



NSF Engineering Research
Visioning Alliance

Engineering Opportunities to Combat Antimicrobial Resistance

Visioning Event Report

Engineering Opportunities to Combat Antimicrobial Resistance

A visioning report of the Engineering Research Visioning Alliance
Report Finalized December 10, 2024

Based on proceedings from an event hosted by:



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The Engineering Research Visioning Alliance (ERVA) is a neutral convener that helps identify and develop bold and transformative new engineering research directions, directly supporting the nation’s ability to compete in a rapidly changing global economy. Funded by the National Science Foundation (NSF) Directorate for Engineering, ERVA is a diverse, inclusive, and engaged partnership that enables an array of voices to impact national engineering research priorities. The five-year initiative convenes, catalyzes, and empowers the engineering community to identify nascent opportunities and priorities for engineering-led innovative, high-impact, cross-domain research that addresses national, global, and societal needs. Learn more at ervacommunity.org.

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ERVA visioning events enable the engineering research community to identify nascent opportunities and priorities for engineering-led, innovative, high-impact research that address global and societal needs. Each event relies on the efforts of organizations and individuals who volunteer to lead, guide, and participate in its activities.

ERVA extends its gratitude to Houston Methodist Research Institute for providing a fitting location to host the visioning event, and to the event co-host, the National Institute of Antimicrobial Resistance Research and Education (NIAMRRE). We are also grateful to Anita Shukla, the Elaine I. Savage Professor of Engineering at Brown University, who proposed the ERVA workshop and served as chair of the event's Thematic Task Force. Serving with her by developing the framework for the event and facilitating breakout sessions were Thematic Task Force members Robin Patel, Mayo Clinic; Stuart Tyner, Defense Health Agency; Kara Spiller, Drexel University; Paul Plummer, NIAMRRE; Ejaz Haque, Beckton Dickinson (BD); Andrés J. García, Georgia Institute of Technology; César de la Fuente, University of Pennsylvania; and Lefteris Mylonakis, Houston Methodist Hospital. Veronica LaMastro, Shukla's former biomedical engineering doctoral student at Brown University, drafted the event report.

Two panel discussions at the event brought perspectives from clinical settings. ERVA is grateful for the contributions from ERVA Technical Task Force members and Cameron Kim, Duke University; William Musick, Houston Methodist Hospital; and Ashley Wilde, Norton Healthcare.

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Participants from diverse settings contributed to the event, representing large companies and startups, academic researchers, and government program officers. ERVA is grateful to all the workshop participants who contributed their time to create a valuable discussion and visioning report and to their organizations for the liberty to share their expertise for this effort.

Rebecca Silveston, ERVA executive director, led the event planning, program development, and execution. The event and report development were executed under the guidance of ERVA Principal Investigator Dorota Grejner-Brzezinska, The Ohio State University, and ERVA co-principal investigators Anthony Boccanfuso, UIDP; Charles Johnson-Bey, Booz Allen Hamilton; Pramod Khargonekar, University of California, Irvine; and EdI Schamiloglu, University of New Mexico. Development of the visioning session theme was informed by input from the ERVA Standing Council, Advisory Board, and NSF Directorate for Engineering collaborators.



Antimicrobial test. Source: Canva



Executive Summary

Microbial infections that were once easy to treat are now less responsive to treatment and sometimes impossible to cure. Some microbes, including bacteria and fungi, harbor the ability to circumvent current treatments through a phenomenon known as antimicrobial resistance (AMR), which may result in poor clinical outcomes. The World Health Organization has defined AMR as a critical global health threat, with deaths associated with AMR-related infections surpassing those caused by cancer. Unfortunately, there is a dearth of effective treatment and prevention options. The slow pace of development of novel antibiotics in the pharmaceutical sector, in addition to a lack of antibiotic stewardship, preventative measures, and engineering innovation, create a space for future AMR development. Thus, there is an urgent need to identify and implement novel solutions that treat AMR-related infections and prevent the future development and spread of AMR.

AMR is a multidisciplinary problem that requires interdisciplinary solutions. To develop effective treatments and preventative measures, fundamental concepts within biology, chemistry, physics, and engineering must be combined in a translatable manner. Engineering can function as the key to bridging the gap between fundamental principles and successful implementation into tangible and scalable treatments and tools that both patients and clinicians can use.

At the Feb. 6-7, 2024 visioning event convened by the Engineering Research Visioning Alliance (ERVA), it was the goal of 55 researchers, industry leaders, and policymakers representing a broad range of expertise to create a roadmap of innovative, less-explored lines of multidisciplinary engineering research that can transform efforts to mitigate AMR. During the two-day event, participants actively discussed grand challenges and identified engineering research priorities spanning improved diagnostics, alternative therapeutics and therapeutic delivery systems, drug-free treatment approaches, prevention, and advanced modeling as key components needed to address drug-resistant infections and prevent AMR spread across communities. Specifically, five key areas for engineering research investment were identified. These research areas are listed below, along with key research priorities identified during vigorous discussion.

Grand Challenges

01

Diagnostic Biosensors and Wearables

- Develop new biosensors with improved sensitivity and broad-spectrum detection capabilities.
- Design biosensors to sample biomarkers from a variety of patient specimens, ideally those that are non-invasively collected and/or at low volumes.
- Design biosensors with enhanced chemical stability for improved shelf-life.
- Integrate diagnostic technology into wearable devices for rapid detection of infections in clinical and non-clinical settings

02

Engineered Antimicrobial Surfaces

- Develop antimicrobial surfaces that prevent bacterial and fungal attachment and/or effectively eradicate bacteria and fungi upon contact that are compatible with existing medical devices and high-touch surfaces.
- Explore different surface functionalization strategies (e.g., nanostructures, coatings, chemistries) to ensure the stability of antimicrobial surfaces following exposure to sanitation protocols.
- Incorporate diagnostic/sensing materials into antimicrobial surfaces to improve preventative measures and reduce the spread of AMR.

03

Smart Biomaterials

- Develop smart delivery systems using materials that locally release encapsulated antimicrobials following exposure to bacterial infections.
- Develop and design immunomodulatory materials as novel drug-free therapeutics that can stimulate the host immune response to combat infection.

04

Cell Engineering for Drug-Free Approaches

- Engineer different immune cells to appropriately respond to and treat AMR-related infections.
- Engineer commensal microbial cells to prevent the development of infections originating from within the microbiome and prevent the spread of AMR-related genes within endogenous bacterial communities.
- Investigate ideal administration of engineered immune and microbial cells to ensure viability and therapeutic efficacy.

05

Advanced Modeling Approaches

- Develop *ex vivo* “body-on-a-chip” models that accurately recapitulate complex infection sites or organs to study the response and efficacy of novel therapeutics.
- Design and investigate the efficacy of novel therapeutics that are effective against drug-resistant bacteria utilizing computational and artificial intelligence (AI)-based tools.



Bacteria on nanosilver-modified antimicrobial cotton. Source: University of Brighton.

Taking Action

AMR challenges the clinical treatment of infections daily, and the development of resistance has only been accelerated by inappropriate use of and exposure to antibiotics. Significant improvements are imperative to reduce infections and deaths associated with AMR. Engineering-directed research and technologies are needed to bridge the gap between patient needs and clinical translation. The priorities discussed in this report describe the innovative research needed to prevent or halt the progression of AMR and its consequences in the lives of patients. Engineering research enabling new preventive and therapeutic approaches and modeling can significantly contribute to addressing this global challenge.

Preventative Measures

Preventing the future development of AMR and the spread of AMR-related infections is essential. Several engineering approaches can be adopted to enable preventative measures in the clinic and in our daily lives at home. Diagnostic biosensors could provide accurate information to health care providers while allowing the required treatments to be administered promptly. These biosensors should be designed to diagnose any bacterial

pathogen while maintaining sensitivity, stability, and the ability to be integrated into wearable technologies. Novel antimicrobial surfaces can be developed to control the spread of infections for multiple applications. Work on nanostructured surfaces has already shown that it is possible to engineer the shape and size of nanostructures to eradicate specific pathogens. Significant work remains to understand the causal relationship between specific bacteria and the shape and size of repeating structures on surfaces. Beyond identifying effective tailored nanostructures, it is imperative to develop manufacturing technologies that can be scaled to produce large surfaces. While the semiconductor industry has mastered the art and science of creating nanostructures on silicon substrates, it cannot be translated to manufacture large surfaces with such structures. Traditional lithography techniques used today will be far too expensive to create large surfaces with the desired patterns. Other mechanical approaches like nanoimprinting that are insufficiently accurate for the semiconductor industry will work well for low-cost applications. However, challenges related to surface stability will require significant research to overcome as well as investigation into manufacturing requirements.

Novel Therapeutic Approaches

Engineering research is required to develop novel antimicrobial therapeutics and therapeutic delivery systems for controlled release of drugs. Necessary research ranges from drug-free cellular engineering approaches to smart antimicrobial delivery systems. Research into synthetic biology approaches utilizing immune and host-microbial cells is required to successfully integrate these cells within the body without adverse reactions. Smart drug delivery systems must be designed to ensure on-demand, tailored drug delivery under the desired (and often complex) conditions. These delivery systems should prevent inappropriate release of therapeutics to minimize development of AMR. Researchers and engineers must ensure the stability and viability of cell-based therapeutics and encapsulated agents within smart delivery systems. These novel approaches must also be designed as effective therapeutics against pathogenic bacteria without compromising the health of the commensal microbes, the microorganisms that reside on or within the human body normally without harming human health. Importantly, commensal microbiota frequently confers beneficial functionality to the human host.

Modeling Advancements

Research involving both *ex vivo* and computational modeling can generate powerful tools that provide accurate information rapidly without the need for long and expensive experiments. Specifically, *ex vivo* approaches can assist in developing complex models of bacterial and fungal infections containing commensal microbes and components of healthy tissues. Computational modeling abrogates the need for physical materials, allowing for complex system design without the challenges accompanying *in vitro* and *ex vivo* models. These models can be utilized as predictive measures following certain therapeutic approaches or to develop novel antimicrobial therapeutics that are effective against resistant microbes. Integration of AI-based approaches could also significantly improve the development of computational models and improve the design of future therapeutics with enhanced accuracy and speed.

The ideation and directed breakout sessions developed by the Thematic Task Force promoted open discussion, leading to identification of key research areas where engineering can pave the way for progress. The grand challenges discussed throughout this report can be utilized to develop novel antimicrobial therapeutics as well as preventative measures to limit future development and spread of AMR.

This report underscores the urgent need for new approaches to combat AMR and AMR-related infections while identifying specific directions for engineering researchers and funding bodies to pursue that have the potential to significantly address this global health threat.

Engineering Opportunities to Combat Antimicrobial Resistance

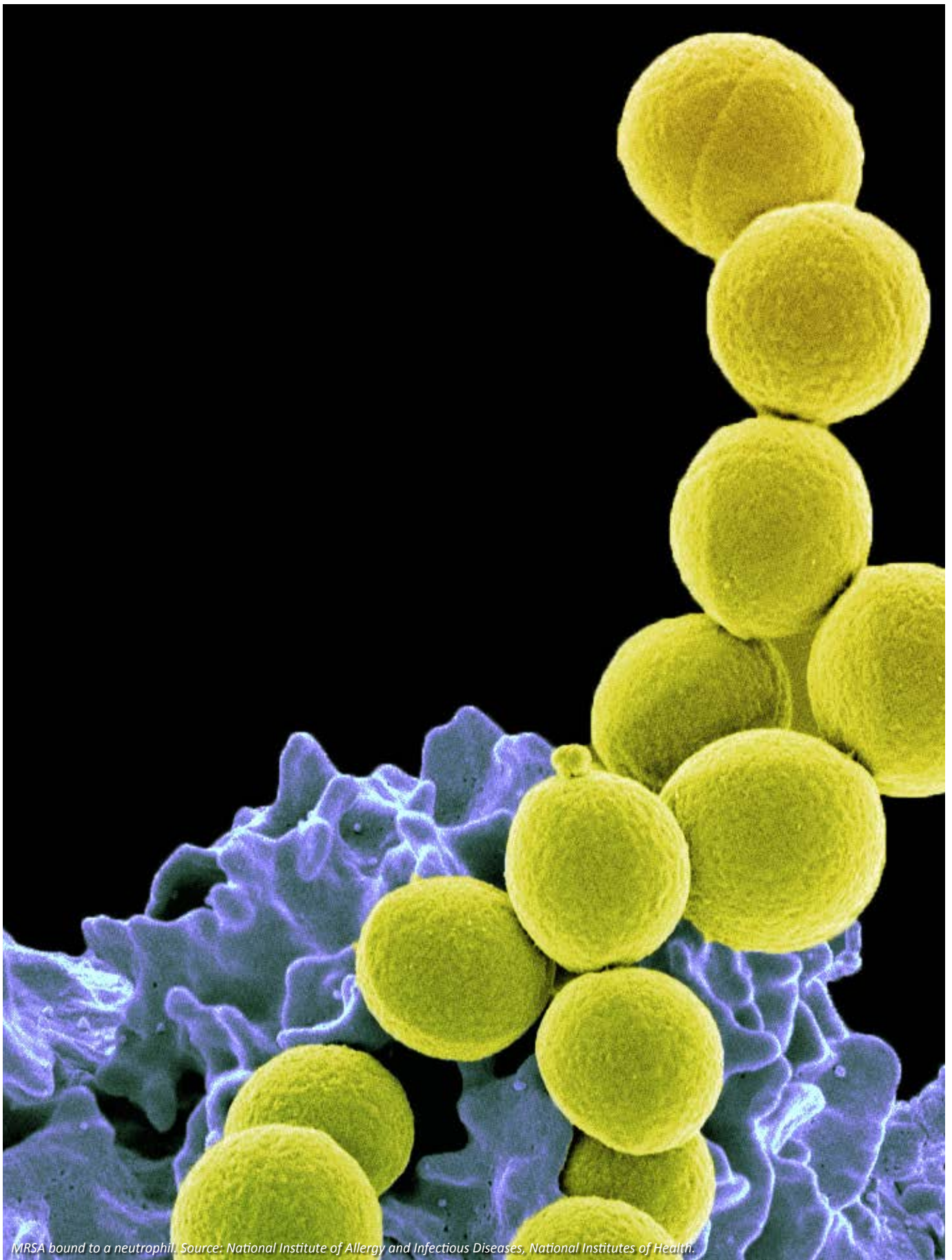
Microbial infections – or infections caused by bacteria, fungi (and less germane to this topic, viruses, and parasites) – can affect any individual. Most people recover with little to no medical intervention. However, some infections can become severe and life-threatening, requiring treatment in the form of antimicrobial medications.¹ Many beneficial and life-saving medical interventions, such as joint replacements, cesarian sections, organ transplants, and cancer treatments, also require antibiotics to reduce the risk of clinical complications.

Once considered “miracle drugs,” antimicrobial medications have seen waning efficacy over the last few decades. Microbes are constantly evolving and can develop defense mechanisms against current methods of treatment.² This results in antimicrobial medications no longer being effective in treating these microbial infections, a phenomenon known as antimicrobial resistance (AMR).³ While AMR occurs naturally due to evolutionary processes, a combination of a lack of antimicrobial stewardship, spread of antimicrobials and AMR genes within wastewater, and limited incentive to develop new antibiotics has exacerbated and accelerated the development of AMR.⁴ The use of antimicrobials in agriculture and improper drug disposal also contribute to the development and spread of drug-resistant microbes, coined as superbugs.⁵

AMR has complicated clinical practice by reducing the number of effective medications available for patients. Instead, today’s serious infections often require potent therapeutics that may cause serious side effects. Due to AMR, some infections have simply become impossible to treat. The impacts of AMR are particularly heavily felt in low-income, low-resource areas, as these areas have limited access to health care, infection prevention strategies, and often little to no antibiotic usage regulation.⁶

AMR is a global challenge. In 2019, it was estimated that 1.27 million deaths were directly attributable to drug-resistant infections worldwide and that AMR was a contributing factor for almost 3.7 million additional deaths.⁷ Although AMR is cited by the World Health Organization as a top global public health and development threat, research into developing new antimicrobial drugs to address today’s strains has stalled, and efforts to prevent further erosion of antibiotic efficacy are ineffective. The United Nations Environment Programme predicts that without significant intervention now, deaths due to AMR-related infections could top 10 million annually by 2050.

The purpose of this visioning event was to identify current research gaps as the springboard for identifying nascent engineering research directions with promise for significant impact in combating AMR and AMR-related infections. Participants representing large companies and startups, academia, and government, were invited based on their expertise in fields pertinent to AMR and microbial infections, including biomedical, chemical, and materials engineering, biology, pharmacology, and medicine. The Thematic Task Force led participants through discussions regarding four critical areas related to AMR: diagnostic technologies, alternative antimicrobials, antimicrobial biomaterials, and immune system engineering. Directed ideation sessions and breakout sessions explored critical subthemes within these four identified areas; from the event, several grand challenges regarding AMR were identified. While the discussion was centered around bacterial infections and bacterial AMR, engineering solutions identified during this event can also be applied to drug-resistant fungal infections, an area of equal concern. Further, while AMR spread through agricultural use and wastewater is an area where engineering solutions can be implemented, the focus of this event was to identify engineering opportunities directed toward clinical usage; future events should discuss preventative measures that can be implemented within the agricultural sector and for wastewater treatments.

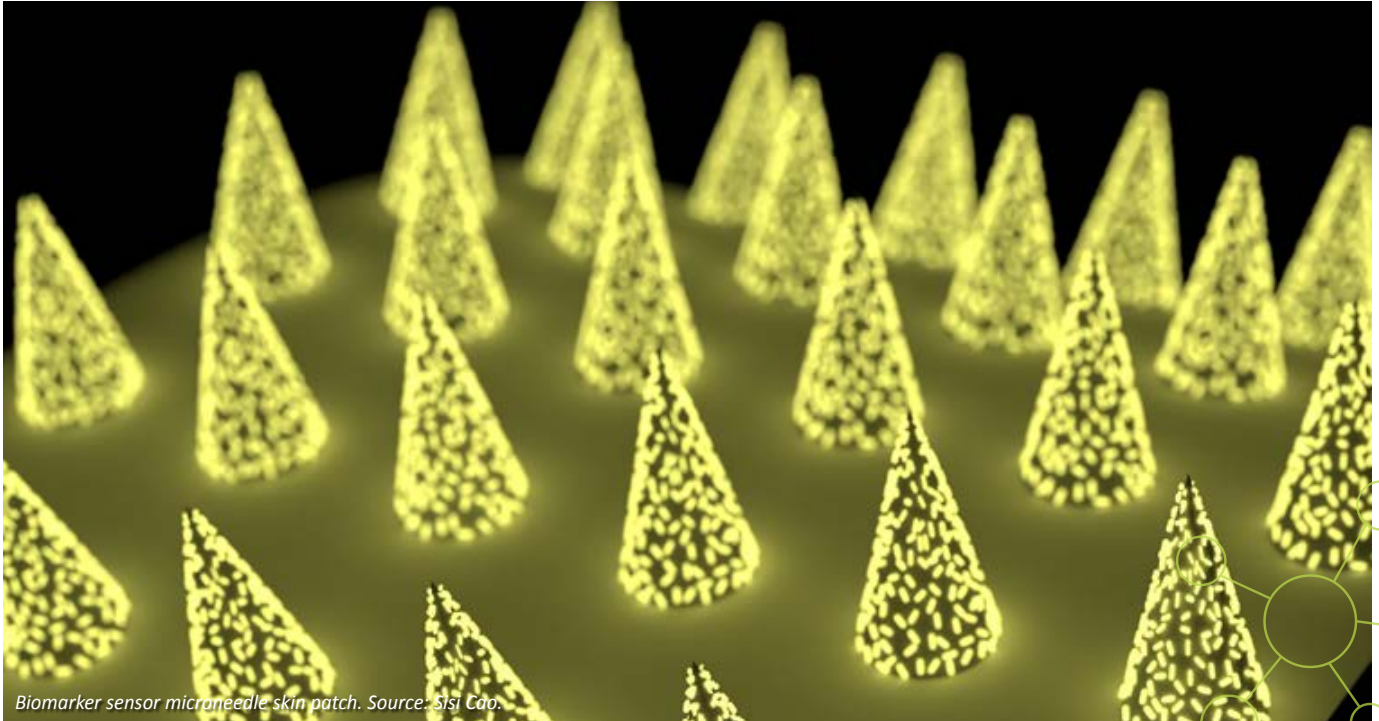


MRSA bound to a neutrophil. Source: National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Grand Challenges

#1

Diagnostic Biosensors and Wearables



Biomarker sensor microneedle skin patch. Source: Sisi Cao.

There is an urgent need to develop fast, accurate, and inexpensive engineered diagnostic technologies to ensure appropriate treatment is provided to combat and prevent AMR. Current bacterial detection methods and antibiotic susceptibility profiling are time-consuming, often requiring several days depending on the bacterial pathogen. Genomic sequencing technologies are more sensitive, yet adoption is lackluster due to high performance costs and difficulty of sample preparation; these technologies are also much less likely to be used in low-income, low-resource areas.⁸

Diagnostic biosensors are a broad category of devices that can detect specific components within a sample with accuracy, sensitivity, speed, and diagnostic power. Research into sensor technology with the ability to detect a wide range of pathogenic bacteria is required, and these sensors must differentiate between pathogenic and commensal bacteria as well as viral, fungal, and parasitic pathogens. Diagnostic biosensors should also provide rapid results, ideally on the scale of minutes to hours, to enable faster treatment initiation, which has been shown to result in better clinical outcomes, faster recovery time, and lower costs.⁹ Rapid diagnosis can help reduce the spread of infections given that it enables faster identification of the cause of infection and effective therapy deployment.

To ensure usability, these devices should be designed to utilize patient samples that are easy to collect in a non-invasive or minimally invasive manner. Engineering research is needed to develop biosensors that can detect low levels of infection-related biomarkers within a wide range of patient samples; collaboration between engineers, clinicians, and microbiologists is particularly imperative to design devices with high clinical potential. Diagnostic biosensors should also be engineered to detect multiple biomarkers present within patient samples to increase

RESEARCH PRIORITIES IN BRIEF

The design and development of diagnostic biosensors and wearables heavily rely on the pathogenic biomarkers present within patient samples; a combination of fundamental knowledge of these biomarkers and the ability to quantify them with high selectivity and sensitivity is an area of research that can be achieved within the next five years. Use of advanced materials (e.g., photoelectric, nanoscale) and chemical enhancements (e.g., catalysts, engineered enzymes, etc.) in sensor technology can expedite this development.

More complex engineering opportunities, including improved detection at low biomarker concentrations, detection of multiple analytes simultaneously (e.g., multiplexing), integration of biosensor technology into at-home testing products and wearable devices, improved chemical stability and shelf-life, and development of a digital infrastructure for data collection, may require longer periods of research (beyond five years).

the diagnostic power of these engineered devices. Research focused on material advancements, such as the use of novel photoelectric surfaces or nanoscale materials, and chemical enhancements (e.g., catalytic mediators, enzyme engineering, enzyme immobilization)¹⁰ within the diagnostic biosensor design should be explored to increase sensor sensitivity, reduce the signal-to-noise ratio, provide point-of-care treatment, and ensure the stability of components within the test to provide diagnostics with long shelf lives.

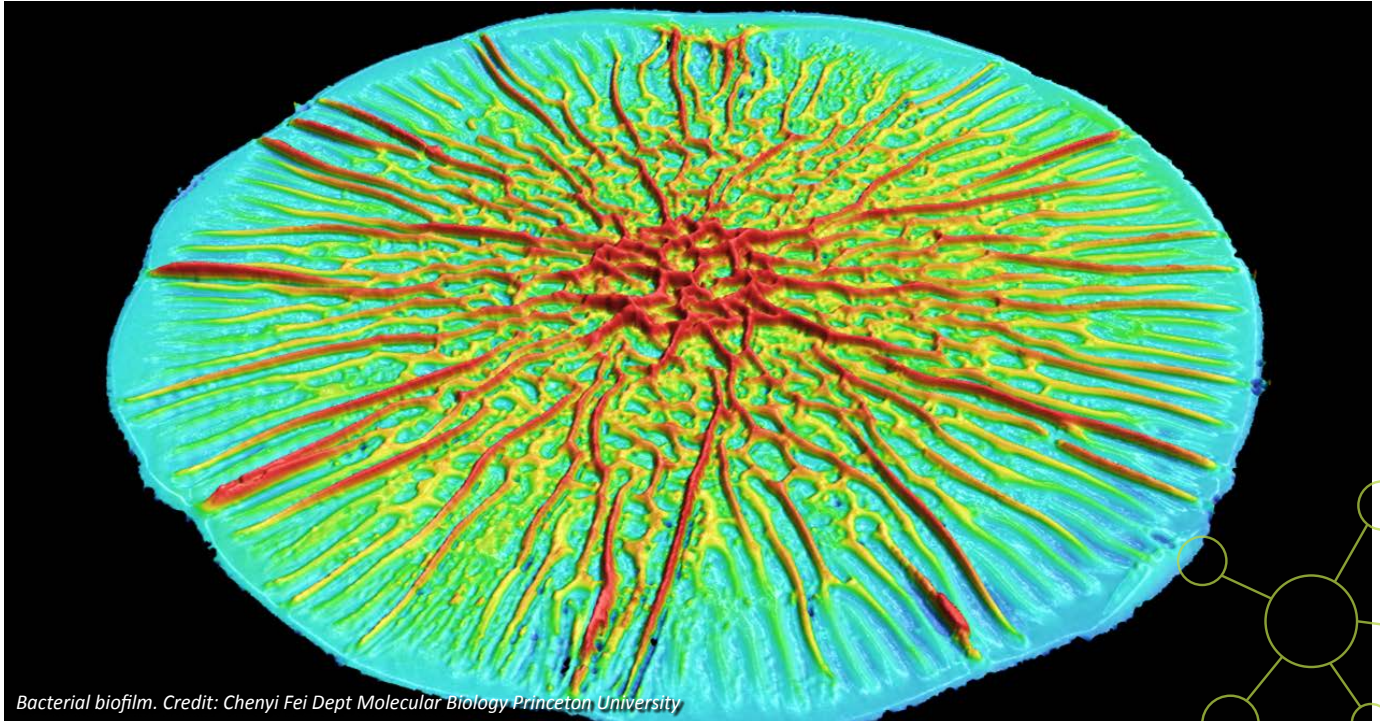
Advancements in wearable devices to enable data collection of specific infection-related symptoms or biomarkers should also be investigated to improve diagnostics, specifically at-home diagnostics. To ensure the successful deployment of these technologies, wearable devices must be designed to capture patient samples non-invasively in non-clinical settings and within short periods of device use. Additionally, engineering is needed to improve sensor technology to accurately detect biomarkers with small sample volumes. These advancements can be incorporated into current smart device technology or implemented within novel devices for infection-specific monitoring. This technology can also be implemented within at-home testing technologies; the COVID-19 pandemic catalyzed a surge in the development of at-home testing to aid in disease management and prevention.¹¹

Data collected from engineered diagnostic biosensors could be leveraged for further research into relationships between AMR incidence and genetic immunity factors present in certain individuals, which ultimately could contribute to development of improved treatment modalities.

Grand Challenges

#2

Engineered Antimicrobial Surfaces



Surfaces that can prevent bacterial attachment and/or cause bacterial death upon contact should be a priority research focus. Bacteria can attach to most surfaces, both living and non-living, despite current sterilization, sanitation, and disinfection protocols.^{12,13} For example, in clinical settings, 92% of privacy curtains become contaminated with bacteria within one week, contributing to hospital-acquired infections.¹⁴ Additionally, the formation of bacterial biofilms on implanted medical devices has been linked to the development of hospital-acquired infections.¹⁵

Thus, it is imperative that research is focused on the design and development of novel antibacterial surfaces for broad-spectrum use. Specifically, studies evaluating the antibacterial properties of different surface topographies and patterns, as well as surfaces with chemical modifications (e.g., hydrophilic/hydrophobic coatings, functionalization of cationic materials, or antimicrobial agents), should be a research priority. These surfaces can be designed to kill bacterial pathogens on contact, preventing initial attachment and biofilm formation, or lead to bacterial killing based on release of active antimicrobial agents from the surface. For successful implementation, these novel antibacterial surfaces must withstand standard sanitation and sterilization protocols required by hospitals. Engineering research efforts to improve the chemical and structural stability of antimicrobial surfaces are crucial. These engineered surfaces must also be capable of being incorporated into different material types, including different medical device materials and materials utilized in high-touch areas. Specific to implanted materials, it will be critical to ensure that these surfaces are able to prevent potentially harmful biofouling that interferes with the functional properties of the surface. Finally, manufacturing scale-up limitations should be considered when designing these antimicrobial surfaces.

RESEARCH PRIORITIES IN BRIEF

Investigations into antimicrobial surfaces capable of killing bacteria on contact and/or preventing bacterial attachment are engineering opportunities that can be achieved within the next five years. These can include the development of surfaces with different topographies, coatings containing antimicrobial agents (e.g., antimicrobial peptides, novel antimicrobial drugs), and chemical modifications (e.g., hydrophobic/hydrophilic materials, functionalized coatings).

However, antimicrobial surfaces with enhanced chemical stability and durability, especially following exposure to sanitation and sterilization protocols, and with the ability to distinguish between commensal and pathogenic bacteria may require a longer developmental timeframe (more than five years).

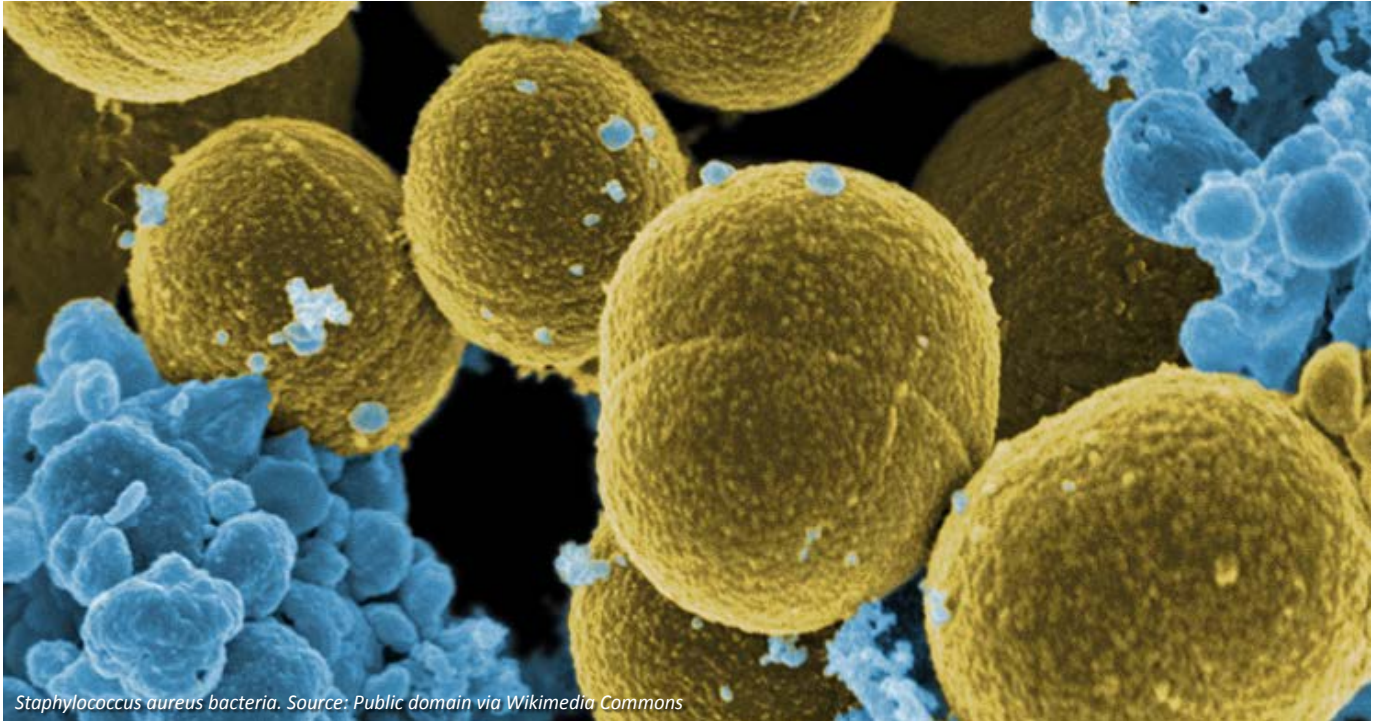
Finally, incorporation of advanced drug-free approaches (e.g., light-based disinfection, microcurrent disinfection), combined with diagnostic and antimicrobial activity in the same technology (e.g., theranostic devices), and incorporation of these novel antimicrobial surfaces within medical devices and high-touch clinical and non-clinical settings may also require more than five years.

Drug-free approaches such as UV-C and other methods for disinfection combined with detection and therapeutic approaches should also be explored. Theranostic surfaces, or those that can simultaneously detect and kill pathogenic bacteria, can also be engineered; this would aid in the rapid removal of contaminants from surfaces and materials within clinical and non-clinical settings. The approaches discussed within the engineered diagnostic space (see the section, “Diagnostic Biosensors and Wearables”) could be incorporated into these antimicrobial surfaces.

Grand Challenges

#3

Smart Biomaterials



Staphylococcus aureus bacteria. Source: Public domain via Wikimedia Commons

Current biomaterials-based antimicrobial drug delivery approaches, like wound dressings, locally release antimicrobial agents to sites of infection yet are unable to modulate or control therapeutic release based on the properties of the infection. Given that exposure to superfluous antibiotics can exacerbate the development of AMR, the generation of smart biomaterials-based delivery systems that release antimicrobials during active infections is an urgent area of research; these technologies can circumvent the need for systemic antibiotic delivery and improve the treatment of localized infections.¹⁶ These smart biomaterials-based delivery systems (e.g., nano- and micro-scale particles, nanogels and hydrogels, films and coatings, etc.) must be designed to release drugs only when a bacterial infection is present and remain stable in the presence of commensal bacteria and fungi. The biomaterial components should be designed to respond to endogenous stimuli (e.g., pH, enzyme, and redox) associated with a wide range of pathogenic bacteria and/or exogenous stimuli (e.g., temperature, light, and ultrasound) to develop broad-spectrum therapeutics. Research investigating material and encapsulated therapeutic stability should be conducted to ensure the long shelf-life of these delivery systems as well as the proper length of administration to generate the desired therapeutic effect.

Development of immunomodulatory biomaterials can help minimize the use of antibiotics and the development of AMR. Immunocompromised individuals are more likely to experience microbial infections, and these biomaterials should ideally be able to stimulate the immune system from a deficient state. Research is needed to design materials to activate or bolster certain immune responses depending on the state and location of the infection. Biomaterials must also be designed to respond to dynamic immune system activity, especially for long-term use, to prevent undesired systemic immune responses. Due to the complexity of the immune system, designing and validating immunomodulatory materials remains a key research challenge and requires interdisciplinary synergy.

RESEARCH PRIORITIES IN BRIEF

Smart biomaterial delivery systems that can respond to exogenous and endogenous stimuli for localized release of encapsulated therapeutics can be achieved within the near future. Research focused on material development that can respond to a range of stimuli and encapsulate and release a variety of cargo should be prioritized over the next five years. Evaluation of these materials, especially in complex infections (e.g., localized, invasive, systemic), development of material selectivity towards pathogenic microbes, and AMR development following long-term exposure to these smart delivery systems may require more than five years before clinical translation.

The development of immunomodulatory materials requires fundamental knowledge pertaining to the immune system and its response toward different infections. Thus, research priorities in this space require a fundamental understanding of immunology (which can be achieved within a five-year timeframe). The design and validation of engineered immunomodulatory materials will be dependent on this fundamental knowledge. Thus, investigation of the antimicrobial activity of novel materials, their long-term efficacy in generating localized and/or systemic immune responses toward bacteria, and their ability to prevent development of new resistant bacteria will require more in-depth research (beyond five years).

Grand Challenges

#4

Cell Engineering



Engineered immune cells can improve and/or bolster the natural immune response toward bacterial infections. However, there are several engineering challenges associated with this approach that require collaboration with other research sectors. First, research investigating immune cell function following genetic manipulation is required to ensure proper specificity toward pathogenic bacteria with no negative, systemic responses. Effective delivery of engineered immune cells is also crucial to maintain therapeutic efficacy and cell function. As bacteria are able to overcome the immune system within persistent infections, it is important to study the long-term interactions between the engineered immune cells and pathogenic bacteria. Finally, research will be needed to study the duration of antibacterial efficacy achieved with this therapeutic approach and to determine the requirement for multiple treatments.

Commensal bacteria within the human microbiome play a fundamental role in maintaining human health and protecting the body from pathogenic bacteria.¹⁷ Research to create engineered microbes with antimicrobial activity may be beneficial for reducing antibiotic use and may prevent the development of infection. Nevertheless, engineered microbes that locally release antibacterial components must specifically target pathogenic bacteria while not disrupting the healthy microbiome. These microbes can also be engineered to prevent the spread of AMR-related genes from one bacterial cell to another in the body, limiting development of AMR. Long-term research is required to ensure the viability of these microbes, safe and effective colonization within individuals, and therapeutic efficacy against a range of infections.

RESEARCH PRIORITIES IN BRIEF

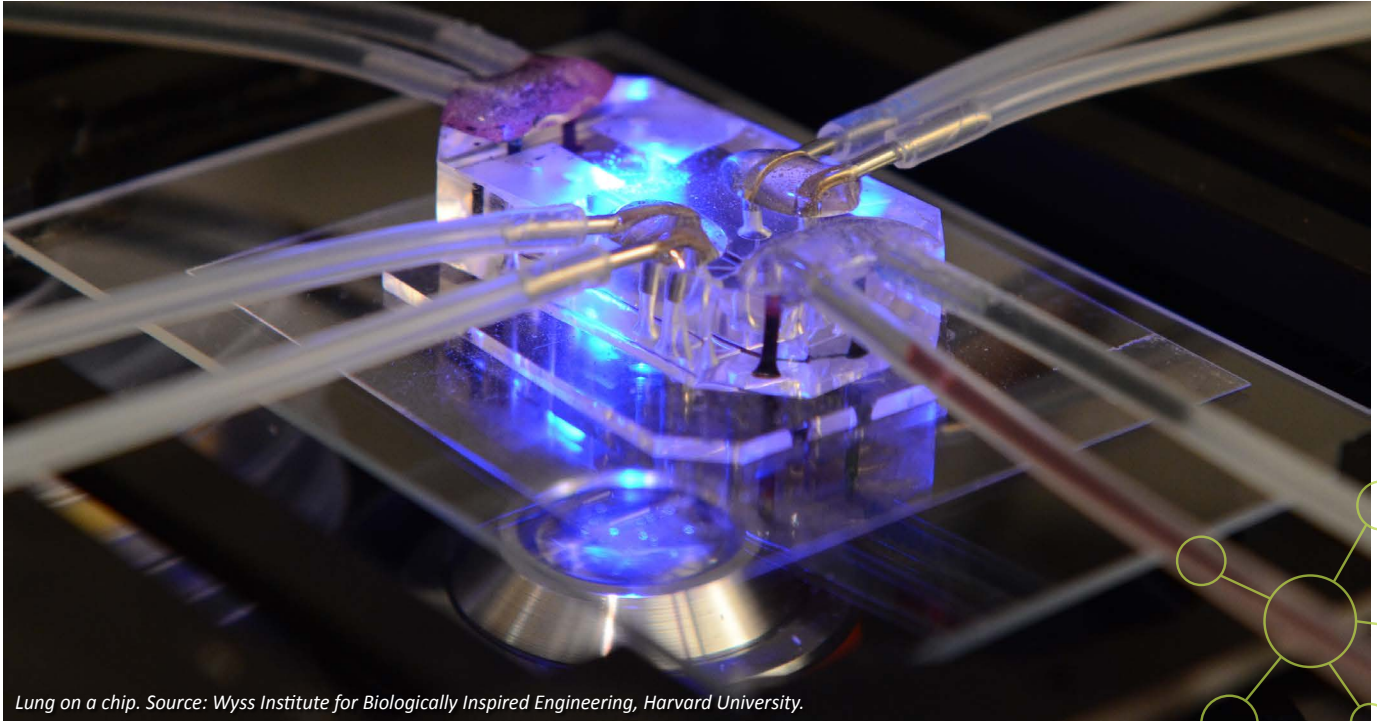
Engineering both immune and microbial cells for drug-free approaches for AMR-related infections will heavily rely on both cellular engineering advances and a fundamental understanding of the immune and commensal microbial responses toward pathogenic bacteria (achievable within five years). Due to the complexity of the immune system and the microbiome, evaluation of these therapeutic approaches, including cell viability after genetic manipulation, broad-spectrum activity, selectivity towards pathogenic bacteria, and delivery methods to ensure cell colonization and viability, will require a longer timescale to ensure efficacy within pre-clinical and clinical settings.

While fundamental knowledge regarding the interplay between the immune system and the microbiome is still being explored, research utilizing engineered immune and microbial cells has the potential to bridge this knowledge gap and improve the future design of engineered cells that can work as a collective against AMR-related infections. Importantly, these interdisciplinary solutions will require collaboration between engineers, immunologists, and biologists.

Grand Challenges

#5

Advanced Modeling Approaches



Lung on a chip. Source: Wyss Institute for Biologically Inspired Engineering, Harvard University.

The development of accurate infection models is an area of significant research potential. Typically, live animal models are used to study the efficacy of novel antimicrobial therapeutics or the body’s response toward infection, yet these models are expensive, associated with ethical concerns, and do not fully replicate an individual human’s response.¹⁸ Engineered “body-on-a-chip” models hold great promise in answering both fundamental questions regarding AMR-related infections and evaluating the efficacy of different treatments.¹⁹ These body-on-a-chip models must be able to replicate different environments that are composed of heterogeneous cell types, including commensal bacteria, other microbial cells, and different mammalian cells. Models containing both human and bacterial components will require careful engineering design constraints to support the growth of individual cell types collectively. These models also have the potential to improve personalized medicine, as patient-derived cells can be utilized.

Computational modeling is another area of significant engineering research to combat AMR-related infections. These models can be developed to rapidly study complex systems, evaluate the potential of novel AMR therapies, toxicity to organ systems, and the response toward therapies. This technology has the potential to increase modeling complexity that may be challenging for *in vitro* and *ex vivo* models. However, these models are challenging to validate without corresponding *in vitro* or *in vivo* data, and large computational power may be needed, depending on the complexity of the model. Integration and application of AI-based tools could improve the complexity of these models, increase the output of novel antimicrobial agents effective against drug-resistant bacteria, and even aid in the development of engineered materials, cells, and biomaterials-based drug delivery systems.

RESEARCH PRIORITIES IN BRIEF

Ex vivo models can be utilized to investigate novel therapeutics and interactions between microbial and mammalian cells. Research investigating growth conditions and designs to generate multi-cellular, simplified models may be possible over the next few years. The increasing complexity of these models, including multi-component infection/body sites containing multiple cell types (e.g., microbial, immune) and incorporation of patient-specific samples to generate personalized models, will require more development (beyond five years).

Computational approaches can be used to rapidly develop complex bacterial infection models and evaluate novel antimicrobial therapeutics, especially with integration of AI-based tools (within a five-year time horizon). Use of these computational approaches to aid in drug and therapeutic development, especially against resistant microbes, may require development beyond five years due to the increased computational power needed to generate multi-component and personalized models that represent holistic and patient-specific responses toward infections and treatments, respectively.

Overall Assessment and Moving Forward

AMR is a significant clinical issue that threatens the health of individuals globally. Patients and physicians view antibiotics as miracle drugs, yet antibiotic efficacy is waning. This broad problem requires interdisciplinary solutions involving engineers, biologists, chemists, physicists, and clinicians. Workshop participants identified five grand challenge research areas, ranging from diagnostic devices to computational modeling, where engineering can revolutionize solutions to AMR over the next few decades. Engineering research is needed to help curb antimicrobial resistance and provide innovative solutions for therapeutics, surfaces, and devices that do not promote resistance development. Engineering also plays a key role in revolutionizing the use of *ex vivo* and computational modeling, enabling research to go forward at a more rapid pace and at a lower cost than *in vivo* approaches.

Preventative Measures

Preventative measures are the primary method to slow the progression of antimicrobial resistance. There is an urgent need for increased engineering-led research efforts to reduce contamination and spread of AMR-related infections through the development of improved diagnostics and antimicrobial surfaces. Research is needed to develop diagnostic devices that can detect a broad range of bacteria and associated susceptibility characterization (i.e., which treatment to use), or conversely, non-bacterial diseases that mimic bacterial diseases, and how to provide fast, accurate detection to ensure deployment of the appropriate treatment.

Design constraints within engineered surfaces need to be addressed to develop surfaces that can effectively prevent bacterial attachment or colonization. The materials and chemistry required may differ between surface types, requiring careful and thorough experimentation during development. Successful implementation of these novel antimicrobial surfaces has the potential to limit hospital-acquired infections that contribute to the spread of AMR.

Novel Therapeutic Approaches

New therapies are required to fight against AMR-related infections, as the efficacy of current therapeutics is waning. Smart biomaterials can be designed to release antimicrobial agents in the presence of active AMR-related infections, improving the treatment of localized infections. The materials deployed in these technologies must be capable of pathogen-specific responses with good chemical stability to be successfully employed as clinical treatments. Engineered surfaces lacking incorporated antimicrobials, including nanostructured materials, light-activated surfaces, and conductive surfaces, may also serve as smart materials exhibiting antimicrobial properties.

Drug-free therapies, such as engineered cells or immunomodulatory biomaterials, may reduce or even eliminate the need for antibiotic therapies in the near future. Fundamental research related to the interplay between immune and commensal microbes with pathogenic bacteria during AMR-related infection must occur to develop viable cell-based therapeutics. The response of immune cells toward bacterial infections can aid in the generation of biomaterials that can provide enhanced immune responses, even in immunocompromised individuals. Careful investigation of the immune response toward different materials must be conducted.

Modeling Advancements

Advanced computational modeling can aid in the validation and screening of new therapies, as well as improve fundamental understanding of how the human body responds to AMR-related infections and treatments. Novel antibiotic compounds can be used to eliminate infections through different mechanisms of action, and discovery of these compounds can be enhanced with AI-based approaches. Engineered models can also eliminate the need for expensive, time-consuming *in vivo* experiments. Integration of these models, especially with patient-specific information or material, can aid in the development of personalized medicine and improve clinical outcomes.



Source: Shutterstock

Engineers urgently need to prioritize the design of novel approaches to curb the future development of AMR. Researchers, health care providers, industry partners, and funding agencies must collaborate to effectively overcome the grand challenges presented in this report. Further, through the dissemination of this report and continued education regarding the threat of AMR, the mindset regarding microbial infection, prevention, and treatment can be shifted, leading to greater communication and successful implementation of new engineering-led technologies.

Appendix A: Visioning Event Participants

Michael Baym, Harvard Medical School
Haluk Beyenal, Washington State University
Christina Boucher, University of Florida
Violet Bumah, University of Tennessee at Martin
Carey-Ann Burnham, Pattern Bioscience
Thomas Chen, Colorado State University
César de la Fuente, University of Pennsylvania
Tejal Desai, Brown University
An Dinh, Houston Methodist Research Institute
Rodney Donlan, U.S. Centers for Disease Control and Prevention
Mohamed Draz, Case Western Reserve University
Paul Eder, U.S. National Institutes of Health/National Institute of Allergy and Infectious Diseases
Brian Finrow, Lumen Bioscience, Inc.
Andrés J. García, Georgia Institute of Technology
Thomas Gilbert, Integra LifeSciences
Devendra Gorhe, Zimmer Biomet
Chunlei Guo, AlchLight LLC and University of Rochester
Ejaz Haque, BD Biosciences
Amber Jennings, University of Memphis
Abraham Joy, Northeastern University
Cameron Kim, Duke University
Veronica LaMastro, Brown University
Rick Martin, MicroGen Diagnostics
Joshua McClure, Maxwell Biosciences
Eleftherios Mylonakis, Houston Methodist Hospital
Robin Patel, Mayo Clinic
Paul Plummer, National Institute of Antimicrobial Resistance Research and Education
Roger J. Pomerantz, Viracta Indaptus Verimmune Collplant
Shaurya Prakash, The Ohio State University
Maria Soledad Ramirez, California State University, Fullerton
Nathan Rohner, Lubrizol
Vincent Rotello, University of Massachusetts at Amherst
Oxana Selivanova, Pfizer
Anita Shukla, Brown University
Kara Spiller, Drexel University
Michal Tal, Massachusetts Institute of Technology

Azra Yaprak Tarman, Texas A&M University
Benjamin Thomas, Texas A&M University
Rachel Tinker-Kulberg, Kepley Biosystems
Stuart Tyner, U.S. Army/Defense Health Agency
Dwight Austin Van Horn, Chitozan Health, LLC
Ekaterina Vert-Wong, Sabin
Hongjun Wang, Stevens Institute of Technology
Ashley Wilde, Norton Healthcare

National Science Foundation Participants

Randy Duran
Louise Howe
Kay-Marie Lamar
Alexis Lewis

ERVA Team and Consultants

Josh Aebischer, ERVA
Mike Brizek, UIDP
David Glazer, Glazer Design
Dorota Grejner-Brzezinska, The Ohio State University
Charles Johnson-Bey, Booz Allen Hamilton
Sandy Mau, UIDP
Ashley Richardson, ERVA
Rebecca Silveston, ERVA

Appendix B: Panel Summaries

Why Engineering Research Is Needed, from a Clinician's Perspective

Moderated by Anita Shukla, Brown University, with panelists Lefteris Mylonakis, Houston Methodist Hospital, Robin Patel, Mayo Clinic, and Paul Plummer, NIAMRRE



This panel highlighted clinical challenges faced by medical professionals associated with treating AMR-related infections, providing the panelists with an opportunity to lay foundational groundwork for why engineering principles are required when developing both preventative mechanisms and therapeutics to combat AMR.

Engineering is necessary to develop practical tools for improved treatment of both mild and severe life-threatening infections. Current technologies are lacking and cannot effectively diagnose and eradicate pathogenic bacteria, preventing clinicians from providing adequate care. Several novel technologies, including improved diagnostic devices, biomaterials, and theranostic tools that can simultaneously diagnose and treat infections, were discussed as critical areas of engineering research to combat current limitations. These technologies should be affordable, provide rapid results for critical cases, and be designed with a “one health” perspective.⁴ Finally, preventative measures are critical to combat AMR-related infections and prevent their spread within local and global communities.

Ethics Considerations

Moderated by Cameron Kim, Duke University, with panelists William Musick, Houston Methodist Hospital and Ashley Wilde, Norton Healthcare



This panel framed ongoing issues with antibiotic stewardship and its contribution to the development of AMR. A disconnect between the development of novel antimicrobials and clinical use was first emphasized. Specifically, while there is some engagement between clinical providers and individuals within industry, pharmaceutical agencies, and regulatory bodies, the level of engagement may be highly dependent on a particular case or community location. This disconnect, in addition to a lack of education and communication, has contributed to the inappropriate administration of antibiotics.

Antibiotic stewardship is a major factor in slowing the development of AMR. Currently, antibiotics are administered in situations where they are not required because it is widely believed that antibiotics can be effective in every situation. Prevention of AMR development will require a combination of appropriate guidance and provider and community education. There is also an urgent need for engineers to develop technologies that can simply and accurately diagnose the cause of infection to aid with the clinical decision-making process; development of this diagnostic technology may be more critical than developing novel therapeutics.

Increasing understanding and trust among clinicians towards novel technologies and the data they can provide is also essential. Poor adoption of novel technologies and tools to diagnose and treat AMR-related infections is a major challenge. Although limited expertise or knowledge regarding particular technologies may contribute to this challenge, the speakers noted that skepticism toward novel diagnostic and therapeutic tools is also a factor. Lack of appropriate adoption into clinical practice allows AMR to persist.

Finally, clear communication across all sectors, including end-users, about the value of new technologies and consequences of lack of antibiotic stewardship is required. Bi-directional communication with a feedback loop is necessary so engineers and developers understand the clinical needs of providers and providers understand the benefits of a particular technology or therapeutic. Raising awareness among end-users is essential to ensure novel diagnostics and therapeutics are accessible, especially in low-resource, low-income areas.

While beneficial, antibiotics have the potential to do more harm than good and cannot be the only solution to treating AMR-related infections. The panelists emphasized the disconnect between engineers and clinicians, identifying a lack of communication between technology developers and end-users as a contributor to poor clinical translation.

Appendix C: Presentation Summaries

Combating AMR

Diane Flayhart, Director, Global Public Health, Becton Dickinson



The presenter discussed current methods to combat AMR and AMR-related infections from a global perspective and identified areas where engineering can address gaps and opportunities.

Several grand challenges are associated with AMR, including a lack of antibiotic stewardship, preventative measures, and effective therapies; diagnostic failures; and high costs for end-users. Innovation and the evolution of technologies are key to addressing these challenges and unmet needs.

Engineered technologies can aid in prevention, antibiotic stewardship, and community-level and global surveillance and reporting. Key areas of engineering innovation for infection prevention (e.g., novel antimicrobial materials and coatings, good manufacturing practices), antibiotic stewardship (e.g., cost-effective, point-of-care diagnostics, data collection), and surveillance (e.g., coordinated infrastructure, from local to global scales) were identified as promising avenues for engineering research to combat AMR and AMR-related infections.

Multiple technologies, including new antibiotics, vaccines, and phage therapy, may be required and used in conjunction to ensure environmental health and accessibility in low-income and low-resource areas and to enable high selectivity to maintain the health of commensal microbes. Further, key engineering innovation should be applied to manufacturing practices to reduce environmental impacts and the spread of AMR.

The Legal and Social Ecology of Resistance

Kevin Outterson, Boston University



The shortcomings of bacterial infection treatment include income inequities associated with infection-related deaths and the declining efficacy of antibiotics. A careful balance of innovation (spearheaded by researchers and engineers), access, and stewardship is needed to prevent and treat AMR-related infections.

Global coordination and communication can serve to limit and prevent the spread of AMR and AMR-related infections. First, there is a need to consider the impacts of antibiotic usage clinically and environmentally to simultaneously sustain both human and microbial activity. It is imperative that novel technologies and therapeutics have high levels of specificity towards pathogenic bacteria yet maintain the health of microbes that can be beneficial for human and environmental health. There is also a need to develop accessible therapies that are effective for large populations alongside preventative approaches that can be applied in different communities.

Development of new antimicrobials has declined due to limited investment interest, poor economic returns, and restrictive regulatory requirements. Further, there are a limited number of researchers within industry sectors developing novel therapeutics. Significant increases in funding, legal tools (e.g., patents, regulations, etc.), and economic returns for preventative measures and/or novel therapeutics are required to overcome this decline in interest and development. To ensure long-term efficacy of current and future therapies, antibiotic stewardship is required; without guidance and careful attention to antibiotic usage, it will be difficult to sustain the number of effective antibiotic therapeutics available for clinical use.

The shortcomings of bacterial infection treatment include income inequities associated with infection-related deaths and the declining efficacy of antibiotics. A careful balance of innovation (spearheaded by researchers and engineers), access, and stewardship is needed to prevent and treat AMR-related infections.

References

1. Leekha S. et al. General Principles of Antimicrobial Therapy. Mayo Clinical Proceedings, Feb. 2011, 86(2):156-167. DOI: 10.4065/mcp.2010.0639
2. Smith, W. et al. Bacterial defences: mechanisms, evolution, and antimicrobial resistance. Nature Reviews Microbiology, April 2023, 21, 519-534. DOI: 10.1038/s41579-023-00877-3
3. World Health Organization, Antimicrobial resistance, Nov. 2023. [who.int/news-room/fact-sheets/detail/antimicrobial-resistance](https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance)
4. American Society for Microbiology, Wastewater as a Key Driver of AMR, 2023. asm.org/magazine/2023/fall/wastewater-as-a-key-driver-of-amr
5. United Nations Environment Programme (UNEP), Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance, Feb. 2023. unep.org/resources/superbugs/environmental-action
6. Antimicrobial Resistance Collaborators, Global burden of bacterial antimicrobial resistance in 2019: a systemic analysis. Lancet, Feb. 2022, 399(10325): 629-655. DOI: 10.1016/S0140-6736(21)02724-0.
7. United Nations Environment Programme (Feb. 2023).
8. Mabey, D. et al. Diagnostics for the developing world. Nature Reviews Microbiology, March 2004, 2, 231-240. DOI: 10.1038/nrmicro841
9. Bassetti, M. et al. Systematic review of the impact of appropriate versus inappropriate initial antibiotic therapy on outcomes of patients with severe bacterial infections. International Journal of Antimicrobial Agents, December 2020, 56, 6. DOI: 10.1016/j.ijantimicag.2020.106184
10. Wu, J. et al. Device integration of electrochemical biosensors. Nature Reviews Bioengineering, Feb. 2023, 1, 346-360. DOI: 10.1038/s44222-023-00032-w10.
11. Centers for Disease Control and Prevention. Self-Testing At Home or Anywhere, Sept. 2023 archive.cdc.gov/www_cdc_gov/coronavirus/2019-ncov/testing/self-testing.html
12. DeAngelis, D. et al. Hospital privacy curtains: Cleaning and changing policies are we doing enough? American Journal of Infection Control. June 2013, 41(6). DOI: 10.1016/j.ajic.2013.03.069
13. Donlan, R. M. Biofilms and Device-Associated Infections. Emerging Infectious Diseases, April 2001, 7(2), 277-281. DOI: 10.3201/eid0702.700277
14. Ohl, M, et al. Hospital privacy curtains are frequently and rapidly contaminated with potentially pathogenic bacteria. American Journal of Infection Control. Dec. 2012, 40(10): 904-906. DOI: 10.1016/j.ajic.2011.12.017
15. Donlan, R. M. (April 2001)
16. Chen, H. et al. Design of smart targeted and responsive drug delivery systems and enhanced antibacterial properties. Nanoscale, Oct. 2018, 10, 20946-20962. DOI: 10.1039/C8NR07146B
17. Khan, R. et al. Commensal Bacteria: An Emerging Player in Defense Against Respiratory Pathogens. Frontiers in Immunology, May 2019, 10:1203. DOI: 10.3389/fimmu.2019.01203
18. Horejs, C. Organ chips, organoids and the animal testing conundrum. Nature Reviews Materials, April 2021, 6, 372-373. DOI: 10.1038/s41578-021-00313-z
19. Loewa, A. et al. Human disease models in drug development. Nature Reviews Bioengineering, May 2023, 1, 545-559. DOI: 10.1038/s44222-023-00063-3



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