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Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics

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Discussion Guide

Introduction

Antimicrobial resistance (AMR) is a serious and growing global threat. Bacteria vary in their virulence and pathologic potential, but all can evolve or acquire mechanisms that give them the ability to withstand antibiotic treatments. In response to frequent antibiotic use, bacteria are likely to develop resistance against most known antibiotic therapies. Because bacteria and their genetic components are easily disseminated throughout an increasingly globalized population, contending with AMR has become an international priority.

In the United States alone, more than 2 million people are infected with resistant bacteria annually and an estimated 23,000 die as a direct result.[1] The combined direct cost of treatment and cost of lost productivity has been estimated in the tens of billions (USD). While the harm is innumerable and costs continue to increase, new antibiotic development has steadily declined.[2,3]

Traditional approaches to antibiotic discovery and development do not encompass all possible strategies to treat or prevent resistant bacterial infections. The therapeutic antimicrobial drug development pipeline has traditionally consisted of small-molecule antibiotics with broad-spectrum activity, but today only 16 developmental candidates have the potential to treat infections from resistant ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species)—especially drug-resistant microorganisms with structured outer layers and resistance mechanisms.[4] The design of new small-molecule antibiotics is further complicated by the difficulty and greater uncertainty in discovering and tailoring compounds with novel mechanisms of action. Notwithstanding scientific challenges, increasingly organized antibiotic stewardship ensures that new antibiotics are subject to heavily restricted use, limiting developers' return on investment. Companies are understandably hesitant to advance new antibiotics under these difficult scientific and economic circumstances.

Although significant barriers exist, stakeholders aim to develop new modalities for treatment and prevention. Resistance mechanisms are a fact of bacterial evolution and antibiotic treatments designed to avoid them are desperately needed. Nontraditional antibiotics, including bacteriophages, antibodies,

[1] Centers for Diseases Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. 114 (2013).
[2] Burki T. Antibiotic development pipeline slows to a trickle. Lancet Infect Dis. 2017;17(11):1128-1129. doi:10.1016/S1473-3099(17)30586-8
[3] Boucher HW, Talbot GH, Benjamin Daniel K. J, et al. 10 × '20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(12):1685-1694. http://dx.doi.org/10.1093/cid/cit152.
[4] ESKAPE pathogens include *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacter species. (http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/03/12/tracking-the-pipeline-of-antibiotics-in-development)

adjuvants (potentiators), antivirulence factors, immune modulators, and microbiome approaches, are of great interest as they offer mechanisms of action that differ radically from traditional small molecule antibiotics and may be less susceptible to antimicrobial resistance.[5] By broadening the pool of therapeutic and preventive choices, these nontraditional products have the potential to save lives and reduce morbidity. Ensuring their continued development and a pathway to successful market authorizations has the attention of regulators, policymakers, and funders.

Combating AMR with non-traditional antibiotics became an established priority in the United States in September 2014, when the President's Council of Advisors on Science and Technology (PCAST) recommended expanded NIH funding for AMR research. PCAST detailed their funding recommendations and described the development of non-traditional antibiotics as a component of their comprehensive approach. Since then, the National Institutes of Health (NIH) and National Institute for Allergy and Infectious Diseases (NIAID) have allocated tens of millions of dollars toward combating antibiotic resistance, funding the development of non-traditional antibiotics[6] alongside funding for an antibacterial resistance clinical research network[7], tools to advance antibiotic discovery[8], and antimicrobial resistance rapid diagnostics.[9] While NIH and NIAID have led the U.S. government's response to antimicrobial resistance, partnerships between different federal agencies, academic institutions, NGOs, and industry are extending the effort to develop non-traditional antibiotics.

CARB-X is one such public-private partnership, investing $502 million over five years into research toward new products to address antimicrobial resistance, including vaccines, diagnostics, and antibiotics, as well as nontraditional therapeutic and preventative products.[10] CARB-X is funded by the U.S. Department of Health & Human Service's Biomedical Advanced Research and Development Authority (BARDA), the Wellcome Trust, the Bill and Melinda Gates Foundation, and the Government of the United Kingdom, with preclinical services provided by NIAID. CARB-X aims to accelerate antibacterial research by supporting a diverse portfolio of products targeting priority bacterial pathogens. As of July 2017, CARB-X has funded the development of thirty-six preclinical antibacterial products, including ten non-traditional antibiotics, nine new classes of small molecule products, six diagnostics, and one vaccine.

Recognizing that the lack of novel therapies to combat AMR creates an urgent unmet medical need, this meeting convened by the Duke-Margolis Center for Health Policy under a cooperative agreement with FDA[11] will bring together stakeholders to discuss non-traditional antibiotic research and clinical

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[5] Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti VA, et al. Alternatives to antibiotics-a pipeline portfolio review. Lancet Infect Dis. 2016;16(2):239-51.

[6] Non-Traditional Therapeutics that Limit Antibacterial Resistance (https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-14-066.html)

[7] Leadership Group for a Clinical Research Network on Antibacterial Resistance (https://www.arlg.org/) (https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-019.html)

[8] Partnerships for the Development of Tools to Advance Therapeutic Discovery for Select Antimicrobial-Resistant Gram-Negative Bacteria (https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-16-081.html)

[9] "Antimicrobial Resistance Rapid, Point-of-Need Diagnostic Test" Challenge (https://www.federalregister.gov/documents/2016/09/08/2016-21328/announcement-of-requirements-and-registration-for-antimicrobial-resistance-rapid-point-of-need)

[10] CARB-X homepage (http://www.carb-x.org)

[11] Funding for this meeting was made possible by the Food and Drug Administration through grant 5U13FD001597. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.

development. Discussion will encompass novel non-traditional antibiotic classes and both nonclinical and clinical issues that need to be addressed with a focus on scientific challenges. This meeting will synthesize stakeholder input to help identify challenges and outline potential means to address them.

Examples Across the Spectrum of Non-Traditional Antibiotic Technologies

Bacteriophages

Bacteriophages (phages) are viruses that selectively infect particular strains of bacteria. Phages bind to bacteria and inject their nucleic acid (DNA/RNA) into the host bacterium, giving rise to new phages and proteins that destroy the host cell membrane. Upon host cell membrane rupture, the new phages are released and the host bacterium is destroyed. While phages are well-adapted to target bacteria, phage therapy is especially appealing because they do so selectively, limiting disturbance of the normal microbiome. Furthermore, because phages only replicate so long as a population of their target bacteria exists, when an infection from is cleared, so too are the phages used to target the infecting bacteria.

These advantageous characteristics have led developers toward two therapeutic strategies. One strategy is to pursue narrow-spectrum phage cocktail therapies that are designed to treat a specific patient's infection. The second strategy is to generate a phage cocktail that targets infections caused by a particular species of bacteria; this treatment would be more broadly applicable than those designed for a specific patient, but would still be considered a narrow-spectrum treatment.

These efforts are enabled by large phage libraries curated by academic institutions, government organizations, and therapeutic developers. Phage libraries allow target bacteria to be screened against thousands of candidate phages, and those phages that are most lethal to the target bacteria are selected for further development or clinical use. As with traditional antibiotics, bacteria can develop resistance to phages, but phage cocktails can reduce resistance formation and can lead to renewed susceptibility to traditional antibiotics, meaning that phage therapies may represent a significant step towards reducing AMR.

Peptides

Antimicrobial peptides (AMPs) and antimicrobial proteins are a diverse class of agents that, unlike chemically synthesized small molecules, have been derived from a number of organisms, including bacteria, plants, insects, and humans, among others. AMPs can target bacterial membranes, extra- and intracellular bacterial proteins, or components of bacterial replication. AMPs that target bacterial membranes kill bacteria by disrupting the integrity of the barrier that protects bacteria from the surrounding environment. AMPs that interact with protein targets lead to bacterial cell death through various mechanisms, not all of which are well characterized. For instance, AMPs that interact with intracellular bacterial proteins may halt processes that are necessary for bacterial replication. AMPs have also been shown to disrupt or prevent the formation of bacterial biofilms—communities of bacteria where traditional antibiotics can have limited efficacy and where immune cells cannot easily penetrate to clear infectious bacteria. These characteristics make AMPs attractive antibiotic candidates. In addition, AMPs may be less susceptible to AMR mechanisms that counter the activity of traditional antibiotics. While these features point toward significant clinical utility, the development of systemically administered AMPs has been hindered by limited activity, toxicity concerns, and difficulty in synthesis and manufacturing.

Antibodies

Monoclonal antibodies (mAbs) are large proteins produced by immune cells that target specific parts of bacteria or bacterial products. Given their specificity, mAbs are being developed as narrow-spectrum agents. mAbs designed to target bacterial surface components act by homing the host immune system to the site of infection, where immune cells can kill bacteria. mAbs designed to target bacterial toxins bind and neutralize the effects of these toxins. Developers are exploring a variety of antibody technologies including human and chimeric mAbs that target bacterial proteins, glycolipids, and toxins, and some mAb therapeutics have been designed to bind more than one target. Potential mAb therapeutics include both treatments for active infections and preventive mAbs given to confer temporary immunity to patients at risk of infection.

Potentiators

The terms potentiator and adjuvant are variously used to refer to molecules that have little or no intrinsic antibiotic activity, but that act either by blocking resistance or enhancing the efficacy of a co-administered traditional antibiotic.[12] Adjuvants are able to restore antibiotic sensitivity in resistant bacteria by a number of mechanisms. Adjuvants can destroy bacterial enzymes that inactivate traditional antibiotics, restrict redundant metabolic pathways bacteria would otherwise engage to survive, inhibit the action of protein pumps that remove traditional antibiotics from within bacteria, and cause an increase in the uptake of traditional antibiotics, among other mechanisms. Adjuvants are attractive to developers because they have potential to restore activity to certain classes of antibiotics. However, similar to traditional antibiotic products, bacteria can develop resistance to adjuvants, which may limit their use.[13]

Antivirulence

Bacteria can produce a number of factors, some of which are toxins that cause damage to the patient or limit the effectiveness of the patient's immune system. These bacteria-derived products are collectively called virulence factors, and they contribute to the severity of infection and overall pathology. Antivirulence therapies are a class of non-traditional antibiotics that target these virulence factors. When virulence factors are diminished, bacteria may be made more susceptible to immune clearance or traditional antibiotics, or they may experience internal dysfunction that limits their pathogenicity but does not kill them. For instance, antivirulence therapies have been designed to foil the action of bacterial toxins and limit the capacity for bacteria to adhere and establish infection or to prevent the formation of biofilms. Because antivirulence approaches target mechanisms that cause bacterial pathogenesis as opposed to directly acting on the bacteria, they are less susceptible to AMR and more likely to spare the normal microbiome. Antivirulence therapies are not themselves bactericidal and their combination with traditional or non-traditional antibiotics is usually necessary for clinical application.

Immune Modulators

The human immune system has the capacity to defend against virtually all infectious bacteria, but the immune response can be overwhelmed or counteracted by bacteria or, in some cases, like sepsis, the magnitude of the immune response can cause damage to the patient. Immune modulators are non-traditional antibiotic therapies that aim to optimize the immune response to particular bacterial infections. Developers are pursuing therapies that act to home immune cells to the site of infection and encourage the activation of specific immune functions. Like antivirulence therapies, immune modulators

[12] Wright GD. Antibiotic Adjuvants: Rescuing Antibiotics from Resistance. Trends Microbiol. 2016;24(11):862-871.
[13] Paul D, Dhar Chanda D, Maurya AP, et al. Co-Carriage of blaKPC-2 and blaNDM-1 in Clinical Isolates of Pseudomonas aeruginosa Associated with Hospital Infections from India. PLoS One. 2015;10(12):e0145823.

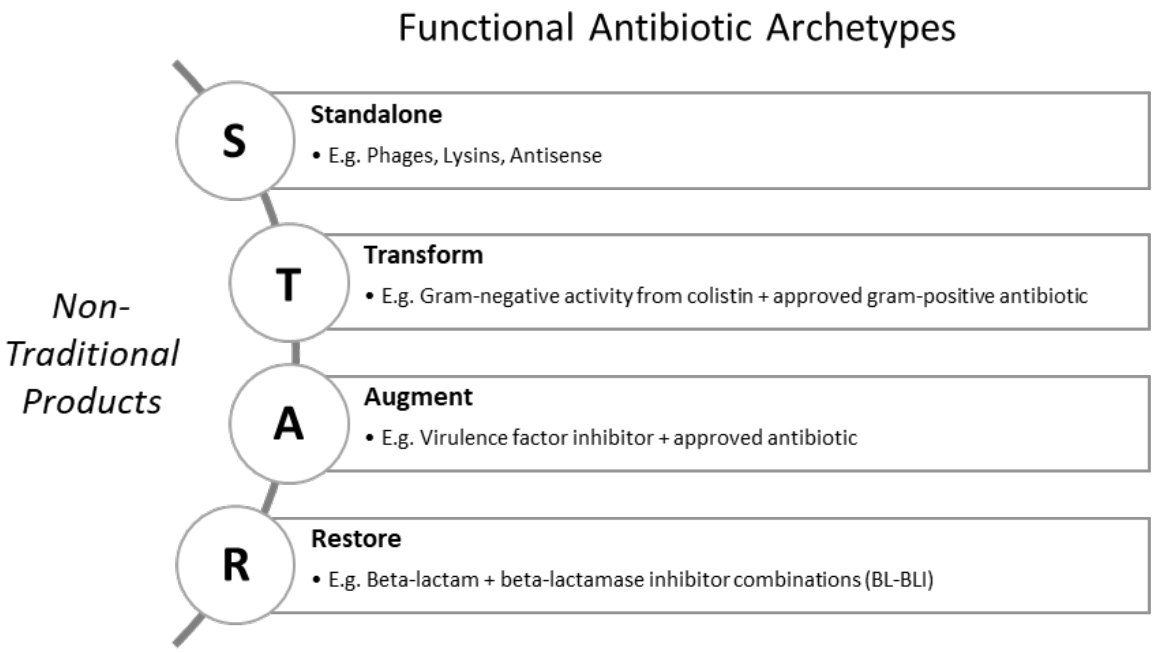
do not act directly on bacteria, reducing the likelihood that bacterial develop resistance. Also like antivirulence therapies, immune modulators are likely to be administered in addition to standard antibiotic therapies.

Preventive Technologies and Microbiome Approaches

Several unique approaches are being tested for the ability to prevent bacterial infections. Beyond vaccine approaches, preventive technologies include antibodies, engineered materials with antibiotic properties, and preparations of live non-pathogenic bacteria. These products are being applied in a number of ways, including through the use of engineered materials with antibiotic properties for surgical applications, and of live non-pathogenic bacteria for prevention *Clostridium difficile* infection and other results of microbiota dysbiosis. Non-pathogenic bacteria may be administered therapeutically to suppress opportunistic infections by bacteria that naturally occur in the gut, to limit damage to the normal microbiome during traditional antibiotic treatment, or to enhance the growth of non-pathogenic bacterial populations. If these treatments are successful, they may help to reduce development of AMR by decreasing the need for antibiotic use.

Nomenclature

This meeting is organized into sessions that address non-traditional products by their proposed application. However, as an array of potential therapeutics have been devised, thinking about potential clinical challenges according to their mechanistic differences may be useful. A set of four archetypes[14] has been proposed:



[14] Rex JH, in collaboration with Cavaleri M, Nambiar S, and Hope W as part of a symposium on 22 Apr 2018 at ECCMID 2018, Madrid, Spain. Slides available at http://amr.solutions/blog/eccmid-symposium-expediting-antibacterial-development-core-lessons-and-key-tools-for-a-rocky-road Note: The original four archetypes have been updated by author JHR for this discussion guide.

These four archetypes are entirely functional and serve to create groups within which common development problems may be resolved. Notably, the terms potentiator and adjuvant can be used to describe products of the Transform, Restore, and Augment archetypes.

- **Standalone** – A novel mechanism agent with the potential to act as monotherapy.
- **Transform** – Addition of a new component transforms the action of a known agent into a previously unused domain. Monotherapy potential exists.
- **Augment** – A novel product lacks activity on its own but augments or enhances the effect of a known agent. Monotherapy potential does not exist.
- **Restore** – Addition of a new component restores the action of a known agent by blocking a resistance mechanism. Monotherapy potential exists.

The archetypes **Standalone** and **Augment** often have the advantages of being especially novel, but they may be difficult to develop because they often have narrow-spectrum activity. Although narrow-spectrum agents may be appealing as best therapy once a given infection has been shown to be due to a specific single pathogen, demonstrating the discrete activity of such agents in clinical trials can be challenging as best initial empirical therapy often requires the novel agent to be combined with other agents. This problem is compounded when the agent is from the Augment category and hence lacks direct activity against the pathogen. As a result of these issues, developers may need to demonstrate superiority in their clinical trials. Additionally, in some cases typical minimum inhibitory concentration (MIC) measures are not relevant and different types of preclinical data will be required. Conversely, the archetypes **Transform** and **Restore** have the advantages of leveraging a known component and utilizing typical MIC and pharmacokinetic and pharmacodynamic measures. These categories are also often suitable for stand-alone development despite the challenge of sometimes being very narrow-spectrum.

Developmental Challenges

While the approaches described above represent promising strategies to combat bacterial infections, they are not without developmental challenges. Developers are contending with scientific issues in both the preclinical and clinical space, which will need to be addressed for these products to have commercial viability and success.

Preclinical Challenges

Accurately predicting how investigational therapies will affect the human body according to their dosing, metabolism, and mechanism of action traditionally involves standard measurements of their pharmacokinetic and pharmacodynamic properties. However, many non-traditional antibiotics are administered and function in atypical fashion as compared to small molecule drugs. As a result, it can be challenging to characterize their pharmacokinetic and pharmacodynamic properties using typical antimicrobial standards. For instance, antimicrobial biomaterials may only be used locally and not absorbed. Further, indirect-acting, non-traditional antibiotics may not have MICs, complicating their comparison with traditional antibiotics or standards of care. For example, antivirulence therapies may only contribute to infection clearance in the presence of traditional antibiotics or when biofilms contribute to infection. Non-traditional antibiotics and their varied mechanisms are likely to require new means of characterization.

Another issue that may need attention is the development of animal models for preclinical studies. Animal models are used to characterize the antibiotic candidate, and they typically allow the collection of efficacy data in support of first-in-human studies. However, some non-traditional therapies may not

have relevant animal models. For example, *S. aureus* virulence factors impact mice and humans differently, so there are difficulties in translating data generated in animals with this infection.[15] Similarly, adjuvant and antivirulence therapies that engage the human immune system to affect bacterial clearance may also be difficult to model in animals. In some scenarios, it may be worth considering alternative ways to generate necessary preclinical data.

Collecting safety data is an important component of the preclinical program and involves understanding how investigational therapies interact with immune functions. Non-traditional antibiotics are likely to interact with the human immune system differently than traditional small molecule antibiotic products. While it is known that larger agents like AMPs have greater potential to elicit adverse immune responses than less immunostimulatory human mAbs, predicting human immune responses in preclinical animal models is difficult and not always useful. However, advances in manufacturing completely human mAbs and in modifying naturally derived AMPs provide mechanisms to improve safety. Early clinical experience with non-traditional antibiotics is already informing the safe development of future products.

Clinical Challenges

Enrolling patients in clinical trials can be challenging for narrow-spectrum non-traditional antibiotics because the number of patients required to reach statistical significance can be difficult to achieve in a relevant timeframe. Rapid diagnostics can help to expedite trial enrollment for these narrow-spectrum products, but they are not always available. Furthermore, acute infections require immediate therapy and patients seek care at the nearest facilities, not necessarily those where a clinical trial can be conducted. When patient outcomes are variable or difficult to characterize, developing meaningful trial outcome measures can be complicated. These challenges create uncertainties that must be considered when designing clinical trials for narrow-spectrum bacterial infections.

Most clinical trials for antimicrobial products are designed to demonstrate non-inferiority, so superiority designs for agents that are used in addition to standard of care will require new approaches. For many products, these approaches may include updated or modified endpoints, which can be challenging if they have not been validated in previous trials. Standard mortality endpoints are unambiguous but are influenced both by infection and underlying disease. Other types of clinical endpoints have the potential of greater sensitivity, but lack consensus definitions.[16] Finally, not all non-traditional antibiotics will be designed to affect clinical cure directly and the development of new measures (perhaps population-level measures) seems necessary.

Preventive investigational products in particular are likely to encounter challenges throughout clinical development and their subsequent acceptance and utilization. Preventive non-traditional antibiotics require adequate methods to conduct dose-optimization and measure their preventive effect. While clinical trials delivering probiotics to patients with active infections have been conducted with primary endpoints measuring infection recurrence, endpoints that further support utilization by adequately measuring preventive effect in patients without prior infection are lacking. Such trials need to efficiently

[15] Parker D. Humanized Mouse Models of Staphylococcus aureus Infection. Front Immunol. 2017;8:512. doi:10.3389/fimmu.2017.00512

[16] Timsit JF, de Kraker MEA, Sommer H, et al. Appropriate endpoints for evaluation of new antibiotic therapies for severe infections: a perspective from COMBACTE's STAT-Net. Intensive Care Med. 2017;43(7):1002-1012. doi:10.1007/s00134-017-4802-4

enroll populations at risk of infection, especially when investigational products aim to prevent rare resistant infections. Defining these target trial populations and achieving enrollment sizes necessary to support meaningful statistical analysis may be challenging.

Some preventive agents deliver mixtures of heterogeneous bacteria to the patients. If these products are derived from human donors, they are likely to deliver some measure of resistant bacteria. While bacteria carrying resistance factors are widespread and not necessarily pathogenic, sponsors may be requested to measure and validate the resistance factors that their investigational products deliver to trial participants. These challenges are unique to the clinical development of non-traditional antibiotics that involve the delivery of live bacteria.

A primary goal for many non-traditional products is to reduce the incidence of resistant bacteria at a population level. Designing ethically acceptable clinical trials to meet public health goals may require new trial models and endpoints that characterize effects on both the individual and the population.

Chemistry, Manufacturing, and Controls Challenges

The complicated molecular structures, modifications, and mixtures that comprise non-traditional antibiotics can slow synthesis or manufacturing. Phage products composed of multiple phages may be difficult to produce with consistency and regulatory parameters regarding their validation are undefined. The circumstances are similar for preventive technologies that deliver a community of living bacteria. Similarly, large mAb and peptide therapeutics with specific chemistry can pose manufacturing challenges that limit output. These and other manufacturing concerns may slow progression to clinical testing for a number of non-traditional antibiotic classes.

Commercial Considerations

The cost of developing antibiotics is significant and non-traditional products may have additional costs. As a result, sponsors will often encounter difficulty securing adequate financial support. Unfortunately, phage products and possibly some mAbs are unlikely to classify under current rules as qualified infectious disease products (QIDPs)[17], barring them from the additional five years of market exclusivity conferred on other new antibiotics by Title VIII—"Generating Antibiotics Incentives Now"—of the Food and Drug Administration Safety and Innovation Act.[18] While push incentives like CARB-X are necessary and important, the most significant unmet need lies beyond FDA approval and may be addressed by pull incentives, such as market entry rewards.[19] For significant numbers of novel non-traditional antibiotics to reach market, additional incentives and scientific support are likely necessary.

Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics

As highlighted above, there is a wide spectrum of activity occurring in the non-traditional antibiotic space, and new challenges and opportunities emerge as the field grows. This public meeting will be focused on better understanding the types of technologies that are being developed, as well as

[17] https://www.gpo.gov/fdsys/pkg/USCODE-2015-title21/pdf/USCODE-2015-title21-chap9-subchapV-partA-sec356.pdf
[18] https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf
[19] DRIVE-AB report: Revitalizing the antibiotic pipeline. Published online January 2018 and available at http://drive-ab.eu/news/drive-ab-report/; UK AMR Review report: Securing New Drugs for Future Generations – the Pipeline of Antibiotics. Published online 14 May 2015 and available at https://amr-review.org/Publications.html; 1. Hall W, McDonnell A, O'Neill J. Superbugs: An arms race against bacteria: Harvard University Press; 2018. 246 pages.

articulating areas for growth and improvement. Sessions are categorized by general areas of research and development, and each will highlight specific issues that developers are facing. Sessions will be focused around the questions detailed below.

Session 1: Developing non-traditional antibiotics that can potentially be studied as a monotherapy

Some non-traditional agents are being developed that have a direct, narrow-spectrum impact on infecting bacteria, and that can be used as a monotherapy in clinical trials. These types of therapies can include bacteriophages, proteins, and peptides. This session will review some of the technologies being developed, and will cover scientific challenges that arise when developing evidence that supports efficacy against a limited set of bacteria.

- What are the most challenging issues in development?
- How does development differ from traditional antibiotics?
- What are the challenges associated with developing a narrow-spectrum agent?

Session 2: Generating agents that restore activity to – and are used in combination with – existing antimicrobials

Many non-traditional antibiotic therapies have an adjunctive impact, meaning that they only have an impact on bacteria when given in addition to traditional antibiotics. Potentiator or adjuvant therapies typically target an existing bacterial resistance mechanism and can have either a broad or narrow-spectrum impact. This session will examine scientific issues associated with the development of these agents, and will consider the potential uses and applicability of candidates currently in development.

- What are the key scientific challenges to developing this type of product?
- How does development differ from traditional antibiotics?
- What are the challenges of demonstrating an impact on resistance?

Session 3: Developing agents that are studied in combination with existing antimicrobials to enhance elimination of bacteria

Some non-traditional antibiotics have an indirect effect on bacteria by targeting virulence factors produced by the bacteria, or by targeting the immune system. While these agents have an impact on the infection, they still need to be administered in addition to standard of care, traditional antibiotics. This session will consider the range of technologies and their application, as well as challenges associated with potential uptake and use.

- What are the challenges with developing a product that does not directly kill bacteria?
- What are measures that can be used to distinguish impact of new agent from SOC?
- What are the differences between single antibodies and antibody cocktails?

Session 4: Preventing infections using non-traditional antibiotic agents

As rates of antimicrobial resistance increase, preventing infections is becoming more important. There is a wide range of technologies being designed to prevent a spectrum of infections. This session will cover the unique scientific and developmental challenges that these technologies face, as well as gaining a better understanding of the technologies and their applications.

- What are the challenges in demonstrating successful prevention?

- What are potential endpoints and timeframe for measuring prevention?
- What tools are needed for these products to be successful?

Session 5: Wrap-up panel to discuss remaining needs and next steps

This session will react to the day's discussions, discuss the most pressing issues facing alternative antibiotic approaches, and outline desired next steps to address these issues.

- Where are the potential areas for improvement?
- What actions should be prioritized to support development of non-traditional products?
- What can developers do to increase opportunities for success?