HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 5, e2058840 (7 pages)
https://doi.org/10.1080/21645515.2022.2058840

Taylor & Francis
Taylor & Francis Group

MEETING REPORT

Partnering on vaccines to counter multi-drug resistant threats: Workshop proceedings, Biomedical Advanced Research and Development Authority

Julie N. Bergmann*, Rushyannah R. Killen-Cade*, Lindsay A. Parish*, Mark T. Albrecht, and Daniel N. Wolfe

Department of Health and Human Services (HHS), Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response (ASPR), Washington DC, USA

ABSTRACT

On March 12, 2021, the Biomedical Advanced Research and Development Authority (BARDA) sponsored a virtual market research workshop, "Partnering on Vaccines to Counter Multi-Drug Resistant Threats," to discuss the threat of antimicrobial resistance in the context of BARDA's mission space and the challenges encountered during the development of vaccines for specific antimicrobial resistant bacteria. The workshop convened representatives with expertise in vaccine development from government, academia, and industry. This report summarizes the presentations and subsequent discussions from the workshop and highlights existing challenges to advance the development of vaccine candidates for antimicrobial resistant pathogens, including *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

ARTICLE HISTORY
Received 24 February 2022
Accepted 24 March 2022

KEYWORDS
Antimicrobial resistance; AMR; vaccine; multi-drug resistance; global health security; BARDA

Introduction

With increasing rates of antimicrobial resistance (AMR) in pathogens where there are few or no alternative therapeutics, AMR has emerged as a serious threat that must be addressed. AMR threatens effective treatment of bacterial, viral, and parasitic infections, as well as successful outcomes from modern medical treatments, such as routine surgeries and chemotherapy. Every year more than 2.8 million people in the United States contract an AMR infection, resulting in 35,000 deaths annually.[1] Globally, AMR infections were estimated to cause 1.27 million deaths in 2019, and if not reduced are predicted to be responsible for more than 10 million deaths per year by 2050.[2,3] The impact of AMR infections is not only measured by morbidity and mortality rates, but also can by the economic impact such infections have on a country. The Centers for Disease Control and Prevention (CDC) estimates that AMR infections currently cost the U.S. $55 billion annually, $20 billion for additional healthcare costs, and $35 billion for lost productivity.[4] By 2050, the World Bank estimates that AMR infections could result in a global gross domestic product (GDP) decline between 1.1% and 3.8% and would disproportionately affect low-income countries.[5]

Over the past decade, AMR has gained recognition as a serious threat to public health and national security as described in the U.S. National Biodefense Strategy (2018),[6] Global Health Security Agenda (GHSA) Framework (2018),[7] and in the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria.[8] The U.S. National Biodefense Strategy outlined methods to mitigate naturally, accidentally, or intentionally occurring biological threats domestically and internationally. The strategy recognizes AMR pathogens as naturally occurring biothreats and underscores how infectious diseases can spread from remote corners of the world to impact the U.S. population's health and security.[9] Within the GHSA, AMR pathogens and genes are recognized as spreading worldwide and pose a threat to global public health and security. AMR is a priority within a GHSA action package that has the goal of addressing the drivers of AMR in human health, animal health, food production, and the environment through multisectoral collaboration.[7] The U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria is a policy document devoted solely to how the U.S. Government will coordinate actions to accelerate responses to AMR.[8] As highlighted by these public policy documents and strategies, inclusion of mitigation strategies and countermeasures against AMR is essential to comprehensive national preparedness plans and efforts to advance global health security.

BARDA's mission is to "develop and procure needed medical countermeasures, including vaccines, therapeutics, diagnostics, and non-pharmaceutical countermeasures, against a broad array of public health threats, whether natural or intentional in origin."[10]BARDA enhances the U.S. Government's capability to respond quickly to chemical, biological, radiological, and nuclear (CBRN) threats, as well as pandemic influenza and emerging infectious diseases, by supporting the development of medical countermeasures (MCMs), thereby strengthening national and global health security. Since AMR pathogens can lead to secondary or co-infections following CBRN mass casualty events, BARDA has a vested interest in ensuring proper MCMs exist to combat AMR pathogens.

CONTACT Daniel N. Wolfe Daniel.Wolfe2@hhs.gov Department of Health and Human Services (HHS), Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response (ASPR), Washington DC 20201, USA.

*All authors contributed equally to this publication.

This article has been republished with minor changes. These changes do not impact the academic content of the article.

To determine which AMR pathogens would likely have the greatest impact after a mass casualty event, we reviewed and ranked the rates of morbidity, mortality, hospitalizations, and economic impact of the AMR pathogens of greatest concern in the U.S. as identified by the CDC.[1,4] We then reviewed which of these pathogens could potentially cause secondary or co-infections of people who are ill from or injured by CBRN threats, pandemic influenza, or COVID-19. A landscape analysis was also conducted to assess: 1) if licensed or late-stage vaccines were already available; and, 2) if there was a target population that would benefit from vaccines for the threat in question. After review, we identified *Klebsiella pneumoniae, Pseudomonas aeruginosa*, *Staphylococcus aureus, and Escherichia coli* as AMR pathogens with the greatest potential to worsen patient outcomes from a CBRN mass casualty event.

- *K. pneumoniae* is responsible for up to 70,000 hospitalizations each year, resulting in about 100 deaths, and leading to approximately $1.2 billion of healthcare costs each year in the U.S.[1,11–13] *Klebsiella* bacteria are also among the most commonly isolated pathogens in burn wounds and a common co-infection in COVID-19 patients.[11,14]
- *P. aeruginosa* infections result in over 30,000 hospitalizations each year, leading to about 3,000 deaths and costing the U.S. healthcare system about $770 million annually.[1] This pathogen is among the main causes of infections and sepsis in people suffering from severe burns.[15]
- *S. aureus* infects more than 320,000 patients each year, resulting in over 10,000 deaths and leading to an estimated $1.7 billion in healthcare expenses each year in the U.S.[1] This pathogen can cause infections in burn victims and is also an observed co-infection in COVID-19 and influenza patients.[15–17]
- *E. coli* urinary tract infections are the cause of more than 10 million doctors' visits each year, as well as over 300,000 hospitalizations and more than 1,300 subsequent deaths.[18–21] This pathogen is estimated to cost over $2 billion annually in healthcare expenses in the U.S.[20] *E. coli* urinary tract infections are common infections of patients receiving long-term care that require the use of catheters, and therefore, have been observed in serious COVID-19, influenza, and sepsis patients.

An additional complication of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *S. aureus* infections is sepsis. Overall, sepsis accounts for 1.7 million hospitalizations and 270,000 deaths in the U.S., costing an estimated $57 billion annually.[22] Thus, secondary bacterial infections in individuals who have a CBRN injury have the potential to cause life-threatening complications such as sepsis.

While AMR infections have traditionally been treated with antibiotics, the increasing rates of resistance to these drugs and the high cost associated with their use have highlighted the importance of research and development for novel preventive approaches like vaccines. Vaccines are one of the most successful public health interventions to prevent or lessen the impact of once deadly diseases. The application of vaccines to the threat of AMR bacteria may diminish the spread and emergence of new AMR pathogens and could be antibiotic sparing (e.g., reduced antibiotic use leads to less AMR), thus preserving the efficacy of existing treatments. One successful example of vaccines reducing AMR infections is the widespread use of the heptavalent pneumococcal conjugate vaccine (PCV7) in children. After the introduction of PCV7, the carriage rates in children of penicillin-resistant strains of *Streptococcus pneumoniae* were reduced by 81%.[23] The further development of additional AMR vaccines could similarly aid in reducing the spread of AMR pathogens.

Currently, there are no licensed vaccines against *E. coli, K. pneumoniae, P. aeruginosa*, or *S. aureus*, all of which are bacterial pathogens that may cause secondary or co-infections in mass casualty events covered in BARDA's MCM portfolio. Therefore, BARDA convened a virtual workshop on 12 March 2021, as part of a market research effort to explore the current landscape of clinical stage vaccines against *E. coli, K. pneumoniae, P. aeruginosa, and S. aureus*. We sought to understand the challenges product developers encounter when developing a vaccine for these pathogens, and discuss the threat overlap of AMR with BARDA's mission space. In total, 131 people from the U.S. Government (BARDA, National Institutes of Health (NIH), Food and Drug Administration (FDA), Department of Defense), external governments (Canada and the U.K.), the World Health Organization, academia (eight unique institutions), and private industry (56 unique institutions) participated in the workshop.

Summary of workshop

Dr. Julie Bergmann (BARDA/CBRN) called the workshop to order and provided an outline of the format; she indicated that all presentations would be made available on the event website following the workshop (https://www.medicalcountermeasures.gov/barda/cbrn/mdrvaccines). BARDA started the workshop with the presentations summarized below. The workshop then allowed for questions from participants, followed by a structured discussion around key AMR issues.

Dr. Gary Disbrow, the BARDA Director, welcomed the participants and outlined BARDA's mission and organizational structure. Dr. Disbrow highlighted the CBRN threats that have material threat determinations (MTD) from the Department of Homeland Security. The issuance of a MTD is the requirement that establishes BARDA's MCM development and procurement priorities. Within the biodefense space BARDA has MTDs for *Bacillus anthracis* (including MDR *B. anthracis*), *Burkholderia mallei, Burkholderia pseudomallei, Francisella tularensis*, *Yersinia pestis*, Ebola and related filoviruses, smallpox, and botulinum neurotoxin. However, secondary and opportunistic bacterial infections will complicate the healthcare response and recovery to any threat agent within BARDA's mission space. These include chemical threats such as chlorine and sulfur mustard, outcomes of radiation exposure such as acute radiation syndrome, and burn and blast injuries that could result from a nuclear detonation. All of these agents can lead to opportunistic infections and sepsis. Therefore, the development of antibiotics for biothreat pathogens and secondary and opportunistic bacterial infections is a priority for BARDA. Dr. Disbrow then tasked the workshop participants to

have an open and transparent conversation with BARDA on challenges to developing vaccines against AMR pathogens, so that BARDA and product developers understand the challenges in the field.

Dr. Chris Houchens, Director of the Division of CBRN Medical Countermeasures at BARDA, opened his presentation highlighting the global nature of today's health security threats, which do not respect geographical or political boundaries. In order to address this, BARDA and the U.S. Government must be prepared to respond quickly and effectively to a wide range of threats including those that emerge naturally as well as those that have been intentionally engineered to do harm. To ensure that the U.S. is prepared to respond to these threats, BARDA's CBRN Division focuses on one goal: to make available at least one MCM against every threat agent that the Department of Homeland Security has determined to be a threat, or a material threat to the national health security of the U.S. Dr. Houchens outlined how BARDA's strategy is focused on three primary objectives to meet this goal. First, supporting the research and development of innovative MCMs to rapidly prevent and/or treat the acute medical consequences following a chemical, radiological, or nuclear event. Second, developing threat agnostic medical countermeasures to counter the unknown threats of the future. Finally, delivering next generation technologies against the wide range of biological material threats, from anthrax and plague to smallpox and Ebola. Related to these objectives, drug-resistant bacteria can complicate the U. S'.s ability to effectively respond to any public health emergency.

For many of these threats, including AMR bacteria, CBRN supports the entire product development pipeline. This includes the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), which accelerates the early-stage development of innovative technologies that address the threat of AMR, to our advanced research and development program that supports the clinical development of promising candidates, enabling many of them to receive FDA marketing authorization. Project BioShield supports post-approval activities, manufacture, and procurement of MCMs targeting CBRN threats. Dr. Houchens stressed that through these multiple mechanisms, BARDA can provide product developers with non-dilutive funding, technical subject matter expertise, and access to core services to reduce programmatic risk and accelerate the research and development of promising MCMs against the most concerning threats to our national health security. Since 2012, CBRN has supported 24 products that have been licensed by the FDA and 22 different MCMs have been procured to prepare for emergency threats (as of January 2022). Dr. Houchens concluded his presentation by stressing that the CBRN Division will continue to support the development of MCMs for these threats, as well as the development of threat agnostic technologies that can be deployed immediately in the case of an emerging threat in the future.

Dr. Mark Albrecht, Chief of the Antibacterials Branch in CBRN, presented his Program's efforts to support the development of antibacterial drug candidates that treat biothreat pathogens and opportunistic/secondary bacterial infections, including those caused by multi-drug resistant pathogens. He opened his presentation by highlighting the fact that bacterial infections can impact the whole of BARDA's mission space, whether a public health emergency is caused by a CBRN threat, pandemic influenza, or an emerging infectious disease. Regardless of the cause, the U.S. Government will need new antibiotics to treat biothreat pathogens and the opportunistic/secondary infections likely to be encountered during patient recovery. The impact of these infections on recovery efforts is amplified by AMR, which creates additional healthcare burdens during a public health emergency, impacts patient survival, and undermines the practice of modern medicine. The Antibacterials Program incentivizes the development of antibacterial drug candidates to address these threats by partnering with pharmaceutical companies, biotech companies, and other government partners to support product development by providing non-dilutive funding and subject matter expertise. Dr. Albrecht highlighted the CARB-X program, which provides start-ups and biotech companies the necessary support to develop their innovative pre-clinical candidates and position them for continued clinical development. He then described the other two funding resources BARDA uses to support countermeasure development—advanced research and development funding, which supports clinical development through FDA marketing authorization, and Project BioShield funding (PBS), which supports late-stage, Phase 3 clinical development, post-marketing commitments, and procurement. To date, the Antibacterials Program has supported 125 antibacterial drug candidates through CARB-X, the advanced research and development portfolio, and PBS, and enabled three products to receive FDA marketing authorization.

Dr. Daniel Wolfe, Chief of the Vaccines Branch, then discussed his Program's focus on priority threats for which vaccines can have a significant impact. He highlighted historical programs to outline the solid progress made toward preparing against high consequence biological threats such as smallpox, anthrax, and Ebola. These mature programs—all products are licensed with next-generation products nearing licensure—are funded through Project BioShield investments. Similar to the Antibacterials Branch, the Vaccines Branch also works with sponsors to develop products with support from our clinical and non-clinical networks and facilitate collaboration with other federal partners, all crucial components for ensuring the development of a robust pipeline of MCMs across the threat space. Dr. Wolfe provided a few examples of BARDA's partners who are working to establish animal models for Marburg and Sudan Ebola viruses: Public Health England, Inserm, Battelle, and the University of Texas Medical Branch. These animal models will be used to develop vaccines against these threats. and the Vaccines Program is working closely with the FDA to make sure sponsors can cross-reference those animal models. In the area of vaccine-based approaches for AMR threats, the Vaccine Program is collaborating with NIAID and CARB-X to identify innovative solutions to address these threats. Additionally, Dr. Wolfe described the Program's interest in working with industry partners to support early clinical-stage programs through advanced research and development investments and to further de-risk vaccine development in the AMR threat portfolio.

Dr. Cameron Bess, Scientist in the Antibacterials Branch, presented additional information on the CARB-X program not covered by Dr. Albrecht. CARB-X is a nonprofit public–private partnership designed to revitalize the preclinical R&D pipeline for antibacterial innovations using non-dilutive funds combined with technical and business wraparound services. It is also a platform for shared international investment in the AMR space. The program accelerates global antibacterial innovation by investing in development of new antibiotics and other life-saving products to combat the most dangerous drug-resistant bacteria. Dr. Bess highlighted key partners of the CARB-X, which include the Wellcome Trust, the Bill and Melinda Gates Foundation, the National Institute of Allergy and Infectious Diseases at NIH, and the governments of the United Kingdom and Germany. He highlighted that CARB-X funds early development projects that seek to address serious bacterial threats in the following areas: antibiotics, therapeutics, prevention (such as vaccines, microbiome, CRISPR-phage), and rapid diagnostics (pathogen identification and automated susceptibility testing). Dr. Bess emphasized that funding for early development was dependent on programmatic priorities and the candidate product's maturity. For therapeutics and preventatives, funding starts at the hit-to-lead stage through to Phase 1; whereas, for diagnostics, funding starts at feasibility through verification and validation.

In its final year of a 5-year mandate, approximately 81 projects (in eleven countries) have been supported by CARB-X. The global investment in this accelerator is $503 million, of which $303 million has been awarded. Seven programs have graduated from this accelerator—with many more still in the pipeline. Supporting a diversity of approaches, the CARB-X portfolio has 58 projects currently active (as of December 2021):

- 35 therapeutics (19 focused on new antibiotic classes);
- 11 rapid diagnostics (two in Verification and Validation);
- 12 preventatives (eight vaccines, one microbiome, two CRISPR-phage, one monoclonal antibody).

Dr. Bess concluded by discussing the CARB-X vaccine strategy, which includes investment in high-quality projects with the potential to significantly impact patients' health by balancing innovation with risk. This strategy allows for more programs to enter into advanced research and development and emphasizes performance characteristics critical to uptake in high-income and low- and middle-income countries. These performance characteristics include cost-of-goods, storage requirements, serotype coverage, combination vaccines, and flexible regimens for varied implantation strategies.

Drs. Julie Bergmann, Lindsay Parish, and Rushyannah Killens-Cade, Scientists in the CBRN Division, then shifted the focus of the presentations to the main topic of the workshop: vaccines being developed for AMR threats. They outlined the threat of AMR to national security across all CBRN areas (surgery, infections, acute radiation syndrome, and burns) and discussed how BARDA conducted market research to identify which pathogens were of most relevance to its mission space.

Ms. Jill Johnson, Chief of the CBRN Branch in the Division of Contract Management and Acquisitions, finished the presentation portion of the workshop by discussing BARDA's Broad Agency Announcement. She discussed the two-step process for submission of White Papers and Full Proposals to BARDA. An Offeror submits a White Paper to BARDA, then a Technical Evaluation Panel (TEP) reviews the White Paper and determines whether to invite the Offeror to submit a Full Proposal. When an Offeror is invited to submit a Full Proposal, a TEP reviews the Full Proposal and determines if the U.S. Government should enter into negotiations with the Offeror.

Question and answer session

Following BARDA's presentations, the workshop then transitioned to a 20-minute question and answer session. Several attendees asked about the necessary stage in development to be eligible for a public–private partnership with BARDA. BARDA highlighted that it typically funds Phase 1 advanced research and development, or programs that are within one year of Investigational New Drug (IND) submission, through approval. BARDA does work closely with NIAID to align collective MCM portfolios, as NIAID can fund earlier-stage development of a technology, which may be able to then transition to BARDA for later stage development.

Several attendees asked about the scope of products that BARDA supports or is interested in supporting. BARDA is open to a continuum of approaches and products that address its threat areas. While BARDA's traditional focus for vaccines is on pre-exposure prophylaxis, we will also consider the post-event and post-exposure prophylaxis spaces, as well as threat agnostic therapeutics. BARDA is actively conducting market research to understand what products are out there as well as the value proposition around those products. Dr. Wolfe also highlighted that BARDA is interested in novel approaches, such as on-demand manufacturing. He stated that a lesson learned from that COVID-19 response is that, while it is important to move candidates through the clinical development pipeline as quickly as possible, there also needs to be a focus on how to better manufacture, distribute, and administer products.

Several other questions arose on how to get in touch with BARDA following the workshop. Dr. Wolfe highlighted that the best way get in touch is to submit a meeting request through BARDA's TechWatch portal (RequestaBARDATechWatchMeeting). The TechWatch program provides a venue for industry to present plans to BARDA to obtain feedback and constructive criticism on the path forward to a potential White Paper/Full Proposal and partnership with BARDA.

Structured discussion

The workshop then transitioned to a structured discussion that featured four questions that were circulated to participants prior to the workshop.

Question 1: From your perspective, what are the major technical and developmental challenges to developing vaccines against these AMR threats?

Workshop participants cited the lack of animal models that can reliably mimic and predict human outcomes of disease. The development of animal models is cost prohibitive for many

smaller vaccine developers and requires a substantial amount of time to test and develop models. Additionally, an established animal model for a particular pathogen could have utility in comparing the efficacy of two different vaccines against the same AMR pathogen. Participants suggested that the U.S. Government could help in this area by developing animal models for the four AMR pathogens that could then be used or cross referenced by multiple vaccine developers.

A second challenge to vaccine development was identifying the appropriate target population for clinical trials. AMR pathogens cause infections in many different patients undergoing surgery, treatment of burns, long-term care, and can cause co-infections with other respiratory pathogens. Selection of the appropriate indication and target population can impact the success or failure of a product during clinical trials and affect the marketability of these products if they achieve licensure.

Question 2: From your perspective, why have past efforts to develop vaccines against AMR threats failed?

Participants cited many causes for failure in past development efforts. One participant noted that the primary vaccine targets have been surface carbohydrates, capsules, and LPS O-antigens, which are highly variable within a bacterial species. Another participant discussed how vaccine development for AMR pathogens should ideally not follow the path of *S. pneumoniae* vaccine development, which focused on the top capsule serotypes. Over time, capsule serotype replacement to non-vaccine serotypes in patient populations has required developers to include additional serotypes to increase coverage in next-generation vaccines. It was also noted that vaccine development for viruses is much simpler due to smaller genomes and fewer vaccine targets in viral pathogens. Thus, many decision makers in the industry who are more familiar with viral vaccine development are more reluctant to start programs for bacteria.

There were several other reasons discussed for past failures. One reason was the poor translation of efficacy observed in animals to clinical trials, and thus, a need for more time and attention to developing better animal models. Interestingly, one participant suggested that controlled human infection models could be developed, where possible, as has been done previously for *Neisseria gonorrhoeae* and *Salmonella typhi* vaccine development. Another participant commented that it is often assumed that vaccine efficacy is achieved through the induction of an antibody response, although *T*-cell and innate immunity often play important roles in vaccine-induced immunity. However, many clinical trials miss opportunities to collect data on *T*-cell and innate immune responses. To gain more insight into the failure or success of vaccine candidates in clinical trials, it was suggested that funding agencies should support the collection of additional immunological samples beyond antibody titers to get the most information out of clinical trials.

Finally, one participant asked BARDA how they envisioned vaccines against the four AMR pathogens would be used. BARDA had previously mentioned that they were not looking to stockpile vaccines and that the end goal would be for vaccines for the four AMR pathogens to be supported by the commercial market. The vision is that these vaccines would be used in identifiable at-risk target populations rather than to control or eradicate a disease.

Question 3: From your perspective, what are the overall and any other challenges for developing vaccines against AMR threats?

Workshop participants discussed six challenges to successful development of AMR vaccines. First, the group discussed a lack of harmonization in various efforts. It can be difficult for vaccine developers to learn about successes and failures from others in AMR vaccine development when there are many different approaches and models. This can make it difficult to identify early predictors of success and focus on winning candidates. One role for BARDA could be to help harmonize standards and models.

A second challenge was that AMR is often regarded as one threat—when each pathogen is actually a unique species and must be addressed accordingly. There are different issues at different points in the development path all AMR pathogens. For example, a vaccine candidate for *K. pneumoniae* will have problems with the frequency of patients to enroll in a clinical trial whereas this will not be an issue for a *S. aureus* vaccine candidate where there is a large, identifiable patient population. A participant suggested that BARDA could look to each of the AMR pathogens of interest and work with the FDA to identify specific needs for each development pathway.

Two technical challenges discussed included how AMR vaccine development may be more successful if the goal is preventing or reducing infection rather than just preventing infection. As colonization is frequently a prelude to infection for bacterial species like *K. pneumoniae* and *P. aeruginosa*, if a vaccine could prevent or reduce colonization, it may be possible to reduce the incidence of disease. Additionally, the group discussed the lack of existing surrogate endpoints for AMR pathogens. A participant noted that one of the reasons why there is a hyperfocus on *S. pneumoniae* vaccine candidates is because it has a validated surrogate endpoint that truncates the development pathway. A role for BARDA and the FDA could be to develop surrogate endpoints for AMR pathogens of interest.

Fifth, the group highlighted the challenge of working through numerous regulatory requirements for vaccine development. It was suggested that BARDA could identify commonalities and issues in AMR vaccine research programs and communicate those to the FDA. This would enable the FDA to have familiarity with vaccine development for these pathogens when and if a company requests a pre-IND and IND meeting with the FDA.

Finally, participants discussed consolidation in the vaccine industry. Specifically, smaller companies that focus on discovery and research need to eventually partner with a larger pharmaceutical company to get a vaccine to market. However, as there are fewer pharmaceutical companies to partner with, the competition for these partnerships intensifies. The threshold of data to garner interest from these large partners continues to increase. The group suggested that a role for BARDA could be to aid in fostering these partnerships between smaller and larger vaccine developers.

Question 4: What threshold or level of support is needed to incentivize the industry/private sector to push vaccine candidates against AMR threats to licensure for a market supported program?

Some participants mentioned that it could be challenging to obtain support from larger pharmaceutical companies because the latter often require Phase 1 and, in some cases, Phase 2 clinical trial data before they consider investing. Additionally, there was some concern regarding market viability for these types of vaccines, making them unattractive to larger private sector investments. It was noted, however, that there may be larger markets than currently realized for AMR pathogen vaccine candidates if they applied their work on a global scale.

Multiple participants discussed the need for government or large foundation commitment to purchase or stockpile vaccines after development, as this can incentivize development because a guaranteed market or purchaser of the vaccines after licensure would exist. Participants noted that CARB-X provides non-dilutive funding and supports vaccine candidates earlier in development through Phase 1 clinical trials, which can help with some of the above challenges. Further, follow on private sector investments with CARB-X program graduates is over $1 billion. Some participants suggested that a BARDA investment in the development of an AMR vaccine candidate may attract similar private sector investments similar to how the CARB-X program graduates have done.

Finally, there was mixed discussion regarding FDA priority review vouchers as potential incentives for vaccine development for AMR pathogens. These vouchers allow for an expedited review of products and can shorten the length of time it takes to get a product licensed. One participant noted that a product had to be advanced in the development pathway to benefit from the vouchers. So, while vouchers can be valuable, they may not be enough of an incentive early on in development to attract investments from larger pharmaceutical companies. Another participant noted that a cholera vaccine had benefited from the use of a priority voucher.

Conclusion

The Market Research Workshop, "Partnering on Vaccines to Counter Multi-Drug Resistant Threats" successfully brought together experts from government, academia, and industry to discuss successes and challenges in this field. The workshop helped to identify the main bottlenecks in vaccine development for both AMR pathogens, as well as recommendations for overcoming these challenges. Challenges included: 1) lack of reliable animal models, 2) the need to identify appropriate target populations for clinical trials, 3) the need to identify appropriate endpoints such as defined immunological correlates of protection for clinical trials, 4) highly variable vaccine targets within these bacterial species, 5) lack of investment from larger pharmaceutical companies, 6) numerous regulatory requirements for vaccine development, and 7) the need for financial assistance for smaller vaccine developers to generate the Phase 1 and Phase 2 data required to attract a larger commercial partner. Recommendations proposed to address these challenges included: 1) increased investment in AMR pathogen animal models; 2) identification of immune correlates that could be used as clinical trial endpoints; 3) refinement of target populations and indications; and, 4) more funding for early- and late-stage development, including antigen discovery.

Acknowledgements

We thank the workshop speakers and panel participants without whom the workshop would not have been possible. We also thank the workshop attendees for providing their expertise and insight during both the presentations and discussion sessions. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the U.S. Department of Health and Human Services or its components.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors reported there is no funding associated with the work featured in this article.

References

1. Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019. [accessed 2022 Jan 11]. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.
2. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, Han C, Bisignano C, Rao P, Wool E, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–55. doi:10.1016/S0140-6736(21)02724-0.
3. World Health Organization (WHO). Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. [accessed 2022 Jan 11]. https://apps.who.int/iris/handle/10665/311820.
4. Centers for Disease Control and Prevention (CDC) Antibiotic resistance threats in the United States, 2013. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2013. [accessed 2022 Jan 11]. https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.
5. World Bank Group (WBG). Drug-Resistant infections: a threat to our economic future. Washington DC: The World Bank; 2017. [accessed 2022 Jan 11]. https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future.
6. White House. National biodefense strategy; 2018. [accessed 2022 Jan 11]. https://trumpwhitehouse.archives.gov/wp-content/uploads/2018/09/National-Biodefense-Strategy.pdf.
7. Global Health Security Agenda (GHSA). 2024 framework; 2018. [accessed 2022 Jan 11]. https://ghsagenda.org/wp-content/uploads/2020/06/ghsa2024-framework.pdf.
8. Department of Health and Human Services (HHS). National action Plan for Combating Antibiotic-Resistant Bacteria 2020-2025. Washington DC; 2020. [accessed 2022 Jan 11].
9. White House. National action plan for combating antibiotic-resistant bacteria. Washington, DC: White House; 2015. [accessed 2022 Jan 11].
10. BARDA. Biomedical advanced research and development authority. Washington, DC: HHS; 2021. [accessed 2022 Jan 11]. www.phe.gov/about/barda/.
11. Ashurst JV, Dawson AKP. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. [Updated 2021 Feb 5]. https://www.ncbi.nlm.nih.gov/books/NBK519004/.
12. Ramirez JA. Overview of community-acquired pneumonia in adults; 2019. [accessed 2022 Jan 11]. https://www.uptodate.com/contents/methicillin-resistant-staphylococcus-aureus-mrsa-in-adults-epidemiology?topicRef=117561&source=see_link.

13. Bartsch SM, McKinnell JA, Mueller LE, Miller LG, Gohil SK, Huang SS, Lee BY. Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. Clin Microbiol Infect. 2017;23(1):e9–e16. doi:10.1016/j.cmi.2016.09.003.
14. Perween N, Prakash SK, Siddiqui O. Multi drug resistant Klebsiella isolates in burn patients: a comparative study. J Clin Diagn Res. 2015;9(9):DC14–DC16. doi:10.7860/JCDR/2015/13837.6576.
15. Lachiewicz AM, Hauck CG, Weber DJ, Cairns BA, van Duin D. Bacterial infections after burn injuries: impact of multidrug resistance. Clin Infect Dis. 2017;65(12):2130–36. doi:10.1093/cid/cix682.
16. Klein EY, Monteforte B, Gupta A, Jiang W, May L, Hsieh YH, Dugas A. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Viruses. 2016;10(5):394–403. doi:10.1111/irv.12398.
17. Zhu X, Ge Y, Wu T, Zhao K, Chen Y, Wu B, Zhu F, Zhu B, Cui L. Co-Infection with respiratory pathogens among COVID-2019 cases. Virus Res. 2020;285:198005. doi:10.1016/j.virusres.2020.198005.
18. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014;28(1):1–13. Epub 2013 Dec 8. PMID: 24484571. doi:10.1016/j.idc.2013.09.003.
19. Klevens RM, Edwards JR, Richards CL Jr, Horan TC, Gaynes RP, Pollock DA, Cardo DM. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep. 2007;122(2):160–66. doi:10.1177/003335490712200205.
20. Simmering JE, Tang F, Cavanaugh JE, Polgreen LA, Polgreen PM. The increase in hospitalizations for urinary tract infections and the associated costs in the United States, 1998-2011. Open Forum Infect Dis. 2017;4(1):ofw281. Published 2017 Feb 24. doi:10.1093/ofid/ofw281.
21. CDC.Guidelines for prevention of catheter-associated urinary tract infections. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2009. [accessed 2022 Jan 11]. https://www.cdc.gov/infectioncontrol/pdf/guidelines/cauti-guidelines-H.pdf.
22. Frank CE, Buchman TG, Simpson SQ, Sciarretta KL, Plopper GE, Finne KP, Sowers N, Collier M, Chavan S, Lin C, et al. Sepsis among medicare beneficiaries: 4. Precoronavirus disease 2019 update January 2012–February 2020. Crit Care Med. 2021;49(12):2058. doi:10.1097/CCM.0000000000005332.
23. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, Thomas AR, Harrison LH, Bennett NM, Farley MM, et al. Active bacterial core surveillance of the emerging infections program network. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant streptococcus pneumoniae. N Engl J Med. 2006;354(14):1455–63. doi:10.1056/NEJMoa051642.