

Man vs Microbes – The Race of the Century

Ericka Anderson¹, Bipin Nair², Victor Nizet^{1,3} and Geetha Kumar^{2,*}

Abstract

The complexity of the antimicrobial resistance (AMR) crisis and its global impact on healthcare invokes an urgent need to understand the underlying forces and to conceive and implement innovative solutions. Beyond focusing on a traditional pathogen-centric approach to antibiotic discovery yielding diminishing returns, future therapeutic interventions can expand to focus more comprehensively on host-pathogen interactions. In this manner, increasing the resiliency of our innate immune system or attenuating the virulence mechanisms of the pathogens can be explored to improve therapeutic outcomes. Key pathogen survival strategies such as tolerance, persistence, aggregation, and biofilm formation can be considered and interrupted to sensitize pathogens for more efficient immune clearance. Understanding the evolution and emergence of so-called 'super clones' that drive AMR spread with rapid clonotyping assays may guide more precise antibiotic regimens. Innovative alternatives to classical antibiotics such as bacteriophage therapy, novel engineered peptide antibiotics, ionophores, nanomedicines, and repurposing drugs from other domains of medicine to boost innate immunity are beginning to be successfully implemented to combat AMR. Policy changes supporting shorter durations of antibiotic treatment, greater antibiotic stewardship, and increased surveillance measures can enhance patient safety and enable implementation of the next generation of targeted prevention and control programmes at a global level.

INTRODUCTION

Antimicrobial resistance (AMR) is a global, multi-factorial problem of immense complexity. Over prescription and overuse of antibiotics, especially of broad-spectrum agents, runoffs from livestock and fish farming, which eventually find their way back into medicine, and poor infection control practices in resource-poor hospitals leading to passage and spread of AMR strains among high-risk populations, are continuing factors that contribute to this expanding global problem. The economic challenges of bringing a successful drug to market during the COVID-19 pandemic are further fueling the AMR crisis. With complex intensive care unit admissions and defensive antibiotic prescription selecting for highly resistant strains of opportunistic pathogens, and returning a profit deterring pharmaceutical companies from further investment, this has led to a dearth in the antibiotic discovery space spanning the last six decades. Staggering estimates of 750 000 AMR-related annual deaths worldwide are dwarfed by a trajectory that predicts up to 10 million deaths by 2050, wherein AMR deaths would exceed those due to cancer and diabetes combined [1]. The AMR crisis is a phenomenon not only intrinsically linked to human health and behaviour, but also inherently connected with our entire ecosystem, deservedly catching the attention of the World Health Organization (WHO) and the United Nations (UN). In response to the gravity of the situation, the UN adopted a resolution and reaffirmed the WHO Global Action Plan on AMR [2]. India, a densely populated country at the front lines of the AMR crisis, reflected these strategic objectives in its National Action Plan (NAP) on AMR in 2017, tailored to its national needs and priorities [3]. In addition to the five priorities of the Global Action Plan on AMR, India has a sixth priority emphasizing India's leadership in pursuing AMR solutions.

The WHO has correctly projected that AMR in bacteria, viruses and parasites is emerging as one of the greatest challenges to public health and could lead to the emergence of a 'post-antimicrobial era', wherein common infections would fail to respond to

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Author affiliations: ¹Collaborative to Halt Antibiotic Resistant Microbes (CHARM), Department of Pediatrics University of California San Diego, La Jolla, CA, USA; ²School of Biotechnology, Amrita Vishwa Vidyapeetham, Kollam, Kerala, India; ³Skaggs School of Pharmacy and Pharmaceutical Sciences University of California San Diego, La Jolla, CA, USA.

***Correspondence:** Geetha Kumar, gkumar@am.amrita.edu

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Abbreviations: AMP, antimicrobial peptide; AMR, antimicrobial resistance; GLASS, Global Antimicrobial Resistance and Surveillance System; IASP, Institutional Antimicrobial Stewardship Program; MRSA, methicillin resistant *S. aureus*; NET, neutrophil extracellular trap; VRE, vancomycin resistant enterococci; XDR, extremely drug resistant.

therapy resulting in tremendous morbidity and mortality. Therefore, a global AMR response has become a core mandate for the WHO, with pertinent efforts to coordinate the activities of several bodies worldwide and in collaboration with key partners. It is self-evident that the successful implementation of AMR containment efforts requires intense global collaboration and sustained solidarity to support context-specific AMR interventions on a global scale [4]. Keeping this perspective in focus, it is pertinent to evaluate and foster greater understanding of the relative contribution of different drivers of AMR development and to implement game-changing strategies and visionary ‘One Health’ approaches to facilitate progression towards a global AMR solution. The diverse aspects of the AMR crisis, could be classified into the broad areas of:

(a) elucidating mechanisms of pathogen persistence and virulence, (b) understanding the evolution and spread of the superbug, (c) exploring innovative alternatives to antibiotics, and (d) deploying effective clinical and public policy interventions.

Keeping this perspective in focus an International Symposium entitled ‘AMR: Man vs Microbes - The Race of the Century’, was hosted by the School of Biotechnology, Amrita University in collaboration with the Collaborative to Halt Antimicrobial Resistant Microbes (CHARM) at the University of California, San Diego, Bugworks Research, Bangalore, and the Centre for Cellular and Molecular Platforms (C-CAMP), Bangalore, as a platform to foster greater understanding and evaluation of the relative contribution of different drivers of AMR development and to inspire and facilitate progression towards a global AMR solution. The vision of the symposium was to brainstorm and define the evolving medical, scientific and policy challenges and opportunities and to help formulate strategies for combating this global pandemic threat. The symposium, which covered multifaceted dimensions of AMR, and comprised featured talks and panel discussions involving leading experts from around the world, provided the ideal setting to combine strengths and effectively leverage the opportunity to address, discuss, deliberate, share experiences, investigate, learn, prioritize, empower, and set sights on being victorious in this battle—which will undoubtedly require game-changing strategies and visionary ‘One Health’ approaches.

UNDERSTANDING HOST-PATHOGEN INTERACTIONS TO AID IMMUNE CLEARANCE

The antibiotic discovery process to date has been focused primarily on screening potential new chemical entities in an *in vitro* setting, and thus centred solely on the bacterium and not reflective of the actual microenvironment during infection in the host. Over time, this pathogen-centric screening has had diminishing returns in providing new functionally active chemical scaffolds, leading many to advocate for greater innovation and a fundamental rethinking of the antibiotic discovery and evaluation paradigm. Many important human bacterial pathogens frequently colonize healthy individuals without symptoms. It is helpful to consider any bacterial infection that spreads to the bloodstream or deep tissue to sicken the patient as a dysfunctional host-pathogen interaction in which the innate immune system has failed to protect against severe infection. This interaction can open new opportunities for therapeutic discovery. Pharmacological interventions can aim for both sides of the exchange – for example boosting the activity or resilience of the innate immune system, blocking bacterial virulence factors, or sensitizing the pathogen to clearance by existing immune defenses [5]. A deeper understanding of key host immune system components and specific pathogen virulence factors is crucial to reinvigorating antibiotic discovery at the host-pathogen interface. The research will highlight knowledge gaps linked to therapeutic failure in classical antibiotic therapy when it occurs. Here we probe pathogen survival strategies of tolerance/persistence, aggregation, and heterogeneous cell populations and discuss potential avenues to pursue sensitizing the pathogen to immune clearance (Fig. 1).

TARGETING PERSISTENT BACTERIAL INFECTIONS

The concept of antibiotic resistance as an inheritable and stable trait of microbes was first proposed by Paul Erlich in 1907, whose development of chemotherapies for trypanosomiasis revealed resistant parasites [6]. Clinical observations of antibiotic resistance were not reported until after the arrival of antibiotics from the mid 1930s. As early as 1944, bacteria were observed to survive extensive antibiotic treatment without acquiring resistance mutations [7]. These findings can be explained by two modes of survival: *tolerance* – survival following transient exposure to an otherwise lethal antibiotic concentration, and *persistence* – survival of a subpopulation of the clonal bacterial cells, whereas most are rapidly killed. For example, multi-drug resistant *S. aureus* is responsible for both community and hospital-acquired infections, downregulates its metabolism to become dormant, tolerating high antibiotic concentrations, resulting in chronic and/or recurrent infections. Therefore, detailed multi-omic analyses can be employed to identify the molecular changes in persisters that can uncover potential pathways to ‘wake up’ such bacteria, rendering them susceptible to antibiotics *in vivo*. Using this technique, studies from the laboratory of Zinkernagel in Zurich, demonstrated that a persister-enriched population downregulated virulence and cell division, upregulated ribosomal proteins, nucleotide, and amino acid metabolic pathways, and accumulated insoluble proteins involved in transcription, translation and energy production [8]. Furthermore, these changes were reversible upon re-growth, consistent with driving the persister phenotype. Armed with these insights, they successfully devised targeted anti-persister therapy.

Salmonella species also exhibit persistence and antibiotic tolerance, displaying a spectrum of growth characteristics even within a single niche. Adding to this complexity is an astonishing heterogeneity in host-pathogen interactions occurring simultaneously

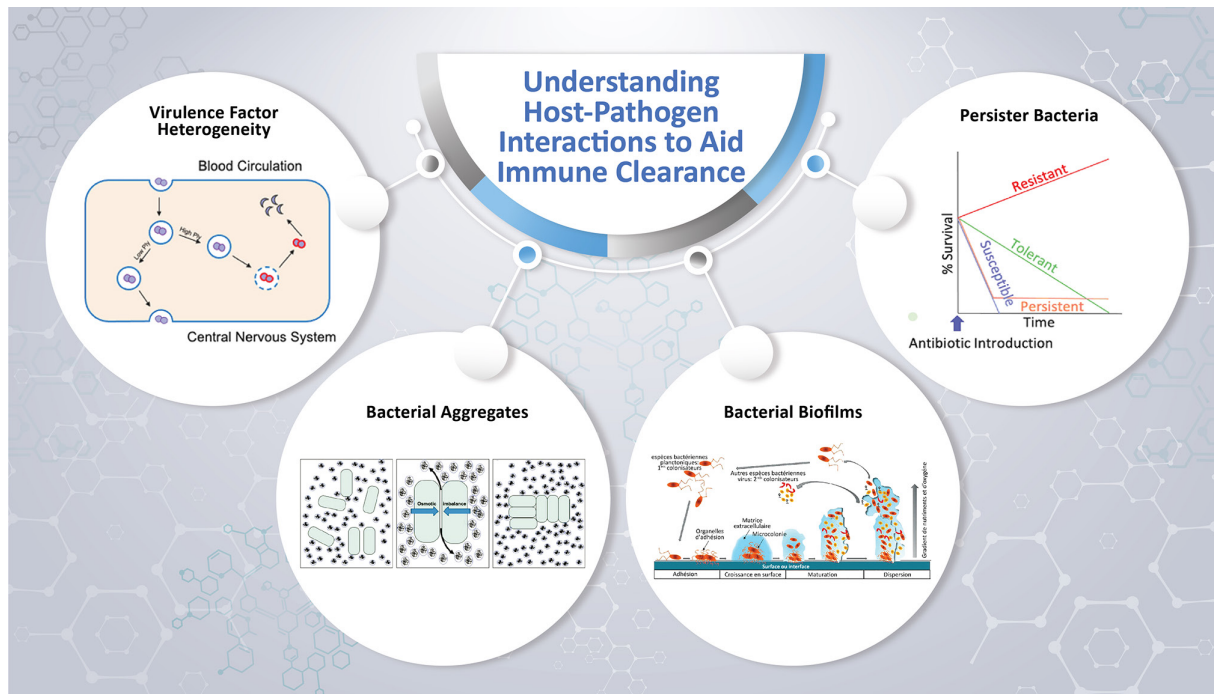


Fig. 1. Understanding host-pathogen interactions to aid immune clearance. The growing problem of AMR requires targeted solutions to microbial mechanisms of persistence, tolerance, and virulence. A clearer understanding of bacterial tolerance and persistence mechanisms, the formation of bacterial aggregates and biofilms, and heterogeneity in virulence factor expression all inform druggable targets.

within the same tissue compartment. Studies by Dirk Bumann's group in Basel have shown that individual pathogen-host encounters can yield disparate outcomes, depending on differential molecular interactions, wherein disease can progress from a failure to control individual infectious foci, despite eradication of others [9]. Single cell techniques can be applied *in vivo* to characterize these growth states and differential molecular interactions to understand the driving factors across distinct host-pathogen interactions. Such work unveiled the importance of a metal-ion transporter SLC11A1 in macrophages, which dictates resistance to *Salmonella* infection via magnesium starvation [10].

ADDRESSING THE CHALLENGE OF BACTERIAL BIOFILMS AND AGGREGATES

Another challenge for anti-infective drug development is that many pathogens form biofilms, the products of secreted proteins, carbohydrates, or DNA that create an extracellular environment to protect the microbe from host immune cells as well as antibiotics [11]. The development of biofilms is composed of four stages: initial attachment, microcolony formation, biofilm maturation, and dispersal. Deciphering the quorum sensing mechanisms, adherence factors and other biofilm components that govern these stages could provide novel targets to identify effective therapies. For example, the drug-resistant human nosocomial pathogen *Enterococcus faecalis* can produce biofilms on wounds and implanted devices such as IV catheters [12, 13]. The recent development of an inducible CRISPRi system for *E. faecalis* in the laboratory of Kimberly Kline in Singapore facilitates the study of gene contribution at all stages of biofilm formation, including the genes involved in antibiotic resistance and persistence in a high throughput manner [14]. Natural products such as clove bud oil that have anti-quorum sensing properties can also effectively attenuate virulence factors of *Pseudomonas aeruginosa* such as inhibition of biofilm formation, as well as enhancing dispersion of already formed biofilms, in addition to enhancing host innate immune defence mechanisms such as NET formation, providing an overall anti-infective effect [15].

Chronic *Pseudomonas aeruginosa* infections have high densities of virulent organisms at the infection site with localized inflammation [16]. Often the infecting bacteria remain sensitive to antibiotics, but persist despite drug therapy [17–19]. Additionally, bacterial isolates from chronic *P. aeruginosa* infections are often impaired in biofilm formation. As demonstrated by the research team of Pradeep Singh in Seattle, they maintain a localized infection by forming bacterial aggregates reducing their motility and, similar to a biofilm, offer protection against antibiotic killing. Bacterial aggregates are an interesting phenomenon whereby self-aggregation is independent of biofilm or quorum sensing genes. In fact, in both wound and cystic fibrosis lung model studies *P. aeruginosa* fitness is unaffected by loss of many virulence or biofilm genes [20–23]. Several mechanisms underpin bacterial aggregation, including electrostatic bridging and depletion assembly that are mediated by host polymers such as DNA, mucin,

and F-actin [24] or by host-independent high-density growth conditions [25]. In chronic *P. aeruginosa* infections, elucidating the molecular mechanisms of bacterial aggregation in the host environment may reveal methods for dispersion and sensitization of these tolerant bacteria.

CONSIDERATION OF HETEROGENEITY IN VIRULENCE FACTOR EXPRESSION LEADING TO DIFFERENT INFECTION OUTCOMES

Stochasticity in virulence attributes contribute to a functionally heterogeneous bacterial population which in turn creates differing infection foci, triggering disparate infection outcomes. For example, *S. pneumoniae*, a leading pathogen notorious for severe infections in young children and the elderly [26], exhibits cell-to-cell heterogeneity of a virulence factor Ply [27]. The research group of Anirban Banerjee in Mumbai found that *S. pneumoniae* switches from a colonizing to an invasive phenotype, resulting in the spread of the infection from the blood to the central nervous system, precipitating the potentially devastating consequences of meningitis. During the transition through the blood-brain barrier, the heterogeneous expression of pneumolysin (Ply), a pore-forming toxin, dictates disparate *S. pneumoniae* infection outcomes. The high Ply-expressing subset of bacterial cells recruit galectin-8, triggering autophagy targeting, autophagosome membrane damage, and finally cytosolic clearance by ubiquitination machinery. In contrast, the low Ply-expressing subset does not recruit galectin-8, nor trigger ubiquitination and successfully traverses the blood-brain barrier by overriding the defence mechanisms [28]. Ply is a classic example, where attenuating the virulence of the pathogen, or enhancing the host immune defence can be studied for successful therapeutic outcomes to counter AMR.

UNDERSTANDING THE EVOLUTION OF SUPERBUG SPREAD

The natural evolution of microbes in response to environmental selective pressures promotes the development of AMR, even in the absence of antimicrobial drugs. Bacteria are primed to evolve rapidly with short generation times and large populations. Additionally, horizontal gene transfer (HGT) across distant species increases the rate of resistance and aids in the evolution of multi-resistant strains. These reasons signify the importance of tracking dangerous trends and emerging clones at the genomic level, and using modern technologies and analytical platforms to stay ahead of the pathogens in this arms race. New insights on the genomics of drug resistance, the emergence of super clones and their rapid spread, and microbes' genetic and physiological responses to stress are important in combating the pathogens (Fig. 2).

GENOMICS OF DRUG RESISTANCE

Resistance to antimicrobials, resulting in poor clinical therapeutic outcomes, can be acquired through several distinct mechanisms such as (i) target site modification resulting in decreased binding affinity or target replacement (loss of target); (ii) inactivation or destruction of antibiotics by chemical modification; (iii) alteration of membrane permeability and; (vii) efflux of antibiotics due to enhanced activity of efflux pumps [29].

Although chromosomal mutations contribute to AMR, in enteric bacteria, the antibiotic resistance genes are mainly linked with the extrachromosomal mobile genetic elements (MGEs), acquired from closely and distantly related bacterial species. Most of the attributes of AMR are often associated with these MGEs, which rapidly spread through the bacterial population by means of HGT [30]. MGEs such as integrons and conjugative plasmids play a key role in the fitness capacity of pathogens like *Vibrio cholerae*, contributing to its adaptation, including antibiotic resistance, virulence, disease development and survival in hostile environments [31]. However, studies with *Helicobacter pylori* have demonstrated a conspicuous absence of MGEs but increased level of ARG-specific point mutations, indicating target modifications as the primary cause of AMR [19]. Studies in the *Pasteurellaceae* family, comprising a diverse group of Gram-negative bacteria, demonstrate a significant association of MGEs with more than 77% of AMR genes, implicating them in playing a crucial role in both acquisition as well as transmission of resistance [32]. Combinatorial strategies involving whole genome sequencing, which can identify antibiotic resistance genes, coupled with the emerging field of functional metagenomics, which provides an insight into their abundance, along with machine learning approaches can be effectively used for predicting emerging antibiotic resistance patterns or trends [32, 33].

EMERGENCE OF 'SUPER CLONES' AND THEIR RAPID SPREAD

The emergence and the rapid spread of super clones are the greatest contributors to global multidrug resistance. The investigative team of Evgeni Sokurenko in Seattle has shown that the rapid spread of a dominant clonal subgroup, especially over the last decade, accounts for a significant percentage of fluoroquinolone-resistant clinical *Escherichia coli* isolates, particularly in UTI infections, both in hospital settings as well as in communities. This super clone originated from a single strain within ST131 as the *fimH*-based H30 subclone, then rapidly expanded and disseminated to become the most dominant and extensively multidrug-resistant lineage of pathogenic *Escherichia coli* globally. This prevalent subclone had a unique *gyrA/parC* fingerprint which was highly conserved and likely evolved via horizontal transfer and recombination involving *gyrA* and *parC*. Strains from

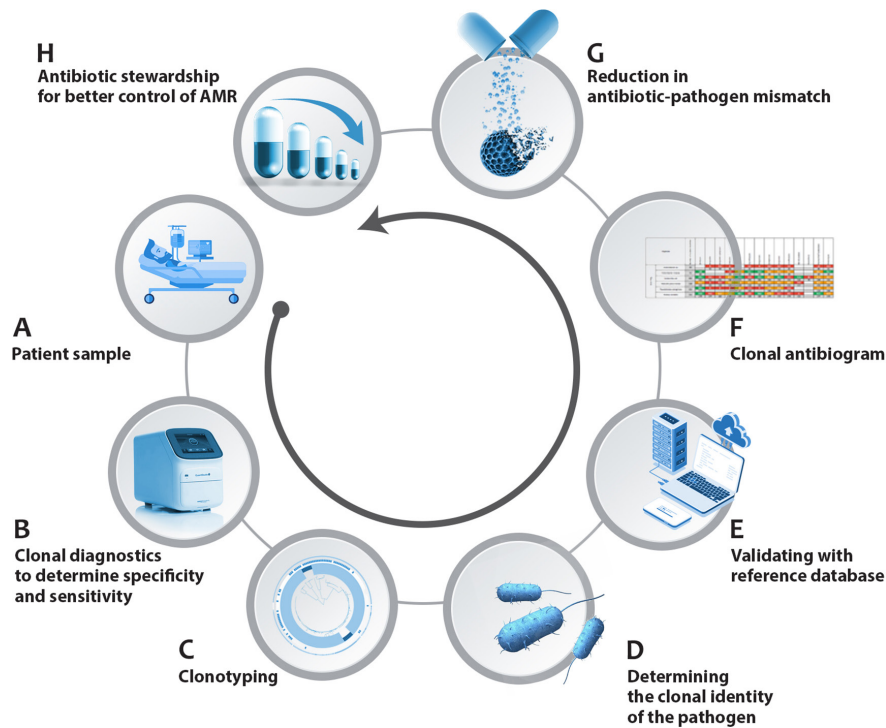


Fig. 2. Tracking the evolution of superbug spread. Modern technologies and analytical platforms can be effectively used to track dangerous trends and emerging clones, as it is extremely important to stay ahead of pathogens. Rapid clonotyping assays effectively identify the pathogen and control AMR by determining the precise antibiotics to be prescribed for the specific clonogenic profile. A: patient sample; B: clonal diagnostics to determine specificity and sensitivity; C: clonotyping; D: determining the clonal identity of the pathogen; E: validating with reference databases; F: clonal antibiogram; G: reduction in antibiotic-pathogen mismatch; H: antibiotic stewardship for better control of AMR.

different clonal groups retain the same antibiotic resistance genes and exhibit distinct antibiotic resistance profiles irrespective of their geographical location [34]. Despite this known clonal distribution of antibiotic resistance, antibiotic selection in the clinic relies on species-level antibiograms, resulting in the overuse of broad-spectrum agents and excessive antibiotic/pathogen mismatch. However, rapid clonotyping assays can be effectively used for diagnostic purposes to identify the specific antibiotics to be prescribed for a particular clonogenic profile [35].

GENETIC AND PHYSIOLOGICAL RESPONSES OF MICROBES TO STRESS

Combinatorial antibiotic therapies are yet another approach to combat AMR in the context of the shortfall in antibiotic development spanning the last six decades or more. The effect of antibiotics (the ‘stressor’) on microbial evolution involves measuring, understanding, and predicting the ecological as well as evolutionary trajectories of populations when they encounter novel environments with multiple stressors. As studied by the laboratory of Pamela Yeh in Los Angeles, the effect of such drug-drug interactions can be additive, synergistic, or antagonistic [36]. Applying combinatorial drugs can benefit from understanding the type(s) of effect that higher-order drug combinations have on a particular microbe, their clinical relevance, and the consequent rise of antimicrobial resistance. The evolution of resistance to one antibiotic often leads to increased resistance (cross-resistance) or susceptibility (collateral sensitivity) to antibiotic(s) [37]. Modelling followed by *in vitro* studies examining the effects of different antibiotic combinations will uncover net and emergent interactions [38]. It has been demonstrated that higher-order interactions increase overall antagonistic and suppressive interactions, net synergy, and emergent antagonism [39].

INNOVATIVE ALTERNATIVES TO TRADITIONAL ANTIBIOTICS

With the alarming rise in AMR and its global threat, it is paramount to develop alternative strategies that can supplement classical antibiotics to improve clinical outcomes. It is also important to consider ‘nontraditional’ therapeutic strategies for severe infections, each distinct from the traditional paradigm of small molecule antibiotics discovered *in vitro* to inhibit bacterial growth or viability (Fig. 3).

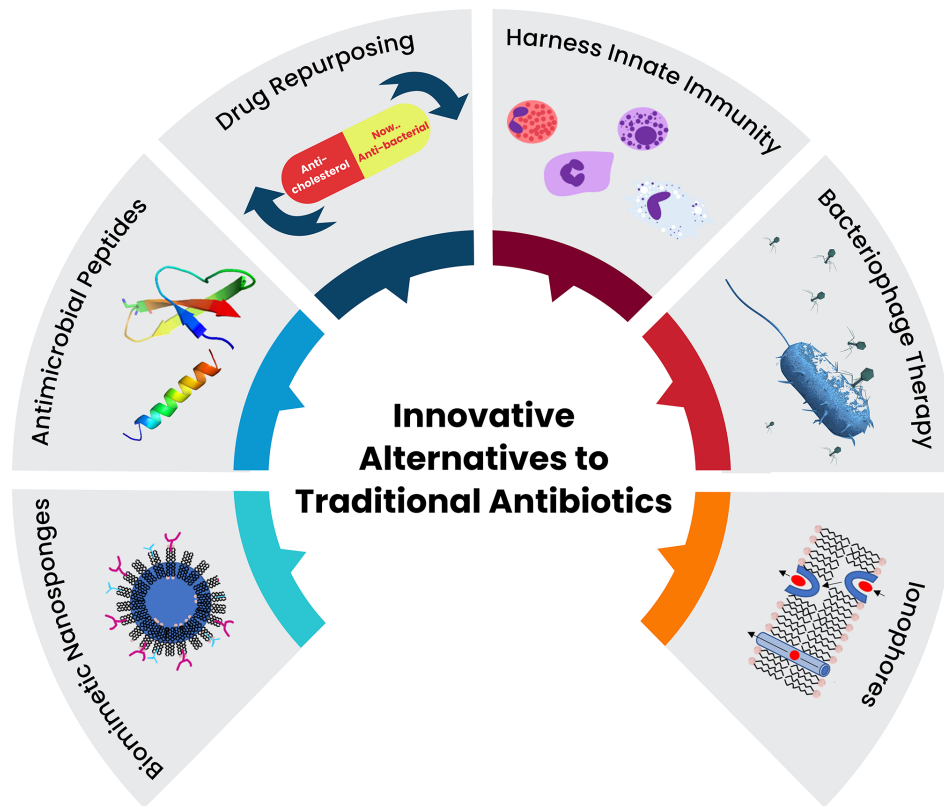


Fig. 3. Innovative alternatives to traditional antibiotics. Beyond the traditional paradigm of small-molecule antibiotics, featured therapeutic strategies that must supplement classical antibiotics in fighting serious infections. These strategies included biomimetic nanosponges, antimicrobial peptides, drug repurposing, harnessing innate immunity, bacteriophage therapy, and ionophores.

BACTERIOPHAGE THERAPY

Lytic bacteriophages that target specific pathogens by replicating within them and killing them are receiving renewed attention as drug entities that can be successfully used as therapeutic agents against MDR pathogens. Multidrug resistant clinical isolates of critical priority ESKAPE pathogens such as *Pseudomonas aeruginosa*, have been shown to be effectively killed by host-specific lytic bacteriophages [40]. A significant advantage of ‘phage therapy’ is the bacteriophages’ specificity to their particular host microbes, while an obvious disadvantage is the frequent development of resistance [41]. Thus, one must always consider genetic trade-offs between phage resistance and virulence/antibiotic sensitivity, depending on the receptor used by the phage to improve fitness [42]. The clinical parameters of phage therapeutics, however, are largely still unknown. Studies from Robert Schooley’s group have emphasized the need for double-blind and placebo-controlled randomized clinical trials (RCTs) with large and diverse cohorts to generate relevant longitudinal data. As with antibiotics, the pharmacokinetics and pharmacodynamics of phage therapy need to be studied. While phages display single-hit kinetics [43] because the effect of phage adsorption to its host bacterium is sufficient in and of itself to mediate killing, in clinical settings, a higher ratio of adsorbed phages to bacteria may be required since the bacterial population to be eradicated is significantly higher. The different stages of adsorption, distribution and penetration followed by adsorption, infection, lysis, and phage release are to be considered, particularly when studying/understanding the pharmacokinetic profile of phage therapy [44].

The use of well-purified phage preparations (so those preparations are composed predominantly of protein and nucleic acids) prevents adverse side effects, does not alter the microbiome composition, nor induces adverse immunological reactions as observed with the use of antibiotics [45–47]. Clinical efficacy is an integrative reflection of both active and passive phage therapy. Passive phage therapy comprises the sequential steps of phage adsorption, DNA/RNA injection, infection, and hijacking of the host machinery, followed by cell death/lysis. In contrast, active phage therapy is caused by the phage progeny released in the first round of lysis resulting in additional infections and lysis cycles [44, 48, 49]. Generally, a multiplicity of infection (MOI)=10 phage/cell is used for phage therapy. Still, given the self-replication and amplification of phages, the MOI at the site of infection must be considered. In addition, the patient’s immune response can potentially impact the pharmacokinetics or effectiveness of therapy, as systemically administered phages could be cleared by phagocytosis or by neutralizing antibodies [50, 51]. These issues could be overcome by changing the composition and concentration of the phage cocktail, increasing the number of administrations, or

using phages in combination with antibiotics. Synography, a novel technique that combines an optically based real-time microtitre plate readout with a matrix-like heat map of treatment potencies, may reveal the optimal design of therapeutic phage-antibiotic combinations [52].

ENDOGENOUS ANTIMICROBIAL AND ENGINEERED PEPTIDE ANTIBIOTICS

The innate immune system contributes significantly to the clearance of pathogens whose defence begins from the inoculation well before clinical signs of disease arise. A prominent element of this initial response is host defence peptides or antimicrobial peptides (AMPs), amphipathic cationic peptides with activity against a broad spectrum of bacteria, fungi, protozoa, and viruses, including MDR strains [53–55]. AMPs have two modes of action: (i) inserting into and disrupting the cell membrane, leading to cell lysis and death, and (ii) entering cells without membrane disruption and inhibiting intracellular functions by binding to nucleic acids or proteins. AMPs are evolutionarily conserved and produced by all life forms. AMPs have anticancer properties and act as immunomodulators in higher organisms [56–62]. Robert Hancock's group has screened and tested peptides that mimic the bactericidal and immunomodulatory behaviour of natural AMPs [63]. For example, arenicins, AMPs with twisted β -turns, and an amphipathic region derived from the sea polychaete *Arenicola marina* (lug worms) attack Gram-negative bacterial cell membranes but possess complement-modulating activities [64]. Drug efficacy studies involving antibacterial and immune interacting mechanisms, including physiologic media and innate immune components, provide a complete understanding of actual antibiotic action. Indeed, antibiotics discounted in standard MIC testing may be effective against MDR strains. In *P. aeruginosa* and *Acinetobacter baumannii*, azithromycin sensitivity is drastically increased in physiologically relevant conditions and synergy with natural and synthetic host-defence peptides *in vitro* and in an *in vivo* mouse model [65, 66].

Polymyxin B and E (Colistin) are currently used as the last-resort polypeptide antibiotics [67]. Matthew Cooper's research team in Queensland is working on a new class of cyclic lipopeptides – the octapeptins [68]. Octapeptins do not exhibit cross-resistance with colistin, have a broad spectrum of activity (both Gram-negative and positive), an extremely slow rate of development of resistance, and show a superior preclinical safety profile [68, 69]. Octapeptin C4, for example, has high efficacy, low toxicity, quick clearance, and antibacterial activity against MDR, NDM-1-resistant, and polymyxin-resistant Gram-negative bacteria [70, 71]. Cooper's team is also re-engineering vancomycin in response to an increasing prevalence of resistant bacterial strains. Attaching membrane-selective elements that bind to the bacterial cell wall precursor lipid II to vancomycin yielded a series of supercharged derivatives dubbed vancaptins [72]. These vancaptins preferentially target bacterial membranes instead of human cells. The highly potent vancaptins are 10–100-fold more active against methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE), extremely stable (>90%) in human plasma, have no measurable cytolytic activity, and a long half-life potentially amenable to once a day dosing [73].

IONOPHORES AND NUTRITIONAL IMMUNITY

Transition metals are essential in biological systems – stabilizing substrates or reaction intermediates in the active sites of enzymes, and their heightened reactivity is harnessed for catalysis. However, this heightened activity renders transition metals toxic at high concentrations. Like all living organisms, microbial pathogens must regulate their intracellular levels of transition metals to balance their physiological needs while avoiding harm. The host seeks to exploit a pathogen's metal dependence (by restricting access) and metal toxicity (by compartmentalized delivery of high concentrations) in the context of 'nutritional immunity'. Ionophores, molecules that bind and transport cations across biological membranes, are a potential therapeutic avenue utilizing nutritional immunity. One candidate explored in Mark Walker's laboratory is PBT2, a derivative of the 8-hydroxyquinoline scaffold, with demonstrated activity as a zinc and copper ionophore in mammalian cells [74]. PBT2, in combination with zinc, has potent antibacterial activity against multiple Gram-positive pathogens. However, the buildup of intracellular zinc toxicity leads to the accumulation of reactive oxygen species and dysregulated manganese homeostasis [75]. Ionophoric drugs have been used in livestock agriculture for over 35 years, with little indication of increasing resistance to these drugs or cross-resistance to medically essential classes of antimicrobials. Advancing next generation ionophores could markedly reduce the administration of antibiotics in animals and lower AMR rates in clinical medicine.

DRUG REPURPOSING TO BOOST INNATE IMMUNITY

Immunomodulatory therapeutics have had a massive impact on patient outcomes in inflammatory diseases and cancer but remain understudied and underutilized in managing acute infections. Victor Nizet and collaborators in San Diego have been exploring whether certain drugs already approved for clinical use in other areas of medicine can have a beneficial impact at the host-pathogen interface in the context of acute infectious diseases. One such example has been the modulation of neutrophil extracellular traps (NETs), a specialized form of neutrophil cell death in which DNA, AMPs, and antimicrobial histones are released and may ensnare and kill bacteria [76]. Statins, inhibitors 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) are a mainstay in the treatment of hyperlipidemia to reduce cardiovascular disease risk, boost NET production and neutrophil and macrophage killing of MRSA *in vitro* and *in vivo* [77]. Similar NET boosting properties that aid in phagocyte bacterial clearance

were demonstrated for Tamoxifen, a well-known oestrogen receptor inhibitor widely used for the treatment and prophylaxis of breast cancer [78], and anacardic acid, a component of cashew nut shells used in traditional Ayurvedic medicine [79].

In a cohort of patients with *S. aureus* bacteremia, low platelet count was correlated with increased mortality, inspiring another drug repurposing concept based on platelet activity. Platelets can release antibacterial peptides that kill *S. aureus*, but the pathogens' pore-forming α -toxin can damage and inactivate the peptides [80]. The α -toxin caused a myriad of changes, namely, decreased viability, induced sialidase to cause desialylation of glycoproteins, and accelerated clearance by the hepatic Ashwell-Morell receptor (AMR), all leading to reduced platelet counts [80]. Ticagrelor (Brilinta), a popular P2Y₁₂ receptor inhibitor drug prescribed after myocardial infarction, blocked α -toxin-mediated platelet injury and stabilized platelet counts to protect against *S. aureus* infection in a murine challenge model [80]. In addition, the anti-influenza sialidase inhibitor oseltamivir (Tamiflu) provided similar therapeutic benefits. This work served as a proof-of-concept for repurposing two FDA-approved drugs as adjunctive therapies to improve clinical outcomes in *S. aureus* sepsis.

NANOSPONGES: CONTROLLING PATHOLOGICAL INFLAMMATION IN PNEUMONIA AND SEPSIS

Sepsis is a disease of immense complexity, often affecting immunocompromised patients, including infants and children, with a high mortality rate. With no approved drugs, exorbitant associated healthcare costs, and 20–30 million estimated cases each year across the globe, a true breakthrough in sepsis therapy is often referred to as a holy grail of clinical medicine. The diverse and sometimes polymicrobial infectious aetiology of sepsis and the multitude of dysregulated host inflammatory factors that drive sepsis pathophysiology mandate a quest for fundamentally novel strategies. Natural biomimicry of host cell membranes is capitalized in one nano-therapeutic approach [81]. The cell membranes of host cells are extruded and coated onto nanoparticles generating up to 50 000 membrane-coated nanoparticles from a single donor cell such as a red blood cell (RBC) or platelet [82]. This biomimetic nanoparticle is a faithful representation of the host cell, and upon encountering bacterial membrane targeting or pore-forming toxins, it will effectively absorb the toxin and prevent host cell injury. Animal studies have shown that these membrane-coated nanosponges can effectively protect animals challenged with *S. aureus* or group A *Streptococcus* from tissue injury and death driven by their pore-forming toxins [83, 84]. However, in the case of sepsis, in addition to the bacterial toxins, proinflammatory factors cause the release of cytokines that ultimately result in a cytokine storm. The next generation of macrophage membrane-coated nanoparticles absorbs bacterial pore-forming toxins, cell wall components such as lipopolysaccharide (LPS) and peptidoglycan that activate host Toll-like receptor signalling, and excessive proinflammatory host cytokines that together drive the pathological inflammation ('cytokine storm') of sepsis. Macrophage nanosponges protected against mortality in a murine model of *E. coli* sepsis [85].

Inflammasomes are multiprotein complexes in the host cell cytosol assembled by pattern-recognition receptors following the detection of microbial pathogens or signals from damaged host cells [86]. Inflammasomes activate inflammatory caspases to promote the maturation of cytokines, interleukin-1 β (IL-1 β), IL-18, and a proinflammatory lytic cell death called pyroptosis [87]. 'Inflabiotics' are a novel drug concept that targets the inflammasome and curtail the exaggerated host inflammatory response in response to certain bacterial infections or systemic viral diseases such as COVID-19. Nod-like receptor family pyrin domain containing 3 (NLRP3) plays a key role in inflammasome biology during the response to infectious diseases. For example, one virulence factor used by *S. aureus* to escape innate immune clearance is the α -toxin, which activates the NLRP3 inflammasome, resulting in the sequestration of mitochondria away from the macrophage phagosome and suppression of ROS-mediated bacterial killing [88]. High α -toxin expression correlates with poor prognosis in patients with *S. aureus* pneumonia [89]. In a murine pneumonia model, treatment with NLRP3 inhibitor MCC950 improved survival and reduced *S. aureus* burden by three-log-fold. This targeted NLRP3 inhibition was superior to blocking IL-1 β receptor and/or IL-18 using anakinra and an anti-IL-18 mAb [88]. Streptococcal toxic shock-like syndrome (STSS) is an acute, severe infection caused by group A *Streptococcus* or the zoonotic pathogen *S. suis* in which hyperinflammation can precipitate multiple organ failure. In a murine model of *S. suis* STSS, MCC950 significantly reduced IL-1 β production, curtailed other downstream cascading cytokines, including IL-6 and IFN- γ , and alleviated organ injury with decreased mortality [90]. Several additional inhibitors of NLRP3 are in the drug discovery pipeline [91] and may be of interest in controlling unregulated inflammation in other conditions, including COVID-19 pneumonia.

CLINICAL AND PUBLIC POLICY INTERVENTIONS

To achieve success, interventions to combat AMR, both at the level of public health policies and clinical guidelines, must support and complement basic and translational research. Here we discuss three potential interventions at the clinical medicine and public policy levels: short course treatment, antibiotic stewardship, and surveillance (Fig. 4).

SHORT COURSE TREATMENT

When demonstrated not to compromise successful outcomes, an overall reduction in antibiotic exposure from shortened courses of therapy will lessen perturbation of the microbiome and selective pressure for resistance. Many randomized control trials (RCTs)

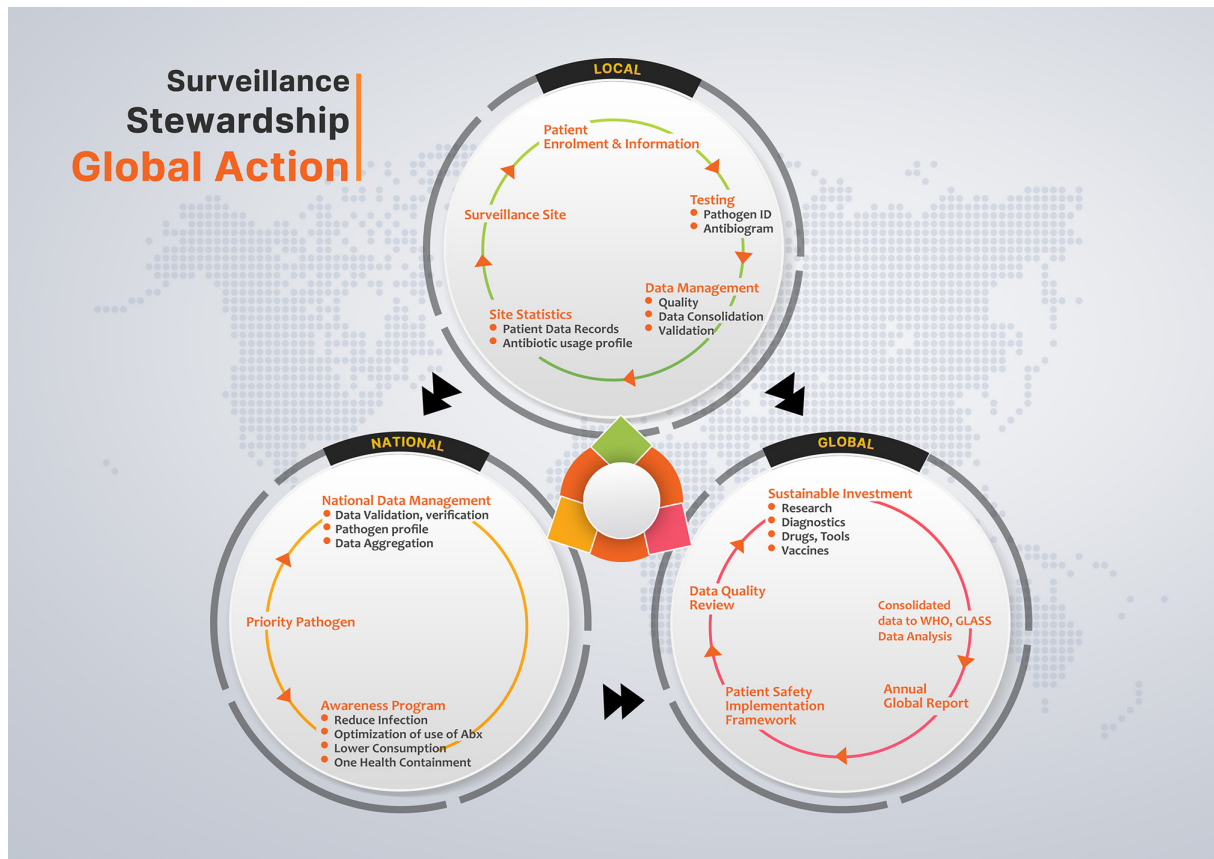


Fig. 4. Clinical and public policy interventions. Surveillance, stewardship and global action is dependent on seamless integration of local, national, and global policies. These efforts will enhance awareness of the implications of AMR along with strategies to prevent infection through optimal use of antimicrobial agents, as well as greater provision for surveillance, research and clinical data management, thereby introducing significant targets for control of AMR, through an increased investment at the global level.

have concluded that there were no significant differences in efficacy between shorter and traditional 2 week courses of antibiotic therapy for many common infections. In community-acquired pneumonia, eight RCTs demonstrated that 3 to 5 day courses of antibiotics are equally effective as 7–14 day courses of treatment [92, 93]. Shorter antibiotic treatment courses likewise decreased AMR strains' emergence in the microbial load of respiratory secretions [94]. Unfortunately, antibiotic prescriptions often still cover longer durations of therapy, even when evidence indicates that shorter treatment would be just as effective. Policies supporting short-course antibiotic therapy should therefore be instituted in hospital regulations promoting antibiotic stewardship – yielding a new mantra for antibiotic therapy of 'Shorter is Better' [92].

ANTIBIOTIC STEWARDSHIP

Antimicrobial stewardship is defined as the optimal selection, dosage, usage, and duration of antimicrobial treatment that produces the most favourable clinical outcome for the prevention or treatment of infection, coupled with low toxicity to the patient and minimal impact on the development of resistance. In this regard, it is vital to consider the 4D's of antimicrobial therapy: Right Drug, Right Dose, Right Duration, and De-escalation to Pathogen-Directed Therapy [95].

Institutions tailor their antimicrobial stewardship programmes to their own unique problem pathogens and overuse of specific classes of drugs. Major steps in establishing an Institutional Antimicrobial Stewardship Programme (IASP) include evaluating problem pathogens and antimicrobial use, establishing post-prescription review, and incorporating pharmacodynamic-based dose optimization [95]. Restriction of overused/misused antimicrobials can require that an infectious diseases physician or pharmacist first authorize them. Establishing post-prescription review allows therapy adjustment, change, or discontinuation based on the clinical attributes of the individual case. Still, it requires active surveillance and may be constrained by available healthcare resources. Antibiotic prescriptions should be made evidence-based, involving the review of local antimicrobial resistance patterns and relevant clinical factors, guiding de-escalation and appropriate length of treatment with specific agents.

Pharmacodynamics-based dose optimization considers the pharmacokinetic and pharmacodynamic properties of specific antimicrobials to optimize patient outcomes based on infection site and patient-specific responses, mitigating the risk of toxic effects [96]. Establishing a computerized physician order entry system can better facilitate antibiotic stewardship guidelines, wherein physicians are required to answer questions appropriately before successful ordering. These questions would reinforce antimicrobial stewardship principles and have been shown to decrease indiscriminate antibiotic prescriptions. Thus, the integration of antimicrobial stewardship can improve patient care along with reduced resistance resulting in controlled and optimal use of valuable antibiotic resources [97].

SURVEILLANCE

Five strategic objectives of a Global Action Plan involve focused activity at the local, national, and global levels to (a) improve awareness and understanding of AMR, (b) strengthen knowledge through surveillance and research, (c) reduce the incidence of infection, (d) optimize the use of antimicrobial agents, and (e) develop substantial targets for the needs of all countries through an increase in investment. It is important to be cognizant of significant gaps in the surveillance or monitoring of bacterial pathogens that cause common infections in humans. These gaps are further exacerbated by a paucity of common standards for methods, and data coordination at local, national, regional and global levels, which attenuate the ability to facilitate comprehensive monitoring and analysis of the occurrence and trends of AMR worldwide [98]. For example, the Global Antimicrobial Resistance and Surveillance System (GLASS) [99] attempts to combine patient, laboratory, and epidemiological surveillance data to enhance awareness of the extent and impact of AMR on populations. Along with analysis and reporting of harmonized data at national levels, GLASS and other surveillance systems improve the detection of emerging AMR and the potential for international spread, as well as the implementation of targeted prevention and control programmes at a global level.

The surveillance systems and programmes responsible for monitoring AMR in selected geographical areas, such as the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR), the European Antimicrobial Resistance Surveillance Network (EARS-Net), and the Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA) along with GLASS, could also work towards improving patient safety by promoting diagnostic stewardship through responsible use of antimicrobial agents, as well as quality-assured standardized identification of pathogens and antimicrobial susceptibility testing (AST) in patient management. The initial focus will be on MDR or XDR (extremely resistant) species limiting available therapeutic options [100].

CONCLUSION

Successful AMR containment efforts demand intense global coordination, collaboration, and sustained solidarity. There is no other pathway for effective AMR interventions on a global scale. Fostering a greater understanding of the relative contribution of different drivers of AMR development and implementing innovative strategies and visionary 'One Health' approaches are pertinent to facilitating progression towards a global AMR solution. In light of these considerations, the 'AMR: *Man vs. Microbes—The Race of the Century*' Symposium set out to brainstorm and define evolving medical, scientific, and policy challenges and opportunities to formulate strategies for combating this global pandemic threat. This review has summarized the collective thoughts, questions, opportunities, and challenges addressed in the symposium.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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