PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

Third Public Meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB)
June 21–22, 2016

Department of Health and Human Services
Great Hall, Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

Table of Contents

Meeting Proceedings—Day 1

Welcome and Overview

Martin Blaser, M.D., Chair

Dr. Blaser called the meeting to order at 10 a.m. He gave a brief overview of the agenda.

Roll Call and Rules of Engagement

Bruce G. Gellin, M.D., M.P.H., Designated Federal Official

Dr. Gellin said the PACCARB is exploring the first task assigned to it by the Assistant Secretary for Health (ASH) of the Department of Health and Human Services (HHS)- identifying incentives for product development to combat antibiotic-resistant bacteria. Dr. Gellin explained the rules governing the PACCARB under the Federal Advisory Committee Act and conflict-of-interest guidelines. He then conducted roll call.

Incentives: U.S. Government (USG) Experience

Introduction

Robert Weinstein, M.D., PACCARB Voting Member

In response to the charge of the ASH, PACCARB invited a panel of USG, international, and industry experts to discuss incentives. The presenters were asked to focus on antibiotics, vaccines, and diagnostics and to address the following questions:

- What incentives have been tried and what has worked?
- Are there opportunities for early successes (i.e., "low-hanging fruit")?
- Which approaches are realistic and can help i) maximize return on investment (ROI) for companies and have the greatest impact on USG resources, ii) encourage stewardship, and iii) maintain access to the product?

Biomedical Advanced Research and Development Authority (BARDA)

Joseph Larsen, Ph.D., BARDA, HHS

Dr. Larsen said that, on average, investigators pursue 12–18 candidates to get one viable product to market. Realizing profits from each product can take as long as 25 years, therefore, investors have little confidence in seeing an ROI under the current model. Incentives to develop antibiotics are needed to counter the uncertainty in the degree of uptake, the limitations on use posed by good stewardship, and the availability of generic products. Net present value (NPV) assesses the overall risks, benefits, and profitability of drug development and takes into account the likelihood of licensure and anticipated future value, among other factors. For antibiotics, the NPV has been estimated at approximately $50 million, which is about a 20th of the NPV of neurological or musculoskeletal drugs. (It has been suggested that an NPV of $200 million would be sufficient to incentivize investment.)

To be effective, incentives should improve the NPV, cause minimal disruption to the marketplace, reward innovation, ensure stewardship to preserve utility, and not have a negative impact on patient access. Push incentives provide direct support to underwrite the cost of

development (e.g., grants, contracts, and tax credits). Pull incentives create market demand or reward successful development; examples include advance market commitments, milestone payments, and regulatory incentives (e.g., exclusivity). There is a growing global consensus that incentives are needed; the USG has no formal position but funds various push incentives (e.g., through BARDA and the National Institute for Allergy of Infectious Diseases [NIAID]) and offers limited pull incentives through the Generating Antibiotic Incentives Now (GAIN) Act. Dr. Larsen said the USG's current approach is missing a robust pull incentive.

Globally, there is growing consensus in favor of delinkage—that is, separating profitability of an antibiotic from the volume sold, so that companies see an ROI while also ensuring stewardship. Full delinkage promises a large payment at some point (e.g., through government purchase of the license), which requires substantial funding ($1–$2 billion) and a lot of political will. Partial delinkage offers, for example, milestone payments (in the hundreds of millions) to generate a known ROI for the developer while the government maintains some restrictions on marketing or sales. Delinkage allows the public health community to target antibiotics for unmet need. Numerous international experts and researchers advocate for delinkage, as did the President's Council of Advisors on Science and Technology (PCAST) in its *Report to the President on Combating Antibiotic Resistance*. Many subject matter experts propose combinations of both push and pull incentives.

Dr. Larsen supported incentives but advised careful planning of the goals and anticipation of potential consequences. Advocates for incentives should consider how to avoid disruptive effects and how to ensure feasibility and sustainability. Dr. Larsen noted that incentives related to pricing only have impact in U.S. markets in the absence of global adoption. He outlined the pros and cons of government administration of incentives. Dr. Larsen concluded that a mix of general and targeted incentives is needed, including more push incentives across all phases of development and some general pull incentives that apply to all (e.g., tax credits for late-phase clinical development) as well as partial delinkage.

Incentivizing Research and Development (R&D) for New Products for Use in Food Animal Agriculture

Stacy Sneeringer, Ph.D., Economic Research Service (ERS), U.S. Department of Agriculture (USDA)

Dr. Sneeringer outlined the argument in favor of a government role in the food-producing animal market in the case of antibiotics. Regulating or taxing antibiotic use in agriculture may be effective in regions with well-functioning regulatory systems but not in less-developed countries—where antibiotic use is most expected to increase. The animal pharmaceutical industry faces the same disincentives to new antibiotic development as the human pharmaceutical industry, so incentives are greatly needed.

Animal pharmaceuticals often are discovered as a result of "discards" from human pharmaceutical research, especially in companies that support both human and animal R&D. However, researchers may not necessarily communicate across laboratories. Thus, decreased human antibiotic R&D means less animal antibiotic R&D. In addition, the use of products by humans may result in restrictions on their use for animals, which increases uncertainty for product developers.

Different incentives may be needed for the animal market. Because animal pharmaceuticals often apply to multiple species, antibiotic development timelines are longer due to additional regulations and labeling (which affects the use of milestone payments). Another difference is that the food-producing animal industry has no third-party payers; it allows for an acceptable rate of loss from death. Diagnostics for livestock must provide instant results to be useful in current production methods. Dr. Sneeringer outlined some key questions and considerations:

Can incentives to develop new human pharmaceutical products be leveraged for animal pharmaceuticals (also called ride-on programs)? The success of such programs may depend on the strength of connections between animal and human pharmaceutical research efforts. Would products deemed not suitable for humans be considered for animal use? Could ride-on programs be designed as part of human pharmaceutical development? Could funds for human pharmaceutical development be directed to animal pharmaceuticals? Possible incentives for ride-on programs are grant programs for early R&D and prizes that place the resulting platforms in the public sphere (which translates to full delinkage). Incentives targeting specific human diseases may not translate to address animal needs.

How would incentive programs specifically for animal pharmaceuticals compare with human pharmaceutical programs? There are no government-funded incentive programs for animals similar to those for human pharmaceuticals. The strengths and weaknesses of incentives are similar across both types but the efficacy and efficiency of incentives differ. For example, prizes that put research results in the public domain help when the barrier to new products is basic research; when the barrier is getting the product to market, then prizes do not work as well in the animal sector. Generics play a smaller role in animal than human pharmaceuticals. In animal pharmaceuticals, patent extensions are more effective than prizes when social and market values are closely aligned.

Are there effective nonmonetary incentives? Reducing regulatory uncertainty—particularly about novel products, international regulations, and long-term stability of the market—is a potential nonmonetary incentive. Another is educating small firms that failed human pharmaceutical products may have potential for use in the animal market. Dr. Sneeringer said an example of low-hanging fruit is helping small firms understand how to navigate the animal market.

Dr. Sneeringer concluded that human pharmaceuticals drive research and dominate policy development. Animal pharmaceuticals could leverage human pharmaceutical R&D.

Council Questions and Answers (Q&A)

Sara E. Cosgrove, M.D., M.S., asked which animal product types are most pressing. Dr. Sneeringer said there has not been a formal prioritization. There is less attention to antibiotic resistance in animal health because of a higher tolerance for some loss from death. Some alternatives to antibiotics have been tested for production purposes, but the biggest concern is whether they can effectively replace antibiotics for prevention or treatment. Richard Carnevale, V.M.D., said a lot of work is focusing on developing new animal vaccines, but that will not address the whole problem. He noted that the U.S. Food and Drug Administration (FDA) is struggling with how to regulate new technology. He did not think the animal industry would

prioritize products except to find alternatives for products for which current use is unfavorable (e.g., growth promotion).

Ramanan Laxminarayan, Ph.D., M.P.H., said it is important to acknowledge that the vast availability of numerous antibiotics crowds the market, which makes manufacturers reluctant to invest in an antibiotic that only targets multidrug-resistant organisms (MDROs). He said that if companies were reimbursed for their products according to their real value, they could sell fewer products. Such an approach represents a delinkage model. Dr. Larsen said the NPV remains much lower for antibiotics than for other drugs, and raising reimbursement for antibiotics would be challenging to implement. Furthermore, raising rates would not delink profits from sales; companies would still seek to sell more products to make money. Dr. Laxminarayan said that hospitals and formularies restrict the use of high-priced drugs, so the price alone limits demand.

Dr. Blaser pointed out that if stewardship were improved, the market for antibiotics would be even smaller. Dr. Larsen agreed, observing that improved stewardship will magnify the low ROI. Therefore, delinkage is appealing, because it rewards investors independent of how much product is sold and can build in stewardship requirements. Beth P. Bell, M.D., M.P.H., added that new models for drug development must be linked to new approaches to stewardship. Congress has asked the Centers for Disease Control and Prevention (CDC) why stewardship is not improving more quickly. For example, the 21st Century Cures Act requires reporting of use and resistance data through the National Healthcare Safety Network (NHSN), as part of the new drug approval process.

Dr. Blaser asked whether products could be developed for people with highly resistant infections and stockpiled in anticipation of a future growing need. Dr. Larsen said BARDA has overseen stockpiling of countermeasures for emergencies for a decade. It uses milestone payments to incentivize development. To effectively incentivize manufacturers and ensure an attractive ROI, the government must agree to stockpile a large supply or supplement payments. Also, products in the stockpile must be replaced periodically, so the long-term, life-cycle costs of stockpiling must be taken into account. Dr. Larsen was unsure that such an approach would be helpful in the long run because it could shackle the USG into maintaining products in perpetuity.

Alicia Cole asked how many of the studies supporting delinkage and other incentives included representatives from drug companies, who might have a conflict of interest. Dr. Larsen said the USG recommendations mostly came from federal advisory groups, which include some industry representatives, but whose members are vetted for conflicts of interest. Ms. Cole asked whether any models support government development, production, and sales of new antibiotics, with profits going back into R&D. Dr. Larsen said that in a full delinkage model, the government purchases the intellectual property (IP) from a company and controls price, access, and distribution. Dr. Larsen had concerns about such an approach, noting that pharmaceutical companies are good at developing and distributing drugs.

Ms. Cole asked what other novel products for animals are under consideration. Dr. Sneeringer said products such as feed additives, probiotics, and prebiotics are being evaluated, and they are not subject to FDA oversight.

Aileen M. Marty, M.D., FACP, said that as technology changes, so will the models of profit and NPV, so any solutions should be malleable, not fixed. She wondered about the transfer of liability to the government with delinkage. She also questioned whether the milestone method creates a bias toward existing products. Dr. Larsen confirmed that all of Dr. Marty's concerns are realistic. He advocated for tax credits available to anyone as a pull incentive (as stipulated by the Orphan Drug Act) and a mixture of general and targeted push incentives.

John H. Rex, M.D., expressed concern about the full delinkage model, pointing out that many centralized approaches have failed. There must be an allowance for failure. The reward should be restricted to products that actually reach the market. Dr. Rex asked what is needed to ensure that once a product is on market, it stays available. Dr. Larsen replied that after approval, continued availability requires a series of commitments as well as continued production at a scale and level of quality that allows for use. In addition, efforts are needed to sustain the infrastructure and knowledge base. Any incentives aimed at drug development should consider the cost of long-term maintenance in the absence of high sales or use.

Dennis M. Dixon, Ph.D., said the National Institutes of Health (NIH) provides a lot of push incentives for antibiotics. Of about 40 candidates in clinical trials, approximately 25 percent bear the fingerprints of NIH research. Dr. Dixon agreed that there must be room for failure. The further upstream in the research process, the higher the failure rate. For pull incentives, there must be a viable market for the product.

Asked about opportunities for early successes in human or animal pharmaceuticals, Dr. Larsen felt that BARDA models could be replicated for animal health with sufficient resources. BARDA is planning a new public-private partnership with multiple entities to bolster the pipeline of products and to encourage collaboration with the USG around decision-making. The effort would allow the USG to bring in new programs as needed and form strategic alliances with companies over the long-term, independent of technical attrition of any one candidate. Dr. Larsen hoped to present on a new initiative, the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator, at a future public meeting.

Dr. Sneeringer said efficiencies could be realized, for example, by identifying platforms that could be used in both human and animal health. She emphasized the need for a mechanism to transfer knowledge from human pharmaceutical R&D to animals. Dr. Dixon said NIH is convening an interagency roundtable on systems biology as a platform that is broadly applicable in both human and animal spheres.

In response to Randall Singer, D.V.M., M.P.V.M., Ph.D., both Dr. Sneeringer and Dr. Larsen said there are no models that incentivize products for disease prevention in animal or human health.

Kent E. Kester, M.D., FACP, FIDSA, FASTMH, asked how to incentivize the USG's own R&D agencies to facilitate, expedite, and streamline knowledge transfer. Dr. Larsen said the question is tough, because it asks how the USG can adopt a culture of entrepreneurship. The BARDA Accelerator is one mechanism, but a cultural shift is needed to translate more work from government laboratories into the marketplace. Dr. Dixon pointed out that government

researchers do share information openly through meetings and publications. He said more conferences that bring human and animal researchers together would help cross the divide.

Dr. Laxminarayan asked about the role of incentives in conservation of antibiotics. Michael Clancy of ERS said patent extensions are more important in human then animal pharmaceutical development. In animal health, the revenue fall-off when a patent expires is not as sharp as it is for human health.

Helen W. Boucher, M.D., FIDSA, FACP, called for a focused look at what current and planned efforts are incentivizing. Elizabeth Jungman, J.D., M.P.H., wondered whether the right questions are being asked. For example, in animal health, instead of incentivizing new antibiotic development, should the concentration be on technologies that avoid antibiotic abuse? Dr. Sneeringer said there has been little discussion about joining the human and animal pharmaceutical incentive structures. In animals, incentives are aimed at alternatives to antibiotics and development of antibiotics for animal use only. She pointed out that colistin is currently available for use in animals but is avoided because of the potential negative health impacts for humans. Dr. Sneeringer added that the needs vary depending on domestic or global use. Thomas R. Shryock, Ph.D., noted that most alternatives are focused on disease prevention, which is key.

Michael D. Apley, D.V.M., Ph.D., DACVCP, stressed that both human and animal sectors have little understanding about correct dosing of current antibiotics or how to balance resistance and disease. Outdated regulations prohibit the food-animal industry from re-evaluating current use of antibiotics. Dr. Apley said modifying the dose and duration of existing antibiotics and re-considering labeling are important steps. Dr. Sneeringer said animal agriculture struggles with incentives around limited use of antibiotics. She reminded the group that in the developing world, reconfiguring labels will not have an effect.

Dr. Blaser pointed out that farmers worry about catastrophic losses and the risks of not treating their flocks or herds. He wondered whether an insurance program could mitigate antibiotic use. Mr. Clancy said he would consider looking at the concept.

Regarding the exchange of information between animal and human researchers, Dr. Shryock said there is always informal discussion, but it is often confidential.

Dr. Blaser said the discussion of animal health centered on U.S. policy, but it is not clear how the United States should respond if other countries continue to overuse antibiotics on farms. Dr. Sneeringer said efforts to reduce use may not be feasible in countries without effective regulatory institutions. Therefore, there is a strong need for alternatives that can reduce antibiotic use.

Incentives: International Experience

Review on Antimicrobial Resistance (AMR)

Hala Audi, Head, Review Team (by phone)

Ms. Audi described the origins of the AMR Review, which began work in 2014. Since then, it has recommended actions across 10 areas, mostly aimed at reducing demand for antimicrobials. Without reducing unnecessary use, said Ms. Audi, fixing the supply side will be meaningless. In

terms of the pipeline of development, the AMR Review categorized priorities according to the urgency of need and adequacy of current funding structures. Ms. Audi urged PACCARB and other international organizations to work together to prioritize needs, although she acknowledged the effort is not as straightforward as one would like.

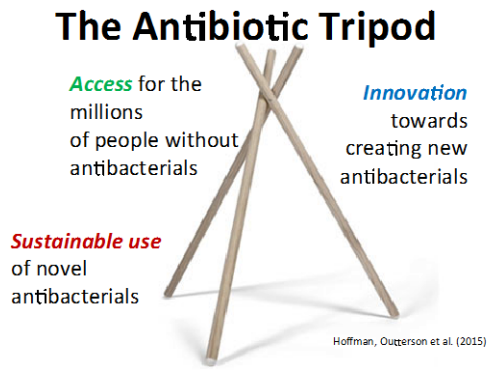
As Dr. Larsen said, there seems to be growing international consensus around the need for a combination of push and pull incentives. More push incentives are needed to address the underinvestment in antimicrobial resistance; even the public sector is divesting, said Ms. Audi. Moreover, the workforce pipeline is a concern. Infectious disease (ID) physicians are the least paid of all specialists, and investments have focused on newer areas of research.

Ms. Audi described some good examples of push investments but said they are not sufficient. She pointed out, for example, that more research on pharmacokinetics and pharmacodynamics would be fruitful, but companies are unwilling to pursue work they cannot patent. Similarly, dosing research is not appealing because it does not enhance careers or merit rewards. Ms. Audi called for focusing some resources on outcomes-oriented research.

Current push incentive programs rely on partnerships with large institutions, but push incentives alone are not enough. Pull incentives are needed to engage small groups and developing countries, moving toward a more competitive playing field with diverse input. Companies must pick up where publicly funded research falls short to get products to market. The AMR Review proposes a global incentive that coexists with diverse national arrangements. A first step is to reward development and ensure stewardship. International coordination is needed to limit unnecessary use and maintain patient access. Incentives should reward development of scientifically important products (not just products that would have been developed anyway). The United Kingdom is working with the G20 nations to facilitate international conversation on improving the rules of stewardship as a step toward international pull incentives.

Current pull incentives are insufficient; they are scattershot approaches that are not even coordinated domestically. The AMR Review believes market entry rewards hold promise. Antibiotics bring in $40 billion per year, but only $4.7 billion of that goes to patented antibiotics. An annual investment of $1.6 billion per year for 10 years in market entry rewards would be a significant, powerful incentive to create innovative antibiotics.

Economic Incentives for Antibiotics: The Driving Reinvestment in R&D for Antibiotics (DRIVE-AB) Approach



Kevin Outterson, J.D., Boston University, Associate Fellow at Chatham House

Mr. Outterson said all of the challenges that make up the "antibiotic tripod"—access, innovation, and sustainable use—are interrelated and must be addressed simultaneously. He echoed that low NPV makes companies unwilling to pursue new antibiotics. However, the social NPV is dramatically higher than the private, or market, NPV. Therefore, patents in the

existing system may need to be adjusted in order to work well.
The Infectious Diseases Society of America (IDSA) called for 10 new antibiotics by 2020. So far, eight have been approved, but they are not necessarily the type of antibiotics needed. Notably, six of the eight approved new drugs were initiated at small firms, but ownership was transferred to large firms when they went to market. Mr. Outterson questioned whether small companies would be eligible for the incentives under consideration.

Mr. Outterson outlined the conflict between the value to society of, for example, a drug targeting a superbug (e.g., carbapenem-resistant Enterobacteriaceae [CRE]) and the limitations on profitability if the drug is reserved for rare cases. Good stewardship undermines the business case for product development. However, "We don't build fire stations when we see the smoke rising," Mr. Outterson observed. There may be lag time between clinical need and market need, so it is important to invest in advance.

A Chatham House report concluded that push incentives, such as NIH investment, are appropriate for preclinical research. The Orphan Drug model and the BARDA Accelerator are useful for clinical research. Once FDA approves a new product, taking a delinked approach, such as market entry rewards, can be effective in getting products to market. Like others, Mr. Outterson noted that there is a lot of agreement around delinkage.

The DRIVE-AB short list of incentives includes the diagnosis confirmation model, in which a provider only receives reimbursement for the full price of a costly drug if the diagnosis confirms the need for that drug; otherwise, the provider receives a lower payment. This model gives the company an incentive to develop and market a drug because it will be paid at a high price—but only if it is the right drug for the condition. Another partial delinkage model is level-setting or "topping up." During the years that the company sells less than a set amount, the government makes up the difference. If it sells more, the company gives the excess to the government. A proposed full delinkage model would involve a large market entry reward. Mr. Outterson and colleagues have published detailed recommendations on how to tailor payments to target needs and ensure that more important drugs get larger rewards.

The Global Access Strategy is bringing together public and private partners to address access, innovation, and sustainable use. Mr. Outterson said the current PACCARB meeting represents the most substantive conversation the USG has ever had about economic incentives.

One potential funding mechanism for incentives is the "pay or play" model, in which companies that are not investing in antibiotic R&D pay fees because they benefit from the advances in antibiotics. For example, a user fee of $25 per kilogram on nonhuman use of antibiotics at the factory level would raise hundreds of millions of dollars. It would increase the cost of routine use but would not prevent antibiotic use for sick animals and could be enough to change antibiotic use around the world. Transferrable exclusivity/patent extension vouchers (with limits) could raise billions for delinkage. Mr. Outterson concluded that the most urgent needs are i) targeted economic pull incentives of $1 billion or more, ii) a fully integrated tripod solution, and iii) global coordination.

Council Q&A

Dr. Laxminarayan said that conserving antibiotics should not be seen as a problem for innovation. Mr. Outterson agreed that conservation is a public health imperative, but by doing that well, it worsens the economic case for innovation. Dr. Laxminarayan called on the USG to offer a sense of direction to alleviate some of the uncertainties of the market. Mr. Outterson responded that some USG meetings on economic incentives are getting underway; he said that releasing the economic incentives report would be a good start.

Dr. Blaser asked about offering training grants to promote careers in infectious disease and antimicrobial research. Ms. Audi said individual training grants make sense, but the field needs broader support so those individuals will stay in the field. Dr. Boucher said IDSA is engaged in discussions about bolstering the workforce. She called for further investigation of ways to accelerate workforce development, such as private-public partnerships that support training across the spectrum from research to public health practice. Dr. Dixon added that training grants are available but not limited to specific disciplines, and IDSA could encourage candidates to apply. He added that there is precedent for public funding in the private sector. Dr. Blaser said a dedicated pool of money encourages people to apply for grants.

In response to Dr. Boucher, Mr. Outterson said incentives for large pharmaceutical companies are still valuable, but incentives should not only work for large companies. Tax credits, for example, are not meaningful to small companies without a lot of revenue. Mr. Outterson suggested partnering with the types of companies that are working on early stage research.

Commenting on the use of user fees for animal health use to support innovations, Elizabeth Allen Wagstrom, D.V.M., M.S., said the industry has difficulty defining routine and appropriate use. She asked whether such a user fee would have unintended consequences on animal health innovation, the cost of food, or the greater good. Mr. Outterson said more work must be done to understand the potential impact on food costs, but the user fee would not lower those costs, so it is a concern. The appeal of a user fee is that it gives an economic incentive to find alternatives. Mr. Outterson clarified that the user fee would not fund human health research only.

Dr. Marty wondered if it would be possible to internationally streamline the patent and approval processes for antimicrobials and to identify standards of safety and efficacy. She noted that the World Health Organization (WHO) has international standards for antibiotics but not necessarily for approving antibiotics. Ms. Audi said the cost of registration and the regulatory approval come up frequently as barriers. There has been some work to improve regulatory approval processes with regards to safety and efficacy, but there is much more to do. Clinical trials and the postapproval period are where costs mount up, so any harmonization that reduces cost would save everyone a lot of money, said Ms. Audi. Mr. Outterson said streamlining the patent system is not a high priority, but he liked the idea that a patent could include stewardship requirements. The regulatory process is improving in the United States and Europe, where several antibiotics have been approved on the basis of small Phase II trials. But the difficulty of registering a drug persists around the world. With AIDS drugs, a prequalification mechanism helped streamline the process. Mr. Outterson suggested antibiotics be the test case for proposals for harmonization that have been under discussion for years.

Ms. Cole asked how incentives could work better for small companies. Ms. Audi said pull incentives should be designed to encourage innovation from any sources. Jeremy Knox, of the AMR Review team, added that market entry awards are attractive to large pharmaceutical companies, and that money trickles down if they buy products from smaller companies. Dr. Rex agreed that incentives must work for both large and small companies.

Ms. Cole supported the idea that the whole industry benefits from the development of antibiotics—because, for example, cancer patients can die from antibiotic-resistant infections during treatment. She also agreed that society must see career opportunities around AMR research as attractive. Therefore, she proposed a Peace Corps model or training grants that require a commitment to work in the field. Ms. Audi said the whole ecosystem of AMR must be addressed (e.g., through a massive public awareness campaign). She added that money is available for training and efforts are on track to make the field more attractive.

Mr. Outterson suggested looking more broadly at the problem of resistance in practice. Hospitals cannot perform surgery without antibiotics, so perhaps there should be a small fee for every use. Also, the new Medicare Conditions of Participation may convince hospitals to hire more ID specialists for infection control, which could impact workforce development.

Dr. Rex requested that the National Vaccine Program Office (NVPO) again ask the White House to release the economic report on incentives. Peter Lurie, M.D., said the United States is probably unwilling to give up its own standards when it comes to safety and efficacy. The regulatory process in this country is in "a pretty good place" at this point, with more guidance on exactly what is required for approval, which is reflected in part in the upswing in the number of new approvals in the antibiotic area. FDA is open to new ideas about improving processes. Dr. Lurie noted that more than 50 percent of all drugs come to market first in the United States, so it is not true that the process here is slow.

Dr. Lurie continued by saying that FDA and the USG overall have roles in providing technical assistance to others. There are a number of areas where cooperation can be improved, even if it stops short of some kind of mutual recognition process. Dr. Lurie added that training in regulatory science in particular is lacking. However, FDA participates in a fellowship program that provides education about FDA processes; the Reagan-Udall Foundation for the FDA is looking at a similar approach in a public-private partnership context.

Incentives: Industry Experience

Incentives for R&D of New Antibiotics for Use in Food Animals

Carel du Marchie Sarvaas, Executive Director, Health for Animals

Mr. Sarvaas, whose organization represents most of the global animal health sector, pointed out that differences between the animal and human health markets have prevented animal health companies from making major investments in antibiotics. The most important hurdles to overcome are the low ROI, growing pressure around antibiotic use, and the business risk for animal health companies and food producers. Unlike human health companies, animal health companies have few financial incentives. The veterinary health sector typically relies on a relatively unfettered market.

Mr. Sarvaas offered 10 recommendations to incentivize development of products in the animal sector, with rationales for each. First, make the most sensible use of existing antibiotics as well as diagnostics, vaccines, alternatives, and biosecurity. Notably, this tactic requires realistic prioritization of medically important antibiotics and a recognition that failure to treat sick animals is both unethical and ineffective. Second, increase the odds of a reasonable ROI by changing the market dynamics, because no market is large enough to warrant a new antibiotic R&D program. The difficulty and cost of regulatory approval are significant factors in investment decisions. This leads to recommendations three and four: improve regulatory processes to make them more predictable and more streamlined globally.

Recommendations five and six call for support for vaccines and alternatives. Increased financial and regulatory incentives, such as expedited approval and early proprietary protections, may drive vaccine investment. The same incentives may also drive investment in alternatives, but it is not clear which alternatives are worth pursuing or improving.

The seventh and eighth recommendations involve improving data protections and defining better performance metrics, recognizing that animal antibiotics may need more and longer patent protection. To measure advancements in animal health, there must be a definition of what improvement is expected. Ninth, stronger political leadership is needed to give direction, provide more certainty, and counter myths propagated. Tenth, smarter financial incentives are needed. Large prizes are good incentives for small companies and academic researchers, but finances are not the key barrier for large animal health companies. Rather, investment should seek to:

- ease regulatory burden,
- promote the benefits of vaccination,
- research antimicrobial resistance transfer pathways,
- develop cheap, reliable, convenient diagnostics,
- finance promising and realistic R&D in academic or focused settings, and
- use tax tools to ease investment (recognizing that antibiotics are a public good).

Mr. Sarvaas concluded that the current business model is not attractive, and more collaboration across entities is needed. Scientific analysis should focus first on understanding AMR pathways. Political leadership must support sound science.

Incentives for Vaccines that Combat Antimicrobial Resistance: Perspective of the Biotechnology Innovation Organization (BIO)

Timothy Cooke, Ph.D., BIO, CEO of NovaDigm Therapeutics

Dr. Cooke described some of the factors that distinguish vaccine development from antibiotic development. For example, vaccine makers must invest a lot in manufacturing even before the product is licensed, and the cost of maintaining the components of a vaccine can increase over time. Vaccine markets are driven either by government purchase or recommendations. Small biotech firms that develop vaccines must usually link to larger companies for manufacturing and sales. The NPV for infectious disease vaccines is lower than for other products because they face longer timelines, higher costs, and more layers of risk. However, vaccines are difficult to make, so competition from generic products is not a concern (and market exclusivity is not an

important incentive). In recent years, most vaccine investment has gone toward oncology and rare diseases.

Vaccines offer the opportunity to prevent use and misuse of antibiotics. They carry a low risk of generating resistance, so there is no need to limit their use. Therefore, delinkage would not be a useful incentive for vaccine development. Vaccines have a longer duration of protection than antibiotics and are effective against susceptible and AMR strains.

New vaccine development faces many challenges, such as novel pathogens and indications. To be effective, new vaccines will likely have to target limited populations (not mass vaccination), which dampens the economic case for development. Of the vaccine candidates in clinical trials for pathogens identified by CDC as potentially resistant, the likelihood of success is low. Other modalities to address AMR pathogens, such as small molecules, monoclonal antibodies, and novel technologies are also under investigation.

Effective techniques for spurring vaccine development have been push incentives from government agencies, regulatory incentives (e.g., accelerated review for orphan drugs), and pull incentives (e.g., GAVI market commitments and BARDA stockpiling agreements). Opportunities for early success include broader use of current vaccines, increased push incentives for R&D of vaccines, funding for supporting research (e.g., correlates of protection for vaccines), and regulatory incentives that make vaccines eligible for priority FDA review.

Additional incentives could include tax credits for trial expenses, harmonization of regulations, and a risk-sharing financial mechanism for vaccines against health-care-acquired infections (HAIs). An attractive market is the best driver of investment, said Dr. Cooke. Therefore, pull incentives are needed to get products through research and into the market. Governments, payers, and the public must recognize the value of vaccines and antibiotic stewardship to society. The USG should eliminate cost-sharing in Medicare Part D and address provider billing issues to drive uptake of vaccines among older adults. Novel pull mechanisms, such as transferrable market exclusivity, should also be considered. Punitive measures, such as "pay or play," should be avoided, because the life sciences industry should not bear the whole economic burden of antibiotic resistance.

Incentivizing the Development of New Diagnostics

Sam Bozzette, M.D., Ph.D., Vice President, Medical Affairs—Americas, bioMerieux

Dr. Bozette emphasized that diagnostics play a very important role in clinical decision-making but account for only 2–3 percent of health care spending. Compared with pharmaceuticals, diagnostics operate in a much smaller market with less research funding and lower reimbursement. Existing tests are underused because of lack of awareness, delayed incorporation into clinical guidelines, low provider and patient demand, and narrow claims. Underdevelopment of new diagnostics is both a clinical and public health issue, driven by poor ROI.

The costs of development are high and rising—in part due to increasing need for complex clinical studies and outcomes research. The ROI is limited by underutilization and the commodity pricing structure. The clinical value of diagnostics is rarely considered in pricing, and social value is not considered at all, said Dr. Bozette.

Effective incentives for diagnostics have been tax credits, contracts and grants for development, mechanisms to enhance market reliability and size (e.g., advance purchase by BARDA and direct subsidies), and increased IP protection (e.g., the GAIN Act). Dr. Bozette questioned the value of prizes as incentives for diagnostics, because the prize amounts are often too small to be of interest to large companies, and smaller firms may lack the capacity to bring products to market. Potential nonfinancial incentives include increased funding for basic science research and a better public infrastructure for clinical research in diagnostics. Education and regulations that emphasize antibiotic stewardship and appropriate testing for reimbursement could optimize the use of diagnostics. Additional IP protections are also desirable. Potential regulatory incentives include fast-track and provisional approvals and more guidance for industry.

Financial incentives may include increased government funding of R&D, alignment of national and international goals, and funding for outcomes research and technology assessments. Guaranteed revenue mechanisms may also be helpful (e.g., advance market commitments, market entry rewards, and top-off payments for sales in developing countries). Incentives should also promote value-based pricing for relevant tests that incorporate clinical and social value and bases reimbursement on outcomes. The lack of direct connection between makers of diagnostics and payers is a problem.

Finally, Dr. Bozette favored increasing tax credits for research and clinical trials of innovative diagnostics (e.g., the Reinvigorating Antibiotic and Diagnostics Innovation [READI] Act) and repealing the device tax (or exempting high-value diagnostics). He called for omitting key tests from reimbursement cuts associated with the Protecting Access to Medicare Act.

Council Q&A

Dr. Kester asked whether clinical trial networks and related mechanisms to facilitate timely, reliable assessment of novel antibiotic agents could be leveraged for diagnostics. Dr. Bozzette responded that including diagnostics, particularly for organisms of high concern, would be useful, and incentives along those lines would be helpful. Such an approach would help the diagnostics and pharmaceutical industry collaborate to target clinical trials. Dr. Bozzette added that the future lies in “panels of tests.”

Dr. Laxminarayan felt that vaccines could be a promising area, especially for developing countries, for which a funding vehicle exists through GAVI. Regarding diagnostics, he said prizes could generate novel ideas, and large companies should keep their eyes on small companies as acquisition targets. Dr. Cooke agreed that GAVI has a good track record in promoting global access to vaccines.

Dr. Rex asked how to predict which diseases can be prevented with vaccines. Dr. Cooke said that every organism is unique, but companies look at whether a vaccine is the best solution, how many people would have to be vaccinated to prevent one case, and whether a vaccine can be priced appropriately to make its use worthwhile. Dr. Rex further asked if there is a good scientific review of the plausibility of certain targets. Dr. Dixon responded that CDC published research on cost assessments that demonstrated a market for antimicrobial vaccines. There is some skepticism about scientific feasibility, but Dr. Dixon said research into novel approaches and alternatives should continue.

Dr. Marty pointed out that vaccines recommended for international travelers are not covered by insurers, which can open the door for transmission of dangerous pathogens. Dr. Cooke agreed that reimbursement for travel-related vaccines is a problem.

Dr. Wagstrom said Mr. Sarvaas' presentation seemed pessimistic about the likelihood of human health discards finding their way into animal health. Mr. Sarvaas responded that better discussions are needed between animal and human health companies about potential products. The biggest barriers are valuation and the burden of regulatory processes; alleviating them would help create the conditions for human health discards to be used in animal health research.

Dr. Blaser asked how to address the clinician's incentive to choose an inexpensive antibiotic over an expensive and time-consuming diagnostic. Dr. Bozzette said that driving unit cost of the diagnostic test down requires payment. Also, improving education and changing clinical standards could help. A common rapid diagnostic test for a range of viruses may be useful. Biomarkers for viral vs. bacterial infections would also help, but the price of diagnostics is a substantial issue, especially when compared to the cost of generic antibiotics.

Dr. Shryock pointed out that rapid diagnostics are the goal; having them available in retail stores could be very effective for stewardship. He asked whether diagnostic and pharmaceutical companies could collaborate to bundle diagnostics and therapeutics together. Dr. Bozzette said that as diagnostics technology improves, the possibility of better diagnostics improves. He did not think a "companion" diagnostic to a therapeutic was possible for the foreseeable future but the approach could be useful in clinical trials.

Dr. Weinstein asked whether some current diagnostics are underused in practice. Dr. Bozzette said following standard quality guidelines for use of diagnostic testing would be a big step forward. Dr. Weinstein asked for input on incentives to encourage diagnostic and pharmaceutical companies to collaborate on research. Dr. Bozzette felt such an approach would be useful.

Summary: Incentives

Thomas Shryock, Ph.D., and Robert Weinstein, M.D., PACCARB Voting Members

Dr. Weinstein said PACCARB members would form working groups to talk more in depth about incentives, informed by the day's presentations. From these presentations, he said he learned that there are important differences between the animal and human health industries and that a lot of available products are underused.

Dr. Shryock said he sees commonalities at the earliest stages, in basic science, so it may be appropriate for incentives to focus there. After that stage, human and animal science and industries diverge, and different incentives are needed. That recognition challenges the One Health framework. More discussion is needed about efforts to encourage pull incentives and the tools to close the gaps. Finally, Dr. Shryock said the image of the tripod—access, innovation, and sustainable use—sums up the issues and points to the need to address all three concerns simultaneously.

Council Discussion

Ms. Cole noted that the tripod image underscores the need for a broad perspective. The fact that it takes 27 years for a vaccine to get to the market and 10–15 years to develop an antibiotic emphasizes the urgency of the task ahead. Therefore, it is more important to focus on practical, immediate actions that can prevent infections and combat AMR. The timeframes, magnitude, and complexity explain why the number one goal is prevention and reducing the spread of resistance. Ms. Cole advocated for incentivizing the use of existing products to combat AMR.

Dr. Laxminarayan pointed to the access leg of the tripod. He proposed reframing the issues to better reflect the desire for sustainable access to effective antibiotics. He cautioned that the problem is complex and unlikely to be resolved by any one or two mechanisms. Neither BARDA nor industry can solve the access problem. Any recommendation will have to build in a long-term commitment, allowing at least 15 years to reach fruition, which is challenging.

Dr. Blaser said PACCARB plans to establish three new working groups on incentives: i) vaccines, ii) diagnostics, and iii) therapeutics and anti-infectives. Each will address both human and animal issues. The new working groups will begin meeting this summer. A fourth working group will address stewardship and prevention and will start a little later.

Plasmid-Mediated Colistin Resistance: USG Findings and Response

Beth P. Bell, M.D., M.P.H., Director, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention

Dr. Bell stated that colistin is a last-resort drug for MDROs, including CRE, in humans. It is used relatively infrequently in the United States but more often in other countries. The *mcr-1* gene makes bacteria resistant to colistin. It exists on a plasmid, a small piece of DNA that can move from one bacterium to another. Plasmids can spread antibiotic resistance among bacterial species.

The *mcr-1* gene was first reported in China in November of 2015, and researchers at CDC, USDA, and FDA have all been searching for the gene since. They began looking in bacterial samples from human, retail meat, and food-animal sources through the National Antimicrobial Resistance Monitoring System (NARMS). They screened 55,000 genomes, plus more from other CDC sources, but none contained the gene. Eventually, USDA discovered the *mcr-1* gene on a plasmid in *Escherichia coli* isolates collected from the intestines of two pigs. The *E. coli* isolates from one pig were resistant to other antibiotics, but the resistant genes were not on the plasmid carrying the *mcr-1* gene.

Almost simultaneously in May 2016, the Department of Defense (DoD) announced the discovery of the *mcr-1* gene in bacterium isolates from a U.S. patient, as a result of its Multidrug-Resistant Organism Repository and Surveillance Network (MRSN). The patient reported no recent travel outside of the United States. Dr. Bell pointed out that the pig plasmids identified by USDA have the same incompatibility type as those from China, but the human plasmid was different.

In its public health response, CDC has been working with the Pennsylvania Department of Health, in coordination with DoD, on a public health investigation. Screening of close contacts

of the patient found with the *mcr-1* gene has been negative. Dr. Bell clarified that the patient did not have CRE, and the bacteria identified was not resistant to all antibiotics.

CDC has used several strategies to increase awareness and detection, including a public announcement for clinicians and clinical laboratories. It is deploying a rapid polymerase chain reaction (PCR) test for use in public health and clinical laboratories to conduct colistin resistance testing. Dr. Bell cautioned that additional plasmid *mcr-1* genes will likely be found, and federal agencies will continue to look for the gene in bacterial isolate collections.

Thanks to funding for combating antibiotic-resistant bacteria, NARMS is phasing in whole-genome sequencing of all *E. coli* and salmonella isolates from humans, animals, and food, with help from the National Center for Biotechnology Information (NCBI). Also, CDC plans to expand the infrastructure and laboratory capacity to detect resistant organisms and new forms of resistance recovered from human samples through its Antimicrobial Resistance Regional Laboratory Network (ARLN).

The DoD's MRSN will continue whole-genome sequencing on all resistant clinical samples. CDC and FDA will collaborate in curating a colistin-resistant isolate panel for the Antimicrobial Resistance Isolate Bank to challenge and test new diagnostics and therapeutics. CDC is exploring ways to measure microbiome disruption as well as opportunities to address restoration of the microbiome. The NCBI website will host assembled genomes, making them available to researchers for further study.

Steve Kappes, Ph.D., of USDA's Agricultural Research Service (ARS) pointed out that colistin is not being used in U.S. food-animal production. He described USDA's efforts to identify *mcr-1* genes in food-animals. Dr. Kappes said ARS and NARMS will continue analyzing samples to better understand newly isolated strains. Paige Waterman, M.D., FACP, FIDSA, of the Armed Forces Health Surveillance Center, explained that the MRSN is DoD's reference laboratory. The discovery of the *mcr-1* gene led DoD to screen all of its existing samples and new isolates. The gene was found in a new isolate. After sending results to the facility that submitted the isolates, DoD alerted other government stakeholders of the findings, which turned out to be critical in this case because of the public health implications.

Council Q&A

Dr. Blaser remarked that the recent findings suggest horizontal transmission; he asked for more information about the gene's origin. Dr. Bell said the *mcr-1* gene has been identified in some other countries, so there is a lot of evidence of transmission, but it is not yet known how the genes got where they are. More information may provide a better picture of the landscape. In response to Dr. Weinstein, Dr. Kappes said there is no way to determine the age of the gene.

Ms. Cole asked whether the Department of Veterans Affairs' universal screening mechanisms contributed to the findings. Dr. Waterman said DoD conducts its own universal screening of isolates. Dr. Bell added that the human carrier in whom the gene was identified was tested for clinical reasons and was not subject to screening for colonization.

Ms. Cole noted that CDC has partnered with patient advocates to raise public awareness, and she hoped all the government agencies would do the same. She suggested that public reporting to the NHSN be mandatory; she also recommended that information about outbreaks be made public through local health departments. Dr. Bell said CDC is working to get more hospitals to use the antibiotics module of the NHSN. She agreed that reporting is important and said funding for combating antibiotic-resistant bacteria will be used to ensure state laboratories have the capacity to detect CRE, which is necessary for prevention and infection control. The funds will also support seven regional laboratories with a mission of identifying new threats early. Denise Cardo of CDC said the new approach to screening will be the standard for the future.

Dr. Blaser asked why the gene appeared if the U.S. is not using colistin in swine. Dr. Bell said Europe and other countries do use colistin in food-animals, which contributes to selective pressure.

Antibiotic Resistance in the Health Care Environment

Patient Perspective

Sherrie Dornberger, R.N., CDONA, GDCN, CDP, CADDCT, FACDONA, PACCARB Liaison Member

Ms. Dornberger gave a moving account of how her life changed dramatically as a result of an infection. She was at the top of her game, in her early 40s, working as the director of nursing at a large long-term-care facility when she suffered severe abdominal pain. That pain led to surgery, which resulted in infection and complications so severe she was in a coma for 18 days. Coming out of the coma, she continued to suffer necrosis and other complications, spending 7 months in an intensive care unit. Despite all these events, Ms. Dornberger said that antibiotics saved her—but what almost killed her was a nurse wearing artificial fingernails who did not wash her hands before giving care. Ms. Dornberger contracted methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile,* and a yeast infection that attacked her eyes and lungs. In her debilitated state, her body could not fight the infections, so she received multiple antibiotics and yeast-killers, resulting in antibiotic resistance.

Ms. Dornberger said the experience left her with only 4 feet of intestine, a port through which she gets minerals (intravenously every 3 days), and a $64 million medical bill. She missed a year of her daughter's life.

While the discussion has been focused on making new antibiotics, Ms. Dornberger emphasized the importance of doing better with the current tools for patient care. Nurses' failure to wash their hands, change their gloves, or turn patients to avoid pressure ulcers all contribute to the problem of resistance. Moreover, clinicians carry equipment from room to room and use stethoscopes on multiple patients without cleaning them. Ms. Dornberger hoped that PACCARB would think of people like her and consider what can be done now to promote basic hygiene among health care providers.

CDC Perspective

Beth P. Bell, M.D., M.P.H., Director, National Center for Emerging and Zoonotic Infectious Diseases, CDC

Dr. Bell said Ms. Dornberger's testimony described exactly the kinds of problems arising in the health care environment. The "dry" environment—including noncritical surfaces such as bedrails—can be contaminated by patients and health care workers and contribute to pathogen transmission. The "wet" environment—such as sink drains—allows contaminated fluids to pass through plumbing, and they can persist in biofilm. Transmission of pathogens in the health care setting can start with colonized patients and spread through gloves, interaction with the environment, and direct patient-to-patient transmission. The problem is multifactorial and should be addressed at multiple points.

In the 1970s and 1980s, efforts to decrease HAIs focused on medical procedures and devices, especially in intensive and acute care settings. With the aggressive improvements in procedures and devices over the past few decades, noncritical surfaces now play a larger part in transmission. Efforts to prevent HAIs must address optimizing cleaning in patient rooms, understanding environmental surfaces as a source of pathogens, and facility design changes that can help.

CDC is supporting research that uses modeling to better understand the role of noncritical surfaces in spreading pathogens. Because not all surfaces can be sterile, other research is evaluating methods for measuring the contamination of noncritical surfaces and determining cleanliness thresholds associated with improved patient outcomes (which are the endpoint). CDC is updating its guidelines for disinfection and sterilization in health care facilities. It is also reviewing emerging technology, such as ultraviolet surface treatments, no-touch cleaning technologies, and surfaces that are not friendly to bacteria.

Dr. Bell said several outbreak investigations identified organisms or plasmids of interest from sink drains. The biofilm in plumbing systems can be a reservoir for CRE, but transmission through such systems has not yet been proven. Dr. Bell said researchers are looking at how organisms persist in biofilm, the potential for genetic exchange, and the role they may play in transmitting pathogens to patients. Dr. Bell concluded that CDC is considering various potential mechanisms and options to minimize the risk of pathogen transmission.

Council Q&A

Regarding potential new findings (e.g., sharkskin's ability to repel bacteria), Ms. Cardo stressed the need for evidence to support recommendations. CDC is funding studies to assess the impact of new products. Studies are also looking at things like facility design and layout. Dr. Bell added that there are a lot of vendors making a lot of claims, but all new products need rigorous evaluation. Products proven to be effective will be discussed in updated guidelines.

Dr. Cosgrove called for further focus on basic infection control practices, such as hand hygiene. New technology will never be a substitute for such practices. Dr. Bell agreed, saying she is concerned that health care workers could fail to wash their hands because they are relying on new technology to prevent the spread of infection.

Public Comment

Dr. Gellin said some comments for the PACCARB were submitted in writing. He noted that the public comments period is an opportunity for the public to express views, but it is not a question-and-answer period.

Sherrie Smart of Thermo Fisher Scientific spoke about the challenges in the diagnostics industry and the underutilization of currently available tests. She sought to raise public awareness about the influence of core measures on clinical adoption of current tests. For example, the core measures for sepsis have a very strong focus on identifying sepsis, identifying microorganisms, and managing resuscitation but do not look at the potential of the host response biomarker for determining the use and duration of antibiotics. It would be useful to assess a biomarker such as procalcitonin for achieving de-escalation safely and economically. Ms. Smart said recent looked showed that procalcitonin guidance for duration of treatment and daily defined doses was associated with decreased mortality, decreased hospitalization, and less exposure to antibiotics. Ms. Smart suggested PACCARB evaluate antibiotic duration and host response of biomarkers.

Laura Gottschalk of the National Center for Health Research (NCHR) said the need for new antibiotics has become increasingly dire and new incentives are needed to encourage the development of new drugs and screening tools to quickly diagnose and treat drug-resistant infections. The key goal is not to develop new drugs but rather to ensure improved health outcomes and safety of patients facing multidrug-resistant infections. It is difficult to improve patient outcomes if new antibiotics are improved based on in vitro results and surrogate endpoints instead of studies of patients with resistant bacteria. Also, under current law antibiotics are approved for a small target group but can be promoted for use by large populations. Of 61 new antibiotics approved between 1980 and 2009, 43 percent were later withdrawn in part due to efficacy and safety issues—about three times as often as other drugs.

Ms. Gottschalk said these data demonstrate the widespread use of new antibiotics that pose risk to patients receiving them while also increasing the risk of developing resistant pathogens. NCHR is not convinced that incentives for the private sector make sense, because there is an inherent conflict between the company's investment to develop new antibiotics for targeted populations and the public health need to prevent widespread use of those drugs. Patent extensions and other financial incentives will always mean the American taxpayer will be footing the bill. NCHR believes the NIH should conduct this work instead and that there should limits on off-label promotion that leads to overuse.

Lucia Mokres of EpiBiome, Inc., said early-stage companies are uniquely positioned to accept the risk inherent in conducting early research. Although biotech venture capital investment has been vigorous in recent years, the pace is slowing. Furthermore, funding for development of antibiotic alternatives, in particular those for agriculture, is not as attractive to investors as a potential blockbuster therapy. To attract private investors, companies need shorter regulatory and submission review timelines and a streamlined clinical trial process. Order contracts that can supplement private funding, such as those from the DoD, are also crucial. Next, biotech startups need access to resources to conduct basic scientific research, preclinical trials, and clinical trials. Private contract research organizations can be cost-prohibitive for an early-stage company, and

technology transfer policies at most universities can stifle academic collaborations. Thus, providing early-stage companies with access to well-equipped research facilities and drug development experts for conducting bench, preclinical, and field clinical trials is essential.

Finally, EpiBiome has benefited greatly from participation in an accelerator and incubator program. The BARDA incubator is an excellent step in the right direction. It should foster companies that are developing antibiotic alternatives for agriculture as well as for human use. The ROI for this program will be enormous. Thus, the incubator should be expedited.

Kevin Kavanaugh of Health Watch USA said controlling the epidemic of resistant bacteria will take a substantial investment by facilities in the prevention of person-to-person transmission, both in the augmentation of nursing staff and patient testing resources—an investment that too many facilities are reluctant to make. This means more nurses, better cleaning of rooms, and surveillance of carriers.

As researchers strive to know the characteristics of a patient's microbiome, there should also be efforts to know who is carrying the major pathogens. The United Kingdom's national health care system demonstrated a more than 50 percent reduction in MRSA with implementation of a well-defined standardized protocol. The United States, with its fragmented health care system, is no longer a leader in control of this dangerous infection, which represents a patient safety and occupational safety issue. Recently, facilities in the Washington, DC, area reported a 5 percent carrier rate of CRE in hospitalized patients. Health care workers should be screened for common pathogens, similar to the screening for tuberculosis.

Animal health is an important component, Mr. Kavanagh continued, but it will not solve the problem. Following a report of polymyxin-resistant bacteria found in a Pennsylvania woman, the initial response came from USDA. They looked at animal production in China, rather than looking in U.S. medicine cabinets for polymyxin-B-containing antibiotics, commonly used in topical antibiotic ointments.

Finally, asking the pharmaceutical industry to invest one-half to 1 percent of capital in antibiotic development is not unreasonable. These are extremely large companies, and such an investment could protect against a future financial loss in cancer therapeutics and immune suppressant drugs, from the emergence of antibiotic resistance. At the same time, it will save many lives.

Richard Wood of Keep Antibiotics Working (KAW) said his organization agrees that incentives for the development of vaccines, diagnostics, and nonantibiotic therapeutics are important for animal health and for addressing antibiotic resistance. KAW has long been concerned about the routine use of antibiotics for disease prevention and sees vaccines as an alternative. Better diagnostics can help identify animals that need treatment or which antibiotic is appropriate, thus reducing overuse. While KAW recognizes the importance of this kind of research, it feels that alternatives should focus more on identifying on-farm practices that reduce the need for antimicrobials in the first place. Such an approach does not require a 30-year approval time, like approving a new drug. For example, much antibiotic use in feedlot cattle is linked to high-energy diets that cause abscesses, which are managed by the continuous use of

antibiotics. Poultry diets are also an important factor in the development of the necrotic enteritis, which is then managed by the routine use of antibiotics.

Regarding priorities on the animal side, KAW calls for a better balance between how animals are raised on the one hand and the development of new products to manage disease on the other. In addition, new policies need to be identified and adopted to encourage the use of new technologies and new management systems that will reduce the need for antimicrobials. Market pressure can help guide this change, but government has an important role to play as well.

Amana Jezek of the IDSA said that to optimize prevention efforts and the use of antibiotics and diagnostics, robust stewardship programs and infection prevention programs are needed, led by ID physicians, who are best positioned to drive medical culture change and impact the prescribing practices of other providers. IDSA's written comments to PACCARB cite examples of stewardship programs that have successfully reduced inappropriate antibiotic use, infections, and health care costs. Ms. Jezek also called for incentivizing R&D of rapid diagnostics to give providers the tools to guide appropriate antibiotic use. Unfortunately, R&D costs are high, and reimbursement for tests often fails to reflect the tests' true value to patients—sometimes not even covering the cost of running the test. New antibiotics are also needed.

The best efforts can slow the development of resistance but cannot stop it. The antibiotic pipeline remains fragile and in need of the types of incentives that the PACCARB has called for—economic incentives, such as tax credits, and regulatory incentives, such as the limited population antibacterial drug approval pathway, which is awaiting a vote in the full Senate. Lastly, a strong pipeline of ID physicians is needed. Fewer and fewer young physicians are pursuing ID specialization, in large part because outdated reimbursement models provide far greater compensation for procedures than for the more cognitive work typically done by ID physicians. Ms. Jezek hoped PACCARB would remember the important role of ID physicians in the broader efforts to combat resistance.

David Wallinga of the Natural Resources Defense Council (NRDC) said he was speaking on behalf of 20 groups who submitted comments jointly. He focused on the need to reduce use and overuse of antibiotics. The 20 groups believe that collecting data on antibiotic use at the farm level should be a higher priority. Current programs like NARMS collect snapshots, which are often spotty. The country is underinvesting in this area.

For example, there are no data on antibiotic use in chicken or turkey production, which represent nine billion animals a year. While the administration asked for $10 million for this kind of data collection in for fiscal year 2017, only $5 million was authorized. Mr. Wallinga asked that the PACCARB address whether $5 million is commensurate with the problem, and, if not, what is appropriate. Mr. Wallinga added that FDA's budget request did not ask for any additional money for data collection.

Finally, the National Action Plan set goals for reducing human use of antibiotics but did not set targets for reducing use or overuse of antibiotics in livestock. The Netherlands set clear targets and exceeded them, achieving a 50 percent reduction in animal use by 2013.

Barrett Thornhill of the Antimicrobial Innovation Alliance said the current antibiotic problem is an economic crisis. PCAST determined that there is no way to sustain a robust pipeline of antibiotic development without a major influx of private investment. The ongoing activities of the USG are highly helpful and very beneficial. However, to significantly counter drug-resistant infections and to redirect commercial activities to address the highest threats, companies need PACCARB's support to incentivize a new system and a new stream of products. This is the critical factor that will determine the ability to stem the tide of resistance and prevent a catastrophic impact on the U.S. health care system.

The Antimicrobial Innovation Alliance recommended six different types of incentives on its website. It urges PACCARB to consider the most significant pull incentives that meet the financial requirements that PCAST, the AMR, and the Eastern Research Group (for the HHS Assistant Secretary for Planning and Evaluation) laid out in their reports. Policymakers have acute trouble with proactivity, so it is important to make very targeted requests. Mr. Thornhill noted that Congressional staff frequently insist that the GAIN Act will work if given more time, but it has not moved the needle one iota to stall the pipeline crisis. This is unacceptable, said Mr. Thornhill, insisting that significant pull incentives must be implemented quickly.

Closing Remarks

Martin Blaser, M.D., Chair

Dr. Blaser commented on the wealth of information presented and looked forward to continued presentations on day 2 of the meeting. He adjourned the meeting for the day at 5:16 p.m.

Meeting Summary—Day 2

Welcome, Roll Call, and Overview of Agenda

Martin Blaser, M.D., Chair; Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair; and Bruce G. Gellin, M.D., M.P.H., Designated Federal Official

Dr. Blaser welcomed the PACCARB members and other participants. He called the meeting to order at 9:02 a.m. Dr. Gellin called the roll. Dr. King provided a brief overview of the agenda.

FDA's Guidance for Industry Number 213

William Flynn, D.V.M., FDA Center for Veterinary Medicine

Dr. Flynn summarized the three key documents that underpin FDA's judicious use strategy for antibiotics in food production. Guidance for Industry (GFI) Number 209 indicated that use of medically important drugs should be limited to animal health (i.e., not for growth) and must take place under veterinary oversight. Next, GFI Number 213 offered an implementation plan and timeline for making those changes, with a target completion date of December 2016. The Veterinary Feed Directive (VFD) aimed to facilitate the transition of over-the-counter drugs used in feed to prescription products under veterinary oversight. The 3-year timeline allows time for outreach so that producers, veterinarians, animal health companies, and the feed industry have time to adjust their practices.

About 300 drugs are affected by the judicious use strategy. All the pharmaceutical companies affected gave written commitments upfront to make the suggested changes voluntarily, and FDA has been working closely with them on the transition. In addition to the changes that have already been made, approximately 40 applications have been withdrawn. By design, most of the changes are expected to occur by the end of this year, so that the switch is coordinated and consistent across the market. Dr. Flynn said communication and outreach are key, and FDA is doing all it can to reach all the industry segments. For example, FDA and USDA are developing an education module on the VFD that will be included in the Animal and Plant Health Inspection Service's (APHIS) veterinary accreditation module.

The changes in use of antibiotics are a big step forward but do not resolve everything. By the end of the year, FDA hopes to outline a plan looking forward 3–5 years to address potential concerns on the horizon.

Council Q&A
In response to Dr. Rex, Dr. Flynn agreed that the list of medically important antibiotics needs to be updated. The importance of an antimicrobial to human medicine is part of the risk assessment. Dr. Flynn noted that access to veterinary services is limited in some areas. Reaching producers is also challenging, so FDA is working with producer organizations and others on education efforts. FDA is also convening public listening sessions.

Brian McCluskey, D.V.M., Ph.D., said that educating veterinarians first is a good idea. He noted that APHIS has an extended field force on farms every day, which is helping to reach individual farmers. Dr. Wagstrom, Dr. Apley, and Dr. Singer all described extensive communication efforts throughout the industry.

Ms. Jungman asked how FDA will assess the results of its strategy. Dr. Flynn said FDA and USDA are working closely together to understand the impacts of the changes. A public meeting hosted by FDA, USDA, and CDC outlined a broad vision that involves various data, some from existing sources, to assess whether the use of antibiotics aligns with good stewardship principles. Additional detail is needed on antibiotic use at the farm level, but the lack of funding for 2016 has been a barrier to collecting data. The first goal is to assess that use is in full compliance with the guidance. Next, the impact on farm practices and on resistance patterns will be evaluated. In the future, it is important that a system be in place to assess use to ensure the industry is moving toward good stewardship on farms.

Dr. Shryock suggested FDA and USDA consider very small operations, such as backyard farms, that might have limited access to veterinary services and the VFD and where costs overshadow access to products. He noted that when Europe withdrew antibiotic use on the farm, a surge of disease in swine resulted in increased antibiotic use. He asked what contingency plans are in place to identify and address potential spikes in animal disease. Dr. Flynn responded that FDA is aware of this potential consequence. In its judicious use strategy, FDA encouraged industry to identify gaps that may arise once product uses are removed and consider whether more targeted therapeutic approaches can fill the gap. Dr. Flynn said the issue increases the importance of having sustainable, long-term data collection that demonstrates changes over time.

Ms. Cole asked if there are enough veterinarians to implement the strategy, and, if not, are there plans to train more. Dr. Flynn said the issue has been a big challenge and a focus from the beginning. Dr. McCluskey added that USDA has programs incentivizing veterinarians to work in more rural areas. Dr. King pointed out that the U.S. graduates 3,500 new veterinarians every year, yet veterinary schools lack a standardized accreditation process. He said USDA must work on helping new professionals understand antibiotic resistance.

In response to Dr. Laxminarayan, Dr. Flynn clarified that the VFD is unique to the United States. In some parts of the world, there is a different framework but a similar underlying concept (of veterinary oversight). Dr. Carnevale said that most products in developed countries are available by prescription only, so controls are already in place. Canada is in the middle of a process similar to that described in GFI 213 with a similar timeline, he added.

Dr. Cosgrove asked whether farmers or producer groups have proprietary data that can be used to understand the baseline or track changes. She also asked whether those entities need incentives to provide access to their data. Dr. Flynn acknowledged that getting baseline data before January of 2017 is important, and FDA and USDA are working together to find data. To gather proprietary data, new privacy and confidentiality mechanisms are needed. In March, FDA announced it was seeking proposals for how to collect baseline and ongoing data, including proprietary data; those proposals are being reviewed.

Drivers of Antimicrobial Resistance and Antibiotic Metabolites in the Environment

Introduction

Randall Singer, D.V.M., M.P.V.M., Ph.D., PACCARB Voting Member

Dr. Singer outlined the sessions and said the presenters were asked to address three questions:

1. How should the natural environment be addressed in efforts to combat antibiotic-resistance bacteria or through the National Action Plan?
2. What is the connection between the natural environment and human and animal health?
3. How should data gaps be prioritized?

Human Use and Discharge

Professor David Graham, Newcastle University

Mr. Graham explained that the relationship between antibiotic use and exposure depends on geography. In developed countries, human waste is treated before it makes its way back into the water supply. Developing countries have less waste and water treatment. Humans exposed to resistant genes through water acquire resistance in the gut. International travel contributes to the spread of resistant genes.

Mr. Graham and colleagues have focused their research on identifying antibiotic-resistant genes in wastewater. In animal feedlot lagoons, waste drives the spread of resistance through animal herds. In Cuba, where antibiotics are not used in agriculture, industrial and human waste are contributing to resistance in the environment. In one study, researchers analyzed the effects of annual pilgrimages that bring millions of people to a small, pristine area in India. The pilgrims

overwhelm the waste treatment capacity of the site, bringing resistant genes into the water supply and facilitating the transfer of resistant genes around the world as they travel home.

Antibiotic use is central to resistance, but water quality and inadequate water management is probably the main driver of the spread of resistance, said Mr. Graham. The United States, the United Kingdom, and Europe take clean water for granted. Antibiotic resistance spreads where management is limited, and international travel likely speeds up the spread. The current goals for combating antibiotic-resistant bacteria in the National Action Plan do not mention the role of waste, which represents a significant gap. Surveillance should include international sources, not just domestic ones, Mr. Graham concluded.

Animal Use and Discharge

Randall Singer, D.V.M., M.P.V.M., Ph.D., on behalf of Doug Call, Ph.D., Washington State University

Dr. Singer emphasized that the presentation represents Dr. Call's data and interpretations, not his own. Dr. Call observed that at low concentrations of antibiotics, bacteria can grow. At higher concentrations, selective pressure increases, and resistance develops. At the highest concentrations, growth of all susceptible bacteria stops. In a typical spatial model, antibiotics excreted by animals are at highest concentrations in the area of excretion, then diffuse outward, resulting in variations in selection pressure. Combining this information allows for an estimation of the risk of acquiring and spreading antibiotic resistance. To prevent transmission, efforts should focus on practices that result in the highest concentrations of antibiotics.

Studies of antibiotic-resistant *E. coli* in calves led Dr. Call to conclude that dose has a dramatic impact on the amount of resistant bacteria shed by an animal, which raised questions about its subsequent effect on the environment. These studies prompted researchers to ask whether the increase of such resistant bacteria in soil resulted from more fecal shedding or from residues (primarily in urine) selecting for resistant bacteria already in soil. They questioned whether the residue concentrations were high enough to colonize other animals. Another study sought to determine where resistant *E. coli* bacteria are located on dairy farms. It found high levels of antibiotic-resistant *E. coli* among the heifers, even though they were not receiving antibiotics. Therefore, there appears to be a disconnect between the points in the process where antibiotics are used and where the highest risk of antibiotic resistance lies.

Dr. Singer concluded that not all antibiotics or administration practices confer the same risk of selecting for antibiotic resistance, so there is an opportunity to be "smarter" in the use of antibiotics. Robust soil-borne reservoirs of antibiotic-resistant *E. coli* arise after exposure to excreted antibiotics from therapeutic applications. The density of resistant bacteria often exceeds the estimated infectious dose, indicating that they could play an important role in persistence of resistant bacteria on farms. Reservoirs of resistant bacteria can be found in predictable locations and, therefore, can be targeted for mitigation.

Crop Use of Antibiotics

Virginia Stockwell, Ph.D., USDA ARS (by phone)

Dr. Stockwell explained that the U.S. Environmental Protection Agency (EPA) regulates the use of antibiotics in crops. She described the three antibiotics permitted and the diseases for which

they are used. Antibiotics are primarily used in tree fruits. Through regulations, EPA also limits direct exposure of workers to antibiotics during and after spraying.

When antibiotics are used in orchards, repeated spraying is necessary to counter the short period of suppression as well as the possibility of dilution from rain or degradation from sun exposure. Several studies of streptomycin use concluded that the antibiotic does not result in long-term changes to bacterial communities in soil, leaves, flower, or fruit, nor does it generate resistance. EPA limits consumer exposure through regulations on the use of antibiotics immediately before harvesting and the amount of residue allowed on the fruit. One study of apple trees found that even the highest concentrations of antibiotics used were 10 times less than permitted by EPA, and there was no detectable residue. Dr. Stockwell stated that consumer exposure to antibiotics from fruit is limited.

In summary, Dr. Stockwell said antibiotics have been used in some crops for more than 50 years with no detected negative impact on animal or human health. Antibiotics are important for crop management. Alternatives are available, but their effectiveness is limited and they can mar the fruit finish, so conventional growers are reluctant to use them. The increasing number of organic tree fruit orchards will serve as a proving ground for alternatives. Additional research is needed on some antibiotics and on combination therapies to assess their impact on antimicrobial resistance and resistance genes.

Council Q&A

When asked by Dr. Blaser about surveillance of fruit in supermarkets for antibiotic resistance, Dr. Stockwell said microbes usually do not survive on the wax applied to the surface of tree fruits found in supermarkets, but bacteria could be present in damaged fruit. Orchards generally do not harbor human pathogens. The major threats to food safety come from farm use of manure or fecal matter from wild animals. Regarding importation, Dr. Stockwell said antibiotics are generally not used in fruit production in Europe, but information about antibiotic use in China is difficult to gather. Mexico permits some antibiotics. Dr. Stockwell acknowledged that there is a data gap. She added that the U.S. is less likely to import fruit than it is to import processed materials, and there are limits on the amount of residue allowed on imported items.

It was observed that the doses of ceftiofur cited by Dr. Call's research seem very low, and higher doses might be more effective. Dr. Apley pointed out that ceftiofur is not indicated for *E. coli*. A PACCARB member asked whether new technology or low-tech efforts could help solve the problem of waste treatment in remote areas (e.g., use of portable toilets). Mr. Graham said several efforts are underway, such as the use of worms that eat fecal matter and the development of solar-powered technology. New infrastructure is too expensive, so social and technical solutions are needed to delay transmission of resistance in fecal matter to the river or other people in close proximity.

Ms. Cole appreciated the attention given to wastewater, pointing out that Southern California has a very real problem with antibiotic-resistant pathogens migrating to beaches. EPA said that other states are facing the same problem as a result of hospital sewage in wastewater. Ms. Cole asked what steps can be taken to address the issue. Mr. Graham said he was not sure how large hospitals are contributing to antibiotic resistance in the environment, but the most economical

and practical approach is to treat waste as close as possible to the sources of generation with current technology, which is fairly effective.

Jay C. Butler, M.D., asked if there is evidence of transmission of resistant bacteria through migratory waterfowl. Mr. Graham said there is some evidence of such transmission, but it is not clear how big a role that route of transmission plays. Dr. Singer pointed out that an antibiotic-resistant strain of *E. coli* is spreading globally, so attention should be paid to migratory fowl. Dr. Weinstein asked whether antibiotic residue could persist in fruit flesh. Dr. Stockwell said some antibiotic may persist in the area where the flower was, but it is not expected to show up in the fruit flesh. Dr. Singer asked whether antibiotics are being used for citrus greening in Florida. Dr. Stockwell responded that Florida has requested that the EPA allow use of antibiotics for citrus greening, given that the state has declared the disease an emergency. She did not feel that antibiotics are a good long-term solution for citrus greening, however; breeding for resistance would be a better approach to control that disease.

Environmental Compartments of Antimicrobial Resistance and Antibiotic Metabolites

Wastewater

Timothy LaPara, Ph.D., University of Minnesota

Dr. LaPara pointed out that current wastewater treatment approaches in the United States result in very clean water. Hundreds of clinically relevant genes that encode for antimicrobial resistance can be tracked, which allows investigators to see how genes are shared among pathogens or in other bacteria. However, current tracking does not reveal the host, the functionality of the gene in the host, whether the host is viable, or whether the gene is fully intact.

Dr. LaPara described the steps in wastewater treatment, which aims to bring wastewater up to the quality of surface water before it is pumped out into waterways. Fecal and other matter are collected and sent either to farms for use as fertilizer or to landfills. Wastewater effluents have high levels of antibiotic-resistant genes, even after going through the best wastewater treatment plants.

For sewage sludge, better treatment technology cuts down the half-life of antibiotic-resistant genes from weeks to hours. Half-lives are longer (e.g., 1–2 months) when wastewater is applied to soil. Dr. LaPara noted that if wastewater plants were redesigned to mitigate antibiotic resistance, better approaches are available than the current techniques.

Dr. LaPara concluded that municipal wastewater systems are a large reservoir for antibiotic-resistant genes. Unintentionally, they have been designed to allow dense suspension of cultures that are ideal for horizontal transmission of resistance. Better design could address the problem. However, Dr. LaPara cautioned, antimicrobial resistance is a complex problem that will not be resolved by one intervention.

Manure

James Tiedje, Ph.D., Michigan State University

Dr. Tiedje pointed to the many conditions that contribute to the development of drug resistance and the various environments that foster antibiotic-resistant genes to underscore the need for a comprehensive solution. Manure is the largest source of antibiotic-resistant genes. Studies in China, where antibiotic use is extremely high, found genes resistant to all major classes of antibiotics, which did not necessarily correlate with antibiotics used on farms from which they came. More recent research found gene clusters with mobile genetic elements can travel together.

As manure moves to different environments (i.e., applied directly to soil or mixed with compost), the genes are diluted. Dr. Tiedje said manure is a favorable environment for selection. He also pointed out that different antibiotics react differently in manure.

Dr. Tiedje called for data integration so that researchers can compare findings about antibiotic-resistant genes across different environmental settings. Other gaps related to manure are as follows:

- Understanding the fate and transport of manure, especially which conditions contribute to bacteria growth
- Better understanding horizontal gene transport, which may be facilitated by heat (as in composting)
- Improving databases and nomenclature to allow for discussion about findings on resistant genes
- Enhancing data integration, data mining, and epidemiology
- Developing quantitative risk assessment models

Soil

Ed Topp, Ph.D., University of Western Ontario

Antibiotic-resistant bacteria are common in nature and can be isolated in places that have never been exposed to antibiotics. In fact, resistance can be traced back before the development of antibiotics, and even to genetic samples that are tens of thousands of years old. When fecal material enriched with antibiotic-resistant genes gets in soil, the soil becomes enriched with antibiotic-resistant genes. The questions to consider are i) whether those antibiotic-resistant genes are present in pathogens and represent a higher risk, and ii) whether agriculture techniques are increasing the likelihood of those genes moving into a pathogen of human concern.

Problems that result from the mismanagement of drugs can be addressed through regulations restricting drug use. Animal waste products can be treated just as human waste products are. When waste products are applied to soil, the process can be managed—for example, the timing of application or the type of crops that are fertilized can be restricted to minimize the likelihood of human exposure (e.g., though consumption of uncooked vegetables). On the human side, waste treatment can also be improved, as Dr. LaPara noted, to reduce the spread of contaminants into water, improve the quality of water used for irrigation, and manage biosolids before they are applied to soil. Dr. Topp said the whole chain of production must be addressed.

Once materials are applied to soil, four concerns arise. First, do the biological and chemical contaminants persist in soil, and, if so, are they problematic? Some drugs degrade rapidly, while others persist, and understanding these characteristics will help in prioritizing drug use with respect to the potential environmental impact. Second, will the antibiotic-resistant genes move into water? The key transport pathways to water should be acknowledged and managed. Third, do current approaches compromise the soil by introducing genes into the environmental flora? There are few quantitative data to elucidate this question. Fourth, are chemical or biological residues moving into crops consumed directly by humans without cooking or into crops consumed by animals that are then consumed by humans? In some cases, there is evidence that harvesting a crop in the same season in which it was fertilized with raw manure can transport the residue into humans.

Dr. Topp said the National Action Plan makes a broad call for research in these areas. He suggested addressing the following key knowledge gaps:

- Impact of "fecal fertilizers" and irrigation with reclaimed water on potentiation of antimicrobial resistance in soil
- Transmission of antimicrobial resistance from amended soil to crops and to humans or animals
- Consequences of exposure to soil and manure/biosolids/wastewater-borne antimicrobial resistance for human health (and relative to other sources of exposure)
- Interpretation of the significance of these phenomena within a policy-relevant risk assessment framework

Water

Jean McLain, Ph.D., University of Arizona

Dr. McLain pointed out that antibiotic-resistant bacteria and genes are ubiquitous in aquatic environments, and since 2010, there have been nearly 800 publications in the peer-reviewed literature on resistance in response to real or perceived contamination, with samples from around the world. The five most frequently cited publications identified 32 antibiotic-resistant genes in surface and ground water. However, scientists still do not understand the movement of resistance in water between bacteria and between different sectors of the environment.

As Dr. Topp mentioned, antibiotic-resistant genes predate the development of antibiotics. Dr. McLain emphasized that to understand antibiotic resistance in the environment, studies must consider baseline resistance. She presented data from her study of a site recharged with recycled wastewater for 30 years. The amount of antibiotic-resistant genes appeared to be high at first glance, but were lower than in the control—a groundwater site that was never exposed to recycled water.

A 2014 meeting funded by USDA brought together international stakeholders to reach consensus on methods to assess resistance in the environment. Several papers were published as a result, including one on how to deal with background resistance in research studies. The big knowledge gap that remains is whether the antibiotic-resistant genes in water correlate with human health risk. The question is complex and should be addressed from a One Health perspective. The unprecedented cooperation exemplified by the PACCARB will help. Other gaps are in

understanding the dose-response and risks presented by antibiotic-resistant genes in water. Dr. McLain said more funding will help researchers address these questions.

Council Q&A

Dr. Marty asked whether quarantines are sufficient to protect against antibiotic-resistant genes in animals imported from areas with high antibiotic use. Dr. McCluskey said the United States does not import many animals from countries other than Mexico and Canada, and there are importation regulations for diseases of concern. The U.S. does not quarantine animals from either Mexico or Canada. At this point, there are no requirements for antibiotic resistance testing. Dr. Marty felt that represented a gap.

In response to Dr. Laxminarayan, Dr. McLain said one very good review identifies the gaps in knowledge around antibiotic-resistant genes in aquatic compartments. There are papers showing increases and decreases, but the drivers are not known and merit further research. Dr. LaPara said some research shows that the concentrations of antibiotic-resistant genes in the environment have been increasing since World War II. Other work suggests that the human impact on water and the environment is affecting how rapidly bacteria develop antibiotic resistance.

Dr. Weinstein asked whether any soil or water samples have unexpectedly low concentrations of antibiotic-resistant genes that could provide some insight into treatment. Dr. Tiedje said that as the density of microbes goes down, the amount of resistance is low, but that is not a route to treatment.

Dr. Blaser asked whether antibiotic residue has been found in drinking water in China or the United States. Dr. LaPara said there are very low levels of antibiotics in U.S. drinking water, and he suspected that China might have higher levels. However, residue data is lacking, which is a big knowledge gap. Dr. Tiedje said there is a lot of interest in China in measuring antibiotics and toxins in the environment. Some of his research in China was prompted by farmers raising concerns about upstream sources of pollution from big cities.

Dr. Blaser pointed out that a recent paper described levels of antibiotics in drinking water in the very large city of Shanghai. He asked whether any U.S. cities located downstream of effluents have comparable levels. Dr. Topp said Canadian data indicate that antibiotics in drinking water are very low, and he expected that the U.S. and Europe would have similar findings. He emphasized the need for a global perspective to better distinguish AMR challenges in low-income compared with high-income countries. Dr. Topp added that, currently, investigators cannot make the direct link between exposure and hazard or risk assessment.

Dr. Apley asked whether PCR-quantified genes in dead organisms were transferable. Dr. Topp said it is not clear what these PCR products mean or what they cover. Another approach is the metagenomics approach being used in China, which uses shotgun sequencing and does not have some of the bias that the PCR product does. This issue points to the need for a whole genome context to better understand the potential risks.

Dr. Shryock highlighted the consistent theme of using risk assessments to approach these issues, which is complicated and takes time. He asked the panelists for suggestions on quick, affordable

incentives from the USG or others that could lead to interventions, despite the lack of complete data. Dr. LaPara suggested investing in high-temperature technology for treating raw sewage, which is very effective and similar in cost to competing technologies (although the effectiveness differs among laboratories). Dr. Topp suggested investing in economically feasible mechanisms for making fecal fertilizer more benign before it is applied to crops. Dr. LaPara said the mechanisms that work for human waste treatment are also effective for manure.

Environmental Antimicrobial Resistance Surveillance and USG Activities

Chemistry: Challenges in Antibiotic Analysis in Environmental Samples

Diana Aga, Ph.D., University at Buffalo, State University of New York

Dr. Aga explained how antibiotics used in animals and humans migrate into the environment and develop resistance. For chemical surveillance, investigators must select a subset of antibiotics to analyze. On the animal side, one approach is to look at sales data to identify the most common antibiotics used in food production. Within each class of antibiotics, however, are multiple types. For example, three types of tetracycline are used in animals. When excreted, the molecules transform in subtle ways that can make the product more or less biologically active. If surveillance only monitors the active ingredients, it misses other important components.

Similarly, when animals excrete sulfonamides, the active ingredient in the metabolite is not biologically active. However, when in the environment, including wastewater treatment plants, it can transform back into a biologically active compound. Other antibiotics can also become more concentrated after they are treated. These "emerging contaminants" have only been seen in the past 15 years thanks to new technology such as liquid chromatography and mass spectrometry (LC-MS). Farms use broad biological assays that measure total concentrations of antibiotics, while LC-MS can look at individual compounds and detect them at lower concentrations.

Biological assay results do not always coincide with the results of instrumental analysis, often because the biological assay looks for the parent compound, not the transformed product. Instrumental analysis is tedious and complex, and investigators must have a clear strategy for sample collection and the size of a sample or risk generating false-positive results. Different farms use various treatment mechanisms, such as lagoons or anaerobic digestion, solid separation, and soil fertilization, all of which can distribute antibiotics into the environment, but it is cost-prohibitive to collect samples from all the sources, Dr. Aga observed.

U.S. EPA: Surveillance of Antibiotic-Resistant Bacteria from Wastewater Effluents

Laura Boczek, EPA

Ms. Boczek said EPA regulates the treatment of waste and residues and how they come in contact with the environment. However, EPA does not regulate land application of manure, which is very different from land application of human solids. Regulation is governed by the Clean Water Act. Ms. Boczek pointed out that current regulations are not designed to mitigate risks from antibiotics, and antibiotics rarely come up in discussion about the regulations.

Regulations for drinking water differ from those for wastewater; some bacteria can persist in wastewater. The EPA seeks to mitigate the risk of exposure based on how the residuals could come in contact with humans.

Ms. Boczek described results of a series of EPA surveillance studies of antibiotic-resistant *E. coli* found in treated wastewater across seven geographically diverse parts of the United States. She noted that only 5 percent of the *E. coli* detected in the study was resistant to antibiotics, but resistant samples were found in every region. Furthermore, the samples were collected before final treatment and before release from the plant, so Ms. Boczek thought it was unlikely that these compounds would make their way back into the environment. Key findings of these studies were as follows:

- *E. coli* resistant to common antibiotics used for treating urinary tract infections (UTIs) were found in wastewater treatment plants across the U.S., and 92 percent of the isolates were resistant to at least one other antibiotic.
- Nearly half of the resistant bacteria demonstrated extended-spectrum beta-lactamase (ESBL) production.
- Carbapenem-resistant *E. coli* is widespread in U.S. wastewater.
- Of the antibiotic-resistant *E. coli*, 25 percent were CRE.

Future research will evaluate archived samples for resistance to carbapenem antibiotics, examine biosolid residuals for antibiotic resistance of concern, and determine the effectiveness of disinfection techniques to see whether some approaches make organisms more or less resistant to treatment.

USGS: Antimicrobial Resistance in the Environment

Carrie Givens, Ph.D., USGS (by phone)

Dr. Givens said research going back to the early 2000s demonstrates that antibiotics have been entering the environment. Current USGS studies are looking at the sources, what happens to antibiotics in the environment, and whether unintended exposure to antibiotics has adverse effects on the ecosystem or human health. Specifically, USGS is evaluating the distribution of antibiotic-resistant bacteria or genes in the environment, whether resistance reflects known antibiotic usage, and how antibiotics affect the natural microbial community.

Recent studies of distribution found the number of MRSA genes identified in Great Lakes beaches increased with the number of bathers. Therefore, MRSA appeared to be community-acquired strains. A study of animal feed operations revealed antibiotics and antibiotic-resistant genes frequently in manure, surface water, and streambed sediment. Livestock operations contribute more resistance genes to stream waters than rural background sites.

Another study found little relation between antibiotic concentrations and antibiotic resistance detection in wastewater, suggesting that resistance could arise from a number of chemicals detected. Bacteria in the waste were subjected to an array of antibiotics and potentially biocidal compounds, which uncoupled the direct relationship between resistance genes and specific antibiotics. Another study found that long-term exposure to low sulfamethoxazole concentrations

did not result in increased bacterial resistance but did cause other changes. This suggested that the antibiotic can affect microbial-mediated processes and ecosystem functions.

Dr. Givens said USGS continues to assess antibiotic resistance using multiple methods of screening and assessment. It also seeks to define and better characterize urban and rural agriculture resistance patterns. A recently funded study will look at antibiotic resistance genes in soil and map potential exposure pathways. USGS seeks to understand the influence of antibiotic exposure on the native microbial community, factors that influence gene transfer and maintenance in the environment, and whether resistance translates into environmental or human health impacts. Dr. Givens noted that USGS coordinates with public health agencies to focus on resistance to specific antibiotics of clinical importance.

USDA ARS: Environmental Antibiotic Resistance Research

Lisa Durso, Ph.D., ARS

Dr. Durso clarified that ARS performs research and has no regulatory role. ARS collects data at the local level and uses the information to evaluate the efficacy of agricultural management practices as they relate to drugs, bacteria, and genes in soil, water, and air. Manure is the primary vehicle by which bacterial resistance enters the environment, so it is a common target for monitoring and for control.

Among ARS surveillance activities is the Agriculture Antibiotic Resistance (AgAR) network, which began as a grassroots effort among scientists focusing on land applications of manure and biosolids and has expanded to include food safety and animal health experts. The network is working with ARS agronomists and soil scientists to coordinate storage of resistance gene data, building on soil data in the Greenhouse Gas Reduction through Agricultural Carbon Enhancement network (GRACEnet) and Renewable Energy Assessment Project (REAP) databases. Using these data, ARS will examine relationships between soil's physical and chemical parameters, agricultural management strategies, and antibiotic resistance genes.

A subset of AgAR will measure four gene targets in production systems and samples. It will strengthen local surveillance efforts by providing a platform where information from multiple locations can be shared. ARS is also promoting collaborations between its environmental scientists and those who focus on animal health and food safety through internal workshops. The ARS Bacterial Epidemiology and Antimicrobial Resistance unit is involved with a NARMS study looking at antibiotic resistance in food and animals. The study is set up to harness the potential of the One Health approach.

External activities include collaborations with the USDA's National Institute of Food and Agriculture, which provided $11 million for antibiotic resistance research and supports Small Business Innovation Research and capacity-building projects at universities. ARS organized a state-of-the-science workshop of experts focusing on detecting and measuring drugs, bacteria, and genes in soil, water, and air. The workshop included a strong mentoring component to encourage graduate students to develop professional networks and address antibiotic resistance from a One Health perspective. The proceedings were featured in a special issue of the *Journal of Environmental Quality*. Finally, ARS represents the United States in a bilateral working group with Canada on environmental antibiotic resistance.

Council Q&A

Dr. Laxminarayan asked whether USDA has soil samples from decades past, and, if so, if it is accessible to researchers. Dr. Durso said her office has soil samples (dried and stored) going back to the 1980s, and testing is underway to determine how storage conditions impact results. She added that other locations may have older samples.

Dr. Lurie noted that advancements will not be made until surveillance can demonstrate the impact of antibiotics found in the environment on human health. He said case-control studies and outbreak investigations are needed to make that connection. Once human cases are identified, efforts to address the issue will move forward more easily. Dr. Laxminarayan said that with toxic waste cleanup, there are threshold amounts of contamination in soil that should spur action.

Dr. Marty asked whether any studies address the use of probiotics after antibiotics in animals to reduce risk. Dr. Givens said some alternatives include probiotics, vaccines, and others approaches. A sector of the agricultural industry is focusing on feed additives to enhance health, but there are few data on the approach.

Dr. Blaser said that quantitative risk assessment is important, but the field will have to decide what markers or outcomes should be used. Dr. Durso agreed, noting that increasing connections across the field through the One Health approach will facilitate that conversation. Ms. Boczek agreed and added that so many components are involved in resistance; the field needs to get a better handle on how they work together. Shari Ling, M.D., observed that Asia allows a lot of unregulated antibiotic use and has a lot of antibiotics detected in wastewater.

Dr. Bell pointed out that epidemiology has a role to play in risk assessment. If the focus is on human outcomes, investigators must clearly define populations and determine how to measure exposures. Exposure is likely multifactorial and cumulative over years, so there are a lot of methodological questions to sort out. Some of the laboratory-based surveillance will, at the least, yield more sensitive detection mechanisms for human outcomes, said Dr. Bell.

Dr. Weinstein noted that studies have found people traveling to low-income countries and returning with high rates of ESBL carriage and ESBL UTIs. Dr. Lurie added that disease outbreaks (not related to antibiotics) have been investigated among surfers exposed to wastewater.

Summary: Environment and Antimicrobial Resistance

Randall Singer, D.V.M., M.P.V.M., Ph.D., and Aileen M. Marty, M.D., FACP, PACCARB Voting Members

Dr. Singer summarized the a key data gap identified by the panelists: Better data about how antibiotics are being used, how much of which kinds, and in what doses and durations could enable better estimation of the amount of metabolite that is being excreted from humans and animals, which in turn could allow for development of maps about excretion profiles. Without that data, investigators cannot identify where antibiotic resistance is accumulating. So, the challenge is to design a better system to enumerate pharmaceutical compounds in the environment.

Once antimicrobial resistant and antibiotic metabolites exist in the environment, Dr. Singer continued, the challenge is to identify sources and prioritize mitigation efforts around the highest contributors. Also, compounds may change once in the environment, so research is needed to understand the affect on the bacterial population and the possibility of horizontal gene transfer. Finally, all the research must come back to understanding the real or potential burden of disease among humans and animals.

Dr. Marty reiterated some of the key findings from the presentations about the compartments (wastewater, soil, manure, and water) and the data gaps those presenters identified. The panel emphasized that the environment is a complex system, and it is crucial to understand the system to properly address antibiotic resistance, she noted.

Council Q&A

Dr. Weinstein said one major intervention already underway is the VFD, so there must be efforts to measure its impact on antibiotic-resistant genes in the environment, even if that impact is not yet linked to clinical disease.

Dr. King wondered what an antibiotic stewardship program for the environment might entail. He said such a program should go beyond collecting data and yield opportunities for intervention.

Dr. Cosgrove asked if any technology could track resistance genes from early sources and distinguish them from baseline resistance. Along those lines, Dr. Blaser said, some genes have expanded in a clonal manner, and they could potentially serve as markers.

Public Comment

Sharon Morgan of the American Nurses Association (ANA) said ANA is at the forefront of improving the quality of health care for all. She called on PACCARB to remember that, of all health care professionals, nurses spend the most time providing direct care to patients. Nurses are in a unique position to act as an effective communication and education hub for the variety of health care specialists that interact with patients as well as advocates for the patients and their families. When the question arises of who should be at the table of antibiotic stewardship, the nurse needs to be there at all levels. Both the Centers for Medicare and Medicaid Services (CMS) and The Joint Commission (TJC) are setting standards requiring antibiotic stewardship programs across all health care settings.

Nurses, particularly advance practice registered nurses and nurse infection preventionists, have the holistic expertise and collaborative training to take on leadership roles within stewardship programs. The ANA stands ready to work with CMS and TJC as these entities develop antibiotic stewardship standards. As the stage is being set for the next critical phase in expanding and solidifying antibiotic stewardship capacity and capability in the United States, nursing is the vanguard.

Mr. Wood of KAW said the implementation of FDA's judicious use plan has had a relatively long history. However, the plan has some serious loopholes, which FDA acknowledges and plans to address. The KAW's biggest concern is that the plan continues to allow herd-wide or flock-wide preventive use of medically important antibiotics for an unlimited duration without

evidence of disease. FDA has stated that it will eventually address this gap but has not provided any further details. The KAW asks PACCARB to request that FDA provide these details.

The second greatest concern is the failure of the agency to set targets for success. The KAW asks that PACCARB request that FDA provide metrics to measure the plan's success. Finally, FDA has failed to put into place a system to monitor antibiotic use on farms, so that the impact of the plan can be understood. FDA should implement such a system.

Catherine Duff of the Fecal Transplant Foundation said she was a survivor of *C. difficile*, and fecal transplant saved her life. The science of microbiota transplantation has made great strides in recent years and is now thought by many to be one of the most promising areas of research in the world. Ms. Duff said she is a member of the NIH-funded microbiota transplantation working group tasked with developing a legal framework for regulatory use of microbiota transplantation of the oral, nasal, skin, vaginal, and fecal microbiomes.

While new antibiotics are needed, novel non-antibiotic therapies will become increasingly important in the antibiotic resistance movement. Ms. Duff said she is encouraged by the success of examples of fecal transplant, especially in treating antibiotic-resistant infectious diseases. Her organization supports microbiota transplantation therapies, researchers being considered for accelerator programs, and training grant programs, as well as other incentives for development.

As opposed to the current stewardship models, in which patient demand for antibiotics is typically blamed for antibiotic overuse in human health, within the fecal transplant arena, patients are forced to endure multiple rounds of failed antibiotic use before fecal transplant is offered. This approach is one factor driving the spread of antibiotic-resistant *C. difficile*. Fecal microbiota transplantation should be offered earlier in the treatment protocol, as stated by CDC. The Fecal Transplant Foundation urges PACCARB to act swiftly to ensure that microbiota transplantation (natural or synthetic) remains a viable and accessible alternative to antibiotics.

In response to the point made earlier that not enough people have died to make new product development attractive to investors, patient advocates maintain that too many people have died and too many have been told they are out of options. One person dying or one person being told there are no more options is too many.

Lisa McGiffert of Consumer Reports' Safe Patient Project said her organization does not agree that the federal government should hand over billions of dollars to large pharmaceutical companies so they can maximize their ROI. Consumer Reports encourages PACCARB to look at other strategies. Antibiotics take a lot of money and time to develop, but it is in the public interest not to use them much. Relying on private companies, whose success is based on aggressive marketing to use more of their drugs, is not a sustainable model for antibiotics.

Ms. McGiffert called for more creative solutions, such as a holistic approach that would make the entire health care system participate financially in preserving antibiotics. That approach would require acknowledging that surgeons, oncologists, and orthopedists would not be able to do their work without antibiotics. The challenge is for PACCARB to figure out how to turn that concept into a real strategy.

Helen Haskell of Mothers Against Medical Error raised concern about the overall direction of the Council. She said that in her role as a patient advocate, she has dealt with thousands of patients who suffered from medical harm, most as a result of HAIs, many of whom died agonizing, needless deaths. As Ms. Dornberger's presentation showed, these infections do not just happen. They arise from poor medical practice, which is a really weak link in antibiotic resistance. It is also an essential and a central part of PACCARB's mission. The charter, mission statement, National Action Plan, and strategy all identify infection prevention and control as playing a prominent role. But in PACCARB's recent report, it seems to have just disappeared, and there has been very little discussion of it in this meeting.

Antibiotic stewardship is not the same thing as infection prevention. Ms. Haskell asked that the Council return to its original mission of doing as much as possible to directly reduce the incidence of health-care-associated, antibiotic-resistant infections.

Mr. Wallinga of NRDC said that over the past 10 years, researchers have published on how inappropriate microbial risk assessment is as a tool for this particular problem, because it requires too robust a data set to do justice to the microbial ecosystem. Years could be spent collecting data and still not provide a decent risk assessment. A much better policy approach would be something like a public health assessment that would zero in on the key science-informed policy questions.

HHS Secretary Burwell charged PACCARB with prioritizing investments. Mr. Wallinga said the major investment should be looking at the drivers of resistance, which are use and overuse of antibiotics, wherever that occurs. There are good examples in humans, at the farm level, and in other countries to inform that. First, there is robust literature from Denmark and another European country, who are major meat producers. (The NRDC's written comments describe a program on preventing the use of antimicrobials, especially in the agriculture sector.) Second, there are U.S. producers already reducing antibiotic use, and they should be here talking about what they are doing. NRDC estimates that 45 percent of the poultry sector is no longer using routine antibiotics. Third, major meat companies have already made commitments on this score. They see that the market is changing. The research and the questions that are going to best help them respond to their market conditions are the ones that focus on reduced routine antibiotic use.

Finally, Mr. Wallinga noted that an earlier discussion indicated that colistin is not being used in the animal sector in the U.S. However, it is approved for use. One quick, "low-hanging-fruit" effort might be to withdraw that approval.

Christian Lillis of the Peggy Lillis Foundation said clinicians and policymakers must be honest with themselves and the public about the short-term dangers of antibiotic use. He said his mother, Peggy, a healthy 56-year-old kindergarten teacher, died from a *C. difficile* infection less than 2 weeks after being prescribed clindamycin prophylactically by her dentist. At least 30,000 Americans die from just *C. difficile* every year—more than from HIV or drunk driving. Yet only 23 percent of Americans have ever heard of *C. difficile*.

Since this meeting started at 10 a.m. yesterday, approximately 120 Americans have died from this disease. Mr. Lillis called for urgent, coordinated, and robust reforms regarding the use of

antibiotics—not in the next administration, not in 10 years, but today. It is clear that innovation alone will not resolve this crisis. Large-scale public education campaigns are needed. Existing antibiotics must be preserved through stewardship and by preventing infections. Prescribers must be held accountable for antibiotic overuse, as they are for opioids. The public must be educated that antibiotics are a precious social good but also have potentially harmful side effects.

Overuse is setting up a grim future medically. Mr. Lillis urged the Council, the federal government, industry, and fellow citizens to be bold, to be brave, and to act with the urgency that this crisis requires. Given the deep-seated cultural changes that are required to reverse course, Mr. Lillis urged the Council to engage much more deeply with the public, including expanding in-person public commentary and adding opportunities for citizens to question the presenters. He also urged PACCARB to solicit more input from the public and from laypeople. Millions of families like his have lost a loved one and are eager to help.

Suzanne Henry of Consumer Reports' Safe Patient Project said the CDC has a way of measuring antibiotic use in their NHSN system, which allows hospitals to report antibiotic prescribing practices. That kind of data is needed to appropriately design antibiotic stewardship programs. Ms. Henry encouraged PACCARB to use its influence to get states to sign up to use the CDC's NHSN antibiotic stewardship program.

Adjournment

Dr. Martin Blaser, Chair

Dr. Blaser adjourned the meeting at 2:14 p.m.

I hereby certify that, to the best of my knowledge, the foregoing minutes of the proceedings are accurate and complete.

Martin J. Blaser, M.D., Chair
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Appendix A: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Members

June 21–22, 2016

PACCARB Voting Members Present

Martin J. Blaser, M.D., Chair
Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair
Michael D. Apley, D.V.M., Ph.D., DACVCP
Helen W. Boucher, M.D., FIDSA, FACP
Angela Caliendo, M.D., Ph.D., FIDSA (day two)
Alicia R. Cole
Sara E. Cosgrove, M.D., M.S.
Peter Robert Davies, B.V.Sc., Ph.D. (by phone)
Kent E. Kester, M.D., FACP, FIDSA, FASTMH
Ramanan Laxminarayan, Ph.D., M.P.H.
Aileen M. Marty, M.D., FACP
John H. Rex, M.D.
Thomas R. Shryock, Ph.D.
Randall Singer, D.V.M., M.P.V.M., Ph.D.
Robert A. Weinstein, M.D.

Organizational Liaisons Present

Animal Health Institute
Richard Carnevale, V.M.D.
Association of State and Territorial Health Officials
Jay C. Butler, M.D.
National Association of Directors of Nursing Administration in Long Term Care
Sherrie Dornberger, R.N., CDONA, GDCN, CDP, CADDCT, FACDONA (day one)
National Pork Producers Council
Elizabeth Allen Wagstrom, D.V.M., M.S.
The Pew Charitable Trusts
Elizabeth Jungman, J.D., M.P.H.

Ex Officios Present

U.S. Department of Health and Human Services
Beth P. Bell, M.D., M.P.H., Director, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention
Dennis M. Dixon, Ph.D., Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health (day one)
Jeff Kelman (for Shari Ling, M.D.), Centers for Medicare and Medicaid Services (day one)
Jane Knisely (for Dennis M. Dixon, Ph.D.), National Institute of Allergy and Infectious Diseases, National Institutes of Health (day two)
Joe Larson, Ph.D., Acting Deputy Director, Biomedical Advanced Research and Development Authority, Assistant Secretary for Preparedness and Response (day one)

Shari Ling, M.D., Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services (day two)
Peter Lurie, M.D., Associate Commissioner for Public Health Strategy and Analysis, Food and Drug Administration

U. S. Department of Defense
Larry Sipos (for David Smith, M.D.), Deputy Assistant Secretary of Defense for Health Readiness Policy and Oversight (day two)
Paige Waterman, M.D., FACP, FIDSA, Antimicrobial Resistance Lead, Armed Forces Health Surveillance Center-Global Emerging Infectious Disease Surveillance (day 1)

U. S. Department of Agriculture
Neena Anandaraman (for David Goldman, M.D.), Food Safety and Inspection Service
Cyril Gay (for Steve Kappes, Ph.D.), Agricultural Research Service (day 2)
Steve Kappes, Ph.D., Deputy Administrator, National Program Staff, Animal Production and Protection, Agricultural Research Service (day 1)
Brian McCluskey, D.V.M., Ph.D., for Jack Shere, D.V.M., Ph.D., Chief Veterinary Officer and Deputy Administrator for Veterinary Services, Animal and Plant Health Inspection Service

Designated Federal Official
Bruce G. Gellin, M.D., M.P.H., Deputy Assistant Secretary for Health, Office of the Assistant Secretary for Health, Department of Health and Human Services

Advisory Council Staff
Jomana F. Musmar, M.S., Ph.D.c, Advisory Council Committee Manager, Office of the Assistant Secretary for Health, Department of Health and Human Services
MacKenzie Roberston, Committee Management Officer, Office of the Assistant Secretary for Health, Department of Health and Human Services
Ayah O. Wali, M.P.H., Committee Management Officer, Office of the Assistant Secretary for Health, Department of Health and Human Services

Glossary of Abbreviations

AgAR	Agriculture Antibiotic Resistance (network)
AMR	Review on Antimicrobial Resistance
ANA	American Nurses Association
APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
ASH	Assistant Secretary for Health
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Innovation Organization
C. difficile	*Clostridium difficile*
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CRE	carbapenem-resistant Enterobacteriaceae
DoD	U. S. Department of Defense
DRIVE-AB	Driving Reinvestment in R&D for Antibiotics
E. coli	*Escherichia coli*
EPA	U.S. Environmental Protection Agency
ERS	Economic Research Service
ESBL	extended-spectrum beta-lactamase
FDA	Food and Drug Administration
GAIN	Generating Antibiotic Incentives Now (Act)
GFI	Guidance for Industry
GRACEnet	Greenhouse Gas Reduction through Agricultural Carbon Enhancement network
HAI	health-care-acquired infection
HHS	Department of Health and Human Services
ID	infectious disease
IDSA	Infectious Diseases Society of America
IP	intellectual property
KAW	Keep Antibiotics Working
LC-MS	liquid chromatography–mass spectrometry
MDRO	multidrug-resistant organism
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSN	Multidrug-Resistant Organism Repository and Surveillance Network
NARMS	National Antimicrobial Resistance Monitoring System
NCBI	National Center for Biotechnology Information
NCHR	National Center for Health Research
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NPV	net present value
NRDC	Natural Resources Defense Council
NVPO	National Vaccine Program Office
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

PCAST	President's Council of Advisors on Science and Technology
PCR	polymerase chain reaction
Q&A	questions and answers
R&D	research and development
READI	Reinvigorating Antibiotic and Diagnostics Innovation (Act)
REAP	Renewable Energy Assessment Project
ROI	return on investment
USDA	U.S. Department of Agriculture
USG	U.S. government
USGS	U.S. Geological Survey
UTI	urinary tract infection
VA	U.S. Department of Veterans Affairs
VFD	Veterinary Feed Directive
WHO	World Health Organization