthopaedics has evolved through the implementation of novel techniques and biomaterials, nevertheless, infection is still a major concern in the 21st century.[219] Between 1 to 5% of contemporary indwelling prostheses have been shown to develop an infection. Frequently removal of the implanted device and debridement of the surrounding tissue is required.[220] During revision a patient's movement may be impaired or limited, which can impact long-term recovery, increase healthcare costs and reduce economic contributions. More worrying is the adaptability showcased by bacterial isolates present in these clinical settings. Pathogens recovered from implantable orthopaedic devices are often characterized by virulence factors that encourage adhesion and biofilm formation.[221,222] Once such a community environment is formed, the effectiveness of antibiotic treatment is greatly reduced, leading to a higher infection risk with only 30 to 50% of revision surgeries successful in removing the infection source.[100,223,224] The consequences of these hard to treat infections has resulted in the emergence of complementary therapies to antibiotic prophylaxis. The prime example of this approach is antibiotic-loaded bone cement that enables localised delivery of cargo to the implant surface and adjacent tissue.

Historically, the term bone cement has been used as a synonym for polymethyl methacrylate (PMMA) based formulations. These materials are commonly supplied as a liquid monomer and powder polymer with mixing resulting in the formation of a tacky substance that is easily manipulated and formed.[225,226] Over the years, more complex formulations have been developed, generally including additives to prevent leaching of the liquid monomer, stabilization under light and heat, to facilitate cold curing, and increase imagining contrast or render the cement radiopaque. As a result, PMMA cements are a versatile biomaterial for prosthetic cementations, spacer manufacture and reconstructions with commercial products available since the early 70s.[227,228] More recently, there has been a special interest in the incorporation of antibiotics during the mixing process. However, the inherent exothermic reaction of PMMA coupled with the impact of antibiotic selection and dosage on the physicochemical properties of the cement requires careful consideration. The selected antimicrobial molecule must be chemically and thermally stable to maintain its antibacterial efficacy after curing. Moreover, it has been suggested that the antibiotic should be provided in powder form to facilitate integration during mixing and minimise the influence on mechanical properties.[226,229,230] This has led to a preference in the use of vancomycin, gentamicin, erythromycin, colistin, tobramycin, clindamycin or fusidic acid with an inclination for mixtures between different antibiotics for improved bacterial spectrum.[227,228,231] Dosage selection must be high enough to ensure an effective therapy with minimal reduction in mechanical properties and limited detrimental effect on the human body. For this purpose, it is a common rule of thumb to incorporate more than 2 g per 40 g of cement (up to 6 or 8 g) for acute infections, while less than 2 g of antibiotic is acceptable for prophylaxis of first implants.[226,227,232,233] The addition of such substances is commonly done in theatre, however the approval of low-dose antibiotic loaded bone cements by the FDA for second-stage reimplantation after infected arthroplasties in 2003 has led to commercially available pre-loaded products from Howmedica (Antibiotic Simplex), DePuy (CMW1 and CMW 3G), Merck (Copal and Palamed G) and Schering-Plough (Palacos R-G).[226,234]

Antibiotic loaded bone cements may be able to reduce resistance by the rapid elimination of pathogens through a mixture of antibiotics, nonetheless, inadequate elution profiles and concentrations can result in resistance acquisition. The rationale behind current antibiotic elution processes stems from the necessity to rapidly eliminate latent bacteria attached to the implant or introduced during surgery (exogenous).[235] These early or delayed infections are developed during the initial 3 to 24 months after implantation and commonly require a high concentration of antibiotic in the following week after surgery. Thus, the use of elution profiles in the form of high dosage peaks during the first days, which rapidly decay in the coming week but with maintained antibiotic levels still present a

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month later has been encouraged.[227,235] The current approach may be effective in the treatment of early infections, although the reduction in antibiotic load poses a problem for late stage infections occurring more than 24 months after implantation, where the reduction in antibiotic load may stimulate AMR. Statistics have shown that the likelihood of suffering a late stage infection after arthroplasty can be similar to early and delayed infections (30, 29 and 41%, respectively),[236,237] suggesting that current elution profiles should be modified. To promote a higher release in the late stages after implantation, several novel antimicrobial delivery approaches are under development (Fig. 5).

One such localised delivery approach is to anchor a desired antibiotic to the implanted device surface in a single (Fig. 5a)[238] or multi-layered fashion (Fig. 5b).[239] Other systems have focused on direct modification of implant surfaces and geometries to tailor antibiotic delivery, such as varying channel placement (Fig. 5c).[240] Nevertheless, modification of implants may be difficult depending on the selected manufacturing and antimicrobial technologies, therefore the addition of carriers acting as antibiotic delivery systems is becoming of special interest to the field. These materials can be mixed into cement formulations and prepared with minimal changes to the current methodology, resulting in a myriad of possible configurations. Some technologies rely on the attachment of antibiotic molecules to particles in the nano to micro scale (Fig. 5d and e).[241,243] In contrast to simple attachment, antibiotic encapsulation is an alternative approach (Fig. 5f), providing a more controlled form of elution and protection during curing in the form of metallic nanoparticles,[235] liposomes[242] or as a multilayer assembly for bone cement.[244,245] Nevertheless, most of these approaches have been shown to have detrimental effects on the final product, with reduced mechanical properties or limited initial elution. This effect, and the poor understanding of the elution requirements needed to prevent AMR, indicate that there is a critical need to research antibiotic delivery systems and further our understanding of their influence on resistance development.[231,235]

Although the use of PMMA bone cements is highly widespread, reports have shown a significant persistence of infection associated with residual particles.[246,247] Cement and implant debris can result in local inflammatory activity, leading to chronic complications and aseptic loosening.[225] These potential negative outcomes and other disadvantages of PMMA bone cements, namely their lack of bioactivity or osseoconductivity, heat generation during curing, expansion due to

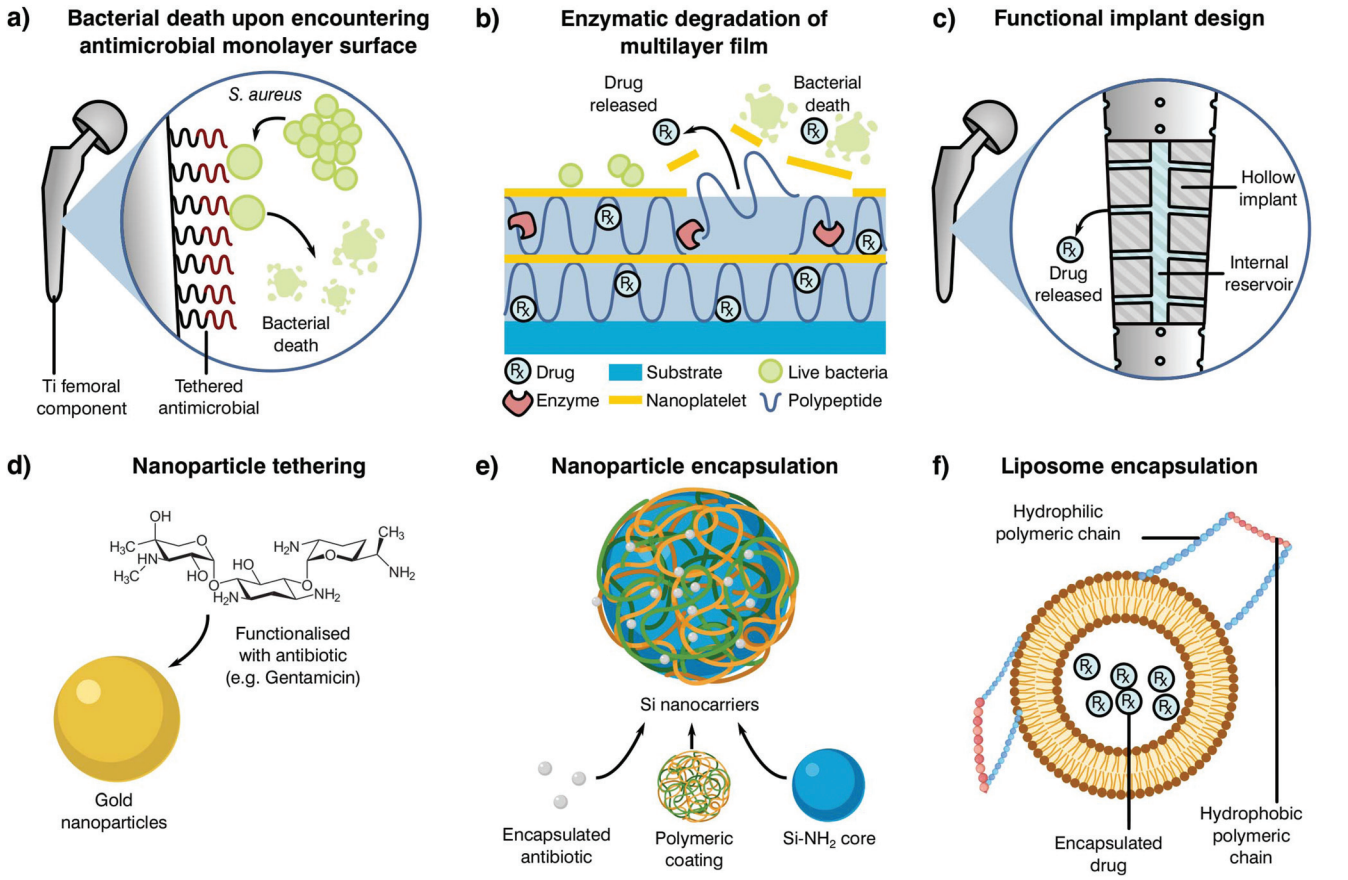

Fig. 5 Examples of alternative delivery systems currently explored in the literature with examples for (a) implant antibiotic attachment as a monolayer,[238] (b) multilayer,[239] (c) direct implant modification,[240] (d) particle tethering,[241] antibiotic incorporation to (e) nanoparticles[235] or (f) liposomes.[242] Adapted from the source material.

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water absorption and the potential allergic reaction to monomer remnants, has pushed forward the development of different formulations. One of the second-generation biomaterials employed in regenerative medicine is calcium and hydroxyapatite bone cement. These materials share a large similarity with natural bone where calcium and phosphate ions result in the promotion of osteoconduction and osteogenesis with antibiotic loading becoming an interesting research niche.[248,249] Similarly, zinc polycarboxylate and glass polyalkenoate formulations have enhanced biological properties compared to common PMMA cements, making these materials especially popular in the dental field.[250] Besides antibiotic loading (*i.e.* fusidic acid) it must be said that other antimicrobial agents are regularly used as antibacterial additives (*i.e.* Chlorhexidine diacetate or Benzalkonium chloride).[251]

The interest in developing antibiotic loaded cements to provide a sustained therapy and controlled dosage may result in a lower risk of infection, nonetheless, with AMR on the rise there is also a critical need to develop and implement novel antimicrobial substances. The natural antimicrobial activity of some metallic ions against bacteria[252–254] has encouraged their use in medical devices, however, their potential toxic effects has restricted use with only a few candidates being granted governmental approval following successful marketing. One such element is silver for which the number of antimicrobial based products has elevated from 200 to nearly 1400 over the last decade.[255] Examples include touch surfaces ("Safe Touch", Dorset), hand sanitizers (Evolut Silver), textiles (Silver Plus®), dressings (Mepilex® Ag) and implant coatings (Agluna®), yet silver loaded cements are still not commercially accessible. Although the available literature presents research on cements loaded with different Ag donors, the detrimental effect that some silver salts have on the curing process of PMMA bone cement has moved the field onto a preferential use of silver nanoparticles (AgNPs).[256–259] This form of silver presents a high surface area to volume ratio, conferring desirable chemical and physical properties to enhance antimicrobial efficacy.[260] Specifically, AgNPs loaded PMMA bone cement tested *in vitro* reveal a broad antimicrobial spectrum against both Gram positive and Gram negative species, nevertheless of special interest is the high effectivity against antibiotic resistance strains showcased by Bistolfi *et al.*[227] These promising results alongside the recent publishing of a clinical trial suggesting the safety of AgNPs loaded cements *in vivo*,[261] solidify the rationale behind the use of this heavy metal to tackle AMR. That said, there is a limited understanding on the antimicrobial efficacy of silver particle loaded cements *in vivo* with only one animal model published to date.[262] In this report, Moojen *et al.* carried out the analysis of AgNPs loaded cements in a rabbit infection model with no significant reduction of *S. aureus* colony forming units between loaded and plain cements after 14 days. Interestingly, available literature[263–265] points to silver nanoparticles as an effective antimicrobial *in vitro*, indicating a disconnection between laboratory and animal methods. This detachment between *in vitro* and *in vivo* models in antimicrobial testing is not an isolated occurrence. Cytotoxicity and other cell work testing methods broadly used in the field have been shown to have a poor correlation with animal models.[266]

Alongside silver, other metals and non-organic species are being studied for their future application in antimicrobial loaded cements. Copper, gold, magnesium, zinc and their oxides have been successfully mixed with bone cements to confer antimicrobial properties, while graphene, paraben, quaternary amine monomers or chitosan are some of the more common non-metallic antimicrobial additives.[227,267] Nevertheless, the clinical relevance of these technologies is diminished by the limited biological assessment available *in vitro*, with little immune response, hemocompatibility or genotoxicity studies available in most manuscripts. Thus, there is a need to develop more fundamental work on promising antimicrobial agents while revisiting old and over simplistic *in vitro* testing methods for the development, screening and implementation of new therapies.

The oversimplification of physiologically relevant processes is not only constrained to cell culture. To test the antibacterial effectiveness of antimicrobial materials it is common to employ a single pathogenic bacterial species generally found in clinical settings for the intended application of the biomaterial. Nevertheless, utilising single-species planktonic cultures for *in vitro* modelling does not compare to clinical reality. An extreme case is the oral microbiome where over 700 species have been identified in the human oral cavity, suggesting that single bacterium are not representative of the complex and mutable *in vivo* environment.[268] Therefore, evaluating antimicrobial approaches to material design requires models of physiologically relevant environments that are likely to incorporate bacteria as a biofilm (possibly multispecies), a relevant implant material, and flow conditions.[269] Several studies have incorporated these elements successfully to evaluate clinical implant materials such as titanium and zirconium, however they have not been frequently utilized in the development of antimicrobial biomaterials.[269–271] Incorporating multiple disciplines, including biology, engineering, and mathematics is likely to become decisive to furthering the field due to the multifaceted nature of co-culture systems.[272]

As the regulatory pipeline becomes more time and cost consuming, it is important to develop a strong case to ensure present and future stakeholder participation. Silver is an attractive antimicrobial thanks to its status as an approved biomaterial, thus, it is possible to ease some of the requirements using predicate devices. Innovation and state of the art research should be a must to tackle AMR, nonetheless, the end purpose of novel technologies should be commercialization. Consequently, it is necessary to adapt the biomaterial community methodology to encompass the regulatory process and its application since the initial steps of promising technologies.

Future recommendations

At the start of the present manuscript, the complexity, risks and costs of developing and bringing to market a novel health-

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care product were indicated. Over the following sections, different strategies to tackle AMR were emphasized and, through the use of two case studies, limitations on current biomaterials approaches were highlighted. As most global changes involving regulatory pathways can only receive a limited push forward from the biomaterials field, our role should be in the innovation and translation of new technologies. Thus, the principal aim of the following section is to clarify these limitations, identify clear areas of interest and put forward recommendations where biomaterial science may improve our response to AMR (Fig. 6).

From the available literature it is becoming increasingly evident that promising materials tested *in vitro* may correlate poorly with *in vivo* analysis, leading to failures in clinical testing.[266] Ethical and effectiveness concerns coupled with the extensive fiscal and time expenditures needed for animal testing has caused a decrease of such practices. Thus, special focus on *in vitro* testing as a screening method to assess and predict the host response to a biomaterial is being made.[266] Despite this, as the number of novel healthcare technologies discovered over the decades has quickened, development of *in vitro* tests to ascertain their safety and effectiveness has stagnated.[273–275] Susceptibility tests are of great relevance to analyse the interaction of antimicrobial agents and different microorganisms with numerous standards available depending on the base material and its application. Albeit methodologies differ, they commonly involve the contact or submersion of the desired material with a controlled bacterial density or plated culture for a specific time, followed by recovery and quantification or measurement of lack of growth on a plate.[276] Comparison between controls and the antimicrobial agent tested will make it possible to ascertain if a material is inert, bacteriostatic or antimicrobial, helping to screen potential novel materials to tackle AMR. These tests are relatively simple with ordinary laboratory set ups required and timescales of days or weeks.[276,277] Similarly to antimicrobial analysis, physicochemical tests rarely study biomaterials in a physiological relevant state. Few manuscripts ensure that samples are preconditioned with complex macromolecules or understand the ability of the added functionality to last in the long term, limiting the extrapolation of the obtained results to *in vivo* models. Nonetheless, the attractiveness driven by their simplicity and recognized status as standards in the field has led to a prevalence of such techniques without realising their potential downsides.

The composition of growth media is another factor that is rarely accounted for during testing and only changed depending on standards recommendations and the bacterial species used.[277] However, elements present such as nutrients or salts to prevent osmotic shock can react with the desired molecule and cation to bias the obtained results (*i.e.* copper and chlorine).[118] Similarly, timescales may be a misrepresentation of the reality. Touch surfaces are quickly becoming of interest to tackle HAI for which direct contact and recovery tests, such as JIS Z2801:2010 are the norm.[55] These typically require the recovery of a deposited inoculum after 24 h of contact, however studies have shown that most surface to hand or hand to hand contact takes place in a few hours,[55] demonstrating that long periods of time do not represent the reality of the intended material and application. Besides media and timescales, the recovery and quantification of survival bacterial populations may be another source of bias. This is commonly done either by spectroscopy (*i.e.* optical density) or by detachment of the bacterial biomass and plating, nevertheless, the former does not discriminate between live and dead microorganisms, while the latter requires complete recovery of bacterial species, which may be a challenge for porous or adhesive materials.[55] Consequently, the biomaterials community should push forward the rework of such methods and encourage the broad use of more novel techniques for antimicrobial growth and AMR evaluation as suggested by Khan *et al.*[278] and Belkum *et al.*[279]

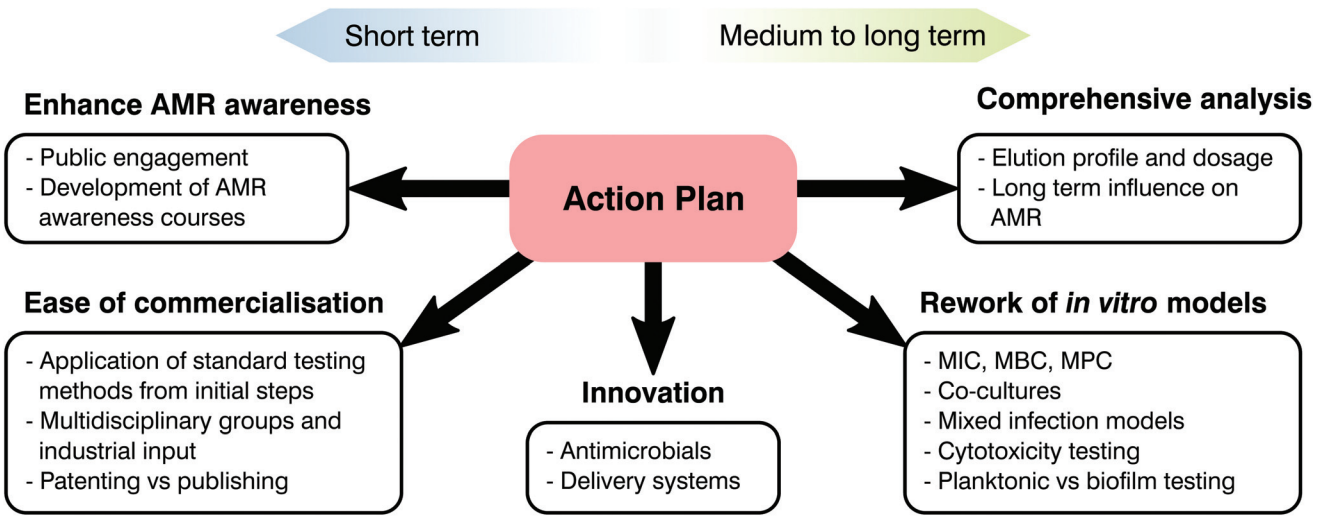

Fig. 6 Diagram showcasing critical areas for the biomaterials community to tackle AMR.

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Currently the biomedical field typically conducts testing on bacterial and mammalian cells separately, which disregards the complex interactions between cell types and infected devices. Similarly, human bacteria flora is multifaceted, with numerous species interacting and exchanging genetic information. Despite this, it is common to test for single bacterium, disregarding most Horizontal Gene Transfers (HGT) between bacterial species, commonplace for the exchange of resistance genes.[12,13] Thus, there is an oversimplification of infection analysis *in vitro* in both bacterial and mammalian cell culture analysis.[280] The prime example of such a scenario is the immune system, where white blood cells have been demonstrated to play a fundamental role in bone regeneration and infection control.[281,282] Nonetheless, it is common to simply conduct separate analysis for inflammation, mineralization and antibacterial effectiveness of antimicrobial agents with different single cell types disregarding interactions. The selection of mammalian cells for each of these tests is also a notable point. Cytotoxicity analysis *in vitro* commonly entails the use of cells derived from tumours, more resilient and less expensive than more relevant cell lines, however, these do not necessary pose an accurate model of the real human tissue and biomaterial interaction.[273,280] Similarly, most antimicrobial tests done *in vitro* to test the antibacterial efficacy of novel biomaterials involve laboratory strains, which may not be a real representation of the main clinical pathogens involved in infections.[283] Consequently, as antimicrobial strategies continue to evolve so must our pre-clinical testing regimes, being the creation of a multicellular infection test, proper selection of bacteria and cell lines, and improved correlation between *in vivo* and *in vitro* models essential to progressing novel AMR prevention strategies.

Analysis of natural resistance acquisition is another aspect where the biomaterials community can help to challenge AMR. In drug development, it is usual to evaluate the possibility of microorganisms gaining resistance to novel and reworked molecules.[20] Nevertheless, this trend is rarely followed during the development of biomaterials technologies where a focus on the initial efficacy of the system overrides long-term analyses. Such is the case for implantable devices functionalised with antimicrobial agents, however, these devices will need to halt infection for extended periods of time. Taking into account the adaptability and flexibility of bacteria, a lack of knowledge in the long-term effect of novel technologies poses a threat to treatment strategies focused on tackling AMR. This absence of long-lasting efficacy is especially critical for the implementation of novel molecules or antimicrobial metals, for which our understanding of the mechanisms driving AMR are still lacking. An example would be silver, microbiologist are aware of Ag resistant species and over the last decade genomic analysis of such bacteria has led to the discovery of the gene thought to encode silver resistance, the sil operon.[284–286] Nevertheless, the natural acquisition of silver resistance is rarely studied with limited papers available dealing with long-term passages of controlled silver dosages to force resistance.[285–287] The overuse of silver and the possibility of bacterial strains resistant to both antibiotics and heavy metals has awoken an interest in natural resistance development,[288–291] exemplifying the importance of long-term analysis of antimicrobials. As a consequence, it is necessary to undertake such studies for novel biomaterials *in vitro* and perform a more complete analysis of resistance acquisition as suggested by Martínez *et al.*[274]

Moving forward, it is important that the way microorganisms develop resistance is understood so that appropriate treatments may be identified. It is well documented that microorganisms have what is known as intrinsic resistance, or the natural ability to resist an antimicrobials mechanism of action, which can occur at two stages: planktonic and community level.[292] Resistance within an organism can occur due to gene mutation or by HGT[293] when DNA is acquired from another resistant organism.[294] This process can arise from the up-take of free DNA (transformation), plasma-mediated transfer (conjugation) or phage-mediated transfer (transduction).[295] Community level organisms can develop further resistance and tolerate far greater stress than individual cells. This is demonstrated by the formation of biofilms that may increase antibiotic resistance up to 1000-fold.[296] Due to the significant implication that the formation of a biofilm has on the ability of an organism to resist treatment, future developments may aim to provide approaches that disrupt or negate this effect.

Alongside this necessity to better understand resistance development, it is required to understand the limitations of current dosage analysis in resistance analysis and its prevention. The use of MIC to describe and classify an antimicrobial is a helpful tool for microbiologist and biomaterial scientist who are tackling AMR[297–299] and is commonly analysed by subjecting controlled concentrations of the desired material to a specific density of a bacterial species either in liquid media or agar plated. After incubation, cultures are inspected visually or through spectroscopy to determine bacterial growth in the liquid media or to assess the size of the inhibition zone created in agar plates.[297,299] For common drugs, standards are available with MIC breakpoints to determine if a specific bacteria species is susceptible, intermediate or resistant to the selected antibiotic which facilitates the following treatment.[300] Thus, MIC has become one of the main tools available to select dosage in the biomaterials community. Nevertheless, by definition the MIC only inhibits the growth of bacteria, with cells still able to survive, but not proliferate, possibly still present in the culture. In contrast, plating of liquid cultures after antibiotic treatment and incubation provide the minimum bactericidal concentration (MBC), revealing the real amount of antimicrobial needed to kill the desired bacterial species.[301] The range of antibiotic concentrations between MIC and MBC can led to a lower dosage being decided where resistant bacterial cells can be selected, enhancing AMR acquisition. This has been recognised in the mutant selection hypothesis

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where drug-resistant subpopulations present before treatment are enriched and amplified if the antimicrobial concentrations fall within a specific range.[124] To prevent such a scenario, authors have shown that dosage selection should be complemented with parameters accounting for the mutant selection window, proposing the MPC (Fig. 4a).[129,302] Selection of antimicrobial dosages taking the MPC into account will mean mutants fail to amplify[124] and will provide a more robust dosage tool.

Further to the antimicrobial dosage being above the MPC, delivery systems should be fine-tuned in order to produce a pharmacokinetic release profile that enables this concentration to be maintained over the treatment period. This can be achieved by developing release kinetics that allow for the MPC to be exceeded shortly after the target site is reached.[125] If the antimicrobial concentration is likely to fall below MPC values during treatment combination therapies or novel dosing profiles (Fig. 4b) should be exploited. In addition to the systemic administration of antimicrobials, localised delivery is highlighted as being preferential in order to prevent AMR. This is because it enables a more targeted approach that does not expose the rest of the body to systemic effects, including that of engaging with other microorganisms.[303]

As the crucial step to bring a novel technology to the market, regulatory approval should be considered as part of the initial steps of novel device research. The nature of contact between device and body, length of contact time and other parameters will decide the regulatory pathway, which will ultimately determine the economic and time investment required.[22] As the main link between technical specifications and regulators, biomaterial researchers should be aware of the implications that the developed technology has in the future regulatory process and ensure that all preclinical data meets governmental requirements. This will require knowledge of the healthcare pipelines,[304,305] however, the complexity of these processes makes it difficult to encompass all possible facets.[22,275] Thus, it is necessary to focus on the two main aspects where one may have the highest impact in a multidisciplinary group: device categorization and preclinical testing. The first hurdle to be tackled consists in properly defining the technology and its intended purpose. If the novel technology intends to act as an implantable with added functionality, such as an antimicrobial coated implant, it will be recognised as a medical device which will follow the European Union Medical Device Regulations (MDR) 2017/745 and 2017/746. These divide medical devices into four categories (Class I, IIa, IIb and III) with increasingly difficult regulatory processes to be met. In contrast, if the developed material is mainly intended to correct or modify a physiological function by exerting a pharmacological, immunological or metabolic action, such as a novel molecule, this will mark the product as a medicinal agent, following Regulation (EC) No 726/2004 and Directive 2001/83/EC with extensive clinical trials required.[306,307] During the inception of the novel biomaterials technology, proper knowledge of these classifications, requirements and similar marketed products alongside fundamental expertise can make it possible to modify the novel product and test it before further steps are taken. This fine-tuning prior to regulatory processes begin would ensure that costly reworks are prevented.[308]

The amount of preclinical data to demonstrate the effectiveness and safety of medical devices is dependent on the technology. In Europe, ISO 10993 2018 provides insight into the assays, data and quality control necessary for the *in vitro* testing of these devices (Fig. 7). Once the end category of the device is known, *in vitro* tests can be arranged following ISO 10993 recommendations. This will be done first through any "in house" capabilities available, limiting failures of future independent tests and early cheaper rework if necessary. It must be pointed out that there may be an apparent contradiction with the previous recommendation to develop and apply novel analytical methods. Nevertheless, tests mentioned and referenced in ISO 10993 are standardized methodologies, which in some cases have been shown to be outdated or poorly correlated with clinical outcomes.[266,309–311] ISO 10993 takes into account the novelty of the field and the idiosyncrasies inherent to novel devices up to some extent, "It is not intended that ISO 10993 provide a rigid set of test methods, including pass/fail criteria, as this might result in either an unnecessary constraint on the development and use of novel medical devices, or a false sense of security in the general use of medical devices. Where a particular application warrants it, experts in the product or in the area of application concerned can choose to establish specific tests and criteria, described in a product-specific vertical standard." However, technology progression still requires an approved methodology, limiting the current tests available to undertake. Consequently, it is still possible to encourage the use of better predictive analysis for future development of better standards.

Scientific work has become a competitive field since the early 2000s where a novel philosophy of "publish or perish" has taken hold.[312] This change in mentality and all previously commented barriers to medical device approval and marketing led to a preference of publications over patents and, although this trend is changing, article writing is still the preferred outcome.[313] Publishing instead of filing a patent ensures that the novel technology is broadly open to the public, which diminishes the prospects of future commercialization. Thus, it is necessary to continue exploring novel approaches to tackle AMR while ensuring that promising technologies are not lost. To achieve such an objective, greater involvement between academia and industry is needed. Finally, it has been shown that part of AMR emergence has been caused by poor use of antibiotics and lack of understanding of antibiotic resistance by the public.[16] Academics have a privileged position from which to help by educating in the danger posed by bacterial resistance and the role of the public in tackling AMR. Consequently, enhancing public engagement, including AMR awareness courses would result in higher penetration of current policies.[37]

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Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/devepmental toxicity[d,e]	Degradation[f]
Surface medical device	Intact skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/bone/dentine[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E[j]			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
Implant medical device	Tissue/bone[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

[a] Refer to ISO 10993-11:2017, Annex F.
[b] Information obtained from comprehensive implantation assessments that include acute systemic toxicity, subacute toxicity, subchronic toxicity and/or chronic toxicity may be appropriate if sufficient animals and timepoints are included and assessed. It is not always necessary to perform separate studies for acute, subacute, subchronic, and chronic toxicity.
[c] Relevant implantation sites should be considered. For instance medical devices in contact with intact mucosal membranes should ideally be studied/ considered in contact with intact mucosal membranes.
[d] If the medical device can contain substances known to be carcinogenic, mutagenic and/or toxic to reproduction, this should be considered in the risk assessment.
[e] Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of device materials in the reproductive organs.
[f] Degradation information should be provided for any medical devices, medical device components or materials remaining within the patient, that have the potential for degradation.
[g] X means prerequisite information needed for a risk assessment.
[h] E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set). If a medical device is manufactured from novel materials, not previously used in medical device applications, and no toxicology data exists in the literature, additional endpoints beyond those marked "E" in this table should be considered. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.
[i] Tissue includes tissue fluids and subcutaneous spaces. For gas pathway devices or components with only indirect tissue contact, see device specific standards for biocompatibility information relevant to these medical devices.
[j] For all medical devices used in extracorporeal circuits.

Fig. 7 Considerations for biological assessment from ISO 10993-1:2018 where "X" means prerequisite information needed for a risk assessment; "E" means endpoints to be evaluated on the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set assessment).

Conclusions

Antibiotic resistance in pathogenic bacteria is driving modern medicine to a bleak future where effective therapies against infection may become scarce. With prospects of a post-antibiotic era on the horizon, numerous organizations have focused their efforts on unearthing the causes behind such phenomena, with both bacterial and human causes identified. Over billions of years, bacterial cells have developed numerous mechanisms to survive and adapt to toxic substances, which coupled with their genomic plasticity, rapid life cycles and large populations, promotes development of antibiotic resistance. Nevertheless, human mismanagement of antibiotics has selected for high prevalence of resistant organisms, exacerbating AMR emergence. This coupled with the complexity inherent in their development and the high risk and low revenue associated with these substances has resulted in a paradox where novel antimicrobials are critically required, however, few products are currently in the development pipeline. This has led to action plans being developed and

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implemented by governmental bodies since the early 2000s. However, the complexity of AMR and the intricacy of moving large relevant associations forward calls for action at all levels. The biomaterials community, as one of the main innovation sources, has responded to the threat posed by AMR with increasing development of materials, substances and delivery systems conceived to halt the prospects of a post-antibiotic era. In this paper, we have conducted a review of available literature to showcase promising technologies under development and, through two case studies, pinpointed the following areas where special focus should be given to push forward a focused front against AMR:

- Continue the current development of novel antimicrobials and delivery systems.
- Develop our understanding of the long-term influence of novel substances and delivery systems on AMR to complement current short-term analysis.
- Rework simplistic *in vitro* analysis broadly used for relevant correlation with *in vivo* analysis.
- Enhance the understanding of requirements and processes behind commercialization of these products to guide the initial research stages.
- Enhance AMR awareness at all levels.

Moving forward, a focus on these areas will make it possible to reduce prospects of bacteria gaining novel resistances, ensure that promising technologies *in vitro* will maintain their effectiveness *in vivo*, reduce costly reworks and failures during regulatory approval and increase the overall response to AMR. Consequently, novel therapies will retain their effectiveness with a smoother transition between laboratory and market, enhancing the critical role of the biomaterial community in confronting AMR.

Conflicts of interest

The authors declare no conflict of interests.

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