

TO: Acting Assistant Secretary for Health
FROM: National Vaccine Advisory Committee
RE: Greater Consideration for the Role of Vaccines in National Strategies to Combat Antibiotic-Resistant Bacteria- INFORMATION

ISSUE

The rapid spread of antibiotic resistance throughout the U.S. and world-wide is considered a major threat to public health and national security. The President has emphasized that tackling this issue is a priority and has requested the development of a national plan to define activities and milestones across the U.S. government agencies for preventing, detecting, and responding to outbreaks of antibiotic resistant infections. Ensuring that available antibiotics remain effective for as long as possible will require a multi-faceted approach that includes the optimal use of all available tools. However, the role of vaccines in preventing bacterial infections, as well as the potential role of vaccines (both direct and indirect) in reducing the overall use of antibiotics, is surprisingly under-represented in these discussions. Vaccines prevent infectious diseases before they occur- often eliminating the need for antibiotic treatments or unnecessary contacts with the healthcare system. Vaccines not only protect the vaccinated individual, but also can decrease circulation of the pathogen in the community. **The purpose of this memorandum is to provide information regarding the role vaccines currently play in promoting antibiotic stewardship and their potential as key instruments in our long term approach to combat antibiotic resistance. Further considerations and recommendations have been provided to better understand how vaccines fit into the President's National Strategy and the National Action Plan to Combat Antibiotic-Resistant Bacteria.**

BACKGROUND

The emergence of a novel virus receives wide-spread attention in the media and among the public. However, the greatest threat to public health in the U.S. is unlikely to be an exotic disease, but rather the mounting threat of antibiotic resistance in commonly acquired bacterial infections. The human and economic costs of this growing crisis are notable^{1,2}. In the CDC's 2013 report *Antibiotic Resistance Threats in the United States*, it is estimated that more than two million individuals contract an antibiotic-resistant infection each year in the U.S. and approximately 23,000 die as a result of their infection². Importantly, the escalating rate of resistance occurring among bacterial pathogens is being facilitated by the abundant (and often inappropriate) use of antibiotics, and there is rising concern that the arsenal of effective products to treat bacterial infections will soon run out³. For example it is now estimated that 6,700 (13%) of the 51,000 healthcare-associated *Pseudomonas aeruginosa* infections that occur in the U.S. each year are resistant to at least three different classes of antibiotics, with some strains showing resistance to nearly all classes of antibiotics². The lack of effective antibiotic therapy will have a

significant impact in nearly all areas of medicine, but especially in surgery, oncology, intensive care and transplant medicine.

In September 2014, the White House introduced the President's National Strategy to Combat Antibiotic Resistant Bacteria (from here referred to as 'the CARB report')⁴, released concurrently with the President's Council of Advisors on Science and Technology (PCAST) report and recommendations to the President on combating antibiotic resistance⁵. Together, these reports identify priorities and guide coordination across U.S. government agencies to 1) better prevent and respond to the spread of antibiotic resistance through better prevention and stewardship of antibiotic use; 2) increased surveillance of emerging antibiotic resistance in humans, animals, and the environment; 3) improved capabilities for detection and diagnostics; 4) accelerated development of new products including new classes of antibiotics, therapeutics, and vaccines; and 5) enhanced international collaboration⁴. The federal commitment to addressing this issue was further emphasized by Presidential Executive Order 13676 calling for the development of a 5-year National Action Plan⁶ proposing concrete activities and milestones for achieving the goals outlined in the National Strategy⁷ and a Presidential budget request to Congress for US\$1.2 billion to support these efforts⁸.

Preventing infections, preventing the spread of antibiotic resistance - highlighting the role of vaccines and prevention in antibiotic stewardship

The PCAST and the CARB Strategy and Action Plan reports strongly emphasize that practical and measurable actions can and should be accomplished towards the goals of improved antibiotic stewardship and the development of new products to treat antibiotic resistant infections. With respect to vaccines, we particularly welcome Objective 4.3 of the CARB Action Plan, which would intensify research and development into new human vaccines to prevent infections, thereby reducing the development of bacterial resistance and the general overuse of antibiotics. However, while vaccines are mentioned as one component of the overall cadre of new products needed to combat emerging antibiotic resistance in human medicine, their potential to significantly reduce antibiotic use and thereby contribute to the overarching goal of "...increasing the longevity of current antibiotics by improving the appropriate use of existing antibiotics, preventing the spread of antibiotic-resistant bacteria and scaling up proven interventions to decrease the rate at which microbes develop resistance to current antibiotics..."⁵ is under-represented. For example, Objective 1.1 of the CARB Action Plan aims to "implement public health programs and reporting policies that advance antibiotic-resistance prevention and foster antibiotic stewardship in healthcare settings and the community," but none of the milestones includes considerations for increasing vaccine uptake. To address this apparent gap, the examples provided below are intended to emphasize the critical contribution vaccines can continue to play to combat antibiotic resistance through prevention of infections and reduced transmission of antibiotic resistant strains.

Haemophilus influenzae Type b (Hib) Conjugate Vaccines

Haemophilus influenzae serotype b disease can result in ear infections and invasive infections such as meningitis, blood stream infections, epiglottitis, pneumonia, and bone or joint infections. Prior to the introduction of Hib vaccines in the late-1980's, there were an estimated 20,000 cases of invasive bacterial disease each year in U.S. children under 5 years old⁹. The majority of these were meningitis cases occurring in children less than 18 months old¹⁰. Notably, ampicillin resistance in Hib isolates, rose to 22% in the late 1970s-early 1980s in some locales, making treatment of invasive Hib infections more challenging¹¹. Fortunately, the widespread use of Hib vaccines in young children has resulted in more than a 99% decline in the incidence of invasive Hib disease⁹. The Healthy People 2020 goals have been exceeded, with only 30 cases of invasive Hib reported in 2012 among children under 5 years^{12,13}. Moreover, the conjugate Hib vaccines have been demonstrated to reduce bacterial carriage in both vaccinated and unvaccinated individuals¹⁴, resulting in reduced transmission and fewer infections thereby reducing need for antibiotics, and reduced opportunities for antibiotic resistant strains to spread.

Pneumococcal Conjugate Vaccines

Pneumococcal disease includes pneumonia, meningitis, invasive disease, ear infections, and sinus infections. Every year there are roughly 1.2 million illnesses and 7,000 deaths due to drug-resistant *Streptococcus pneumoniae*². The first conjugate pneumococcal vaccine (PCV-7) was licensed for use in 2000 and included seven prominent serotypes, five of which accounted for 78% of penicillin-non susceptible invasive infections in 1998¹⁵. Within four years of its licensure, PCV-7 contributed to an overall 57% drop in incidence of multi-drug non-susceptible strains with an 84% decrease in the rate of multi-drug non-susceptible invasive pneumococcal disease (IPD) in children less than 2 years old and a 49% decrease in penicillin-non-susceptible IPD in individuals over 65 years due to reduced transmission from children¹⁶. Moreover, several studies indicated that use of the conjugate pneumococcal vaccines has been associated with decreased use of antibiotics in young children due to decreased incidence of invasive pneumococcal disease and ear infections¹⁷⁻¹⁹. Based on findings from a 2003 study, the authors predicted that use of PCV-7 could potentially prevent 1.4 million antibiotic prescriptions annually in the US.²⁰ In 2010, a 13-valent conjugate vaccine (PCV-13) was licensed for use in the U.S. that comprises six additional serotypes, including penicillin-non-susceptible serotype 19A, which had been increasing in incidence following introduction of PCV-7²¹. Within three years, a significant reduction in cases of antibiotic resistant IPD was observed in both children less than five years old (78-96% reduction) and adults (50-62% reduction)²².

The benefits described above are directly due to the success of the pneumococcal conjugate vaccines administered to children, with indirect benefits observed in adults due to reduced transmission in children. However, data from the CDC's Active Bacterial Core Surveillance (ABCs)

system and from elsewhere estimated that 20-25% of the IPD cases²³ and 10% of community-acquired pneumonia²⁴ that occurred in individuals ≥ 65 years might be prevented with greater use of the PCV-13 vaccine in adults 65 years and older^{23,24}. In 2014, the Advisory Committee for Immunization Practices recommended that all adults 65 years and older receive a single dose of PCV-13 in addition to the previously recommended 23-valent polysaccharide pneumococcal vaccine²³. Combined with prudent use of antibiotics, the increased uptake of the PCV-13 vaccine among adults is predicted to significantly reduce transmission of pneumococcus and thereby slow the spread of antibiotic resistant infections.

Influenza vaccines

Broad spectrum antibiotics are often prescribed to treat acute respiratory tract infections, although the majority of these infections are due to viral infections such as influenza. For example, in one 2011 study, the authors found that inappropriate prescribing of antibiotics for influenza infection occurred in 79% of 58,477 influenza patients²⁵. Secondary bacterial infections requiring antibiotic treatment, can follow influenza infection due to damage to the respiratory epithelium by influenza viruses (and other respiratory viruses), and due to other host and pathogen factors²⁶. Some of these bacterial pathogens, such as pneumococcus and *Staphylococcus aureus*, can be antibiotic-resistant organisms. Influenza infections occur in 5%-20% of the population and more than 200,000 people are hospitalized due to influenza-related complications each year. Despite the wide-spread risk of influenza infection, coverage estimates from 2013-2014 influenza season indicate that only 46.2% of all people ≥ 6 months of age in the U.S received an influenza vaccine²⁷. In one Canadian study, influenza-associated antibiotic prescriptions decreased 64% following implementation of a universal influenza immunization program²⁸. Greater efforts to increase influenza vaccination coverage in the U.S. among all age groups are also likely to result in fewer influenza infections and a reduced number of antibiotic prescriptions.

The potential of new vaccines to target bacterial pathogens

Vaccines will not be a practical or feasible solution for all antibiotic resistant bacteria. There are important scientific challenges unique to many of these organisms that make alternative approaches to vaccination more desirable. Nonetheless, supporting vaccine development against some of these pathogens can have a major impact in decreasing the burden of resistant infections. For some infections, vaccines represent the most logical strategy for protecting high-risk patients who are repeatedly exposed to resistant bacterial pathogens due to frequent interactions with the healthcare system and non-modifiable host factors. In other cases in which there is a high burden of disease for the general population, an effective vaccine, will include protection against resistant strains of the bacterium. We will provide two examples of relevant pathogens with vaccines in development.

Methicillin-Resistant Staphylococcus aureus (MRSA)

Methicillin-resistant *Staphylococcus aureus* (MRSA) causes more than 80,000 invasive infections and 11,000 deaths each year². While significant decreases in healthcare-associated (HA)-MRSA have been reported in the past few years, MRSA infections, particularly community-associated MRSA (CA-MRSA), remain a concern^{29,30}. Unlike HA-MRSA infections, CA-MRSA strains commonly infect young, previously healthy patients causing skin and soft-tissue infections and invasive disease. In 2012, 20% of all reported invasive MRSA infections were attributed to CA-MRSA³¹. In addition, HA-MRSA strains are frequently isolated in community settings and some have argued that vaccination of a wider population, and not just high-risk individuals, should be considered to protect more broadly against *S. aureus* infections^{32,33}. Although progress on an effective vaccine against *S. aureus* has been slow, successful development of a vaccine is an important public health objective.

Clostridium difficile

Clostridium difficile (*C. difficile*) is the leading cause of healthcare-associated infectious diarrhea in the U.S. resulting in approximately 500,000 infections and 29,000 deaths per year³⁴. *C. difficile* infections are directly associated with prolonged antibiotic use that destroys healthy intestinal microflora, creating an ecological niche that favors *C. difficile* colonization³⁵. Compounding this problem, hyper-virulent *C. difficile* strains have emerged over the past 15 years leading to an increase in severe disease outcomes and an increase in community-acquired infections in previously low-risk individuals such as children, peripartum women, and healthcare workers³⁵⁻³⁸.

Despite rigorous infection control practices in healthcare settings, these infections are often difficult to treat, and persistent or recurrent infections are common. Vaccination against *C. difficile* is favored not only as a mechanism to prevent infection, but also because of its potential to strengthen the immune response without further disrupting the host's normal intestinal microflora in patients with recurrent and persistent infections^{38,39}. Importantly, economic modeling suggests that *C. difficile* vaccines would be cost-effective, and in most scenarios, cost-saving across a wide range of disease risk, vaccine efficacies, and vaccine costs due to the burden of *C. difficile* infections on the healthcare system- currently estimated to cost \$1-3 billion dollars per year⁴⁰⁻⁴².

Economic incentives supporting accelerated research and development for new vaccines – identifying what works and what doesn't work

The challenges to antibiotic development have been studied and are well-understood. PCAST, in its 2014 report on antibiotic resistance, outlines a series of “push” and “pull” economic incentive mechanisms that may motivate industry to pursue R&D programs for antibiotics⁵. The Assistant Secretary for Planning and Evaluation (ASPE) published a framework in 2014, for analyzing the impact of various incentives on antibiotic development⁴³. However, while some similar basic economic principles

may apply to both antibiotics and vaccines, there are significant differences between vaccines and antibiotics that warrant a separate examination of incentive approaches. One difference is that the share of the global pharmaceutical market attributable to vaccines remains small (3% in 2010)⁴⁴. Also, traditionally vaccines are sold at low cost compared with many therapeutic drugs, and pharmaceutical companies may not be able to justify the research and development costs for vaccines that are used to prevent diseases that are less-prevalent and therefore have a smaller market. Low cost existing vaccines, such as pertussis and influenza, can also serve as a disincentive for developing improved vaccines that will be considerably more costly to develop than the vaccines already on the market. The analyses that PCAST and ASPE have undertaken have been important for developing research and policy agendas for antibiotic development. Likewise, it would be advantageous to have this kind of careful study of the challenges to developing and deploying vaccines to combat antibiotic resistance. Further, the CARB Action Plan indicates that the CARB Economic Incentives Working Group will release a separate analysis of potential economic incentives to ensure a “diverse and robust pipeline of antibiotics.” We propose that a working group also evaluate the use of incentives to accelerate vaccine development as part of a comprehensive approach to mitigating antibiotic resistance.

The CARB interagency task force should evaluate vaccine development for vaccines most likely to enhance antibiotic sustainability and reduce the prevalence of antibiotic resistant bacteria. This would include both vaccines indicated to prevent bacterial infections, such as a *S. aureus* vaccine, but also vaccines whose indirect effect would be to reduce the use of antibiotics, such as an improved influenza vaccine and a respiratory syncytial virus vaccine. The PCAST report and CARB strategy both propose policies that would change the way antibiotics are evaluated and approved by the Food and Drug Administration (FDA). Vaccines are administered preventatively and potentially to a broader population; thus, there are different considerations for development and use. FDA’s existing expedited regulatory pathways for clinical development and licensure should be utilized, taking into account the different market forces, to address challenges with vaccine innovation and to identify potential policy solutions to those challenges.

RECOMMENDATIONS

In full support of the strategies and objectives outlined in the President’s National Strategy and Action Plan to Combat Antibiotic Resistant Bacteria, and in recognition of the further impact vaccines could make in long-term strategies to reduce overall antibiotic use and prevent the transmission and/or circulation of antibiotic resistant infections, the NVAC makes the following recommendations:

1. The National Vaccine Advisory Committee (NVAC) recommends that the Assistant Secretary for Health (ASH), as the Director of the National Vaccine Program, work with HHS agencies and other federal and nonfederal partners to develop a stakeholder engagement plan to ensure that both vaccine and immunization as well as antibiotic stewardship stakeholder efforts include information

on the role of existing vaccines in minimizing antibiotic use. This should include information on vaccines against bacterial pathogens which may currently be or potentially become antibiotic resistant and viral vaccines that by preventing viral illnesses decrease the inappropriate use of antibiotics for viral infections as well as decrease bacterial superinfections leading to needs for antibiotics.

- 1.1. These efforts should include a comprehensive analysis modeling the reduction in disease burden due to antibiotic resistant bacterial strains, the potential reduction in antibiotic prescribing and healthcare encounters, and the anticipated cost-savings to the healthcare system expected from increased uptake of recommended vaccines in all age groups. Vaccines under development may also be included to support those vaccine development efforts.
- 1.2. These efforts should also tie into surveillance efforts to determine the effects that vaccine uptake has produced on minimizing disease burden due to antibiotic resistant strains in all age groups, and on the ecology of infections caused by strains covered by vaccine as well as non-vaccine strains. When possible, surveillance efforts also should inform on the effects vaccine uptake, and the reduction in disease caused by vaccine, has had on the prevalence of antibiotic resistant strains.
2. The NVAC strongly recommends that the ASH ensure NVAC remains regularly informed of efforts to address antibiotic resistance by revising the NVAC charter to include a liaison representative from the President's Advisory Council on Combating Antibiotic Resistant Bacteria on the NVAC. The NVAC also encourages the ASH to support the future inclusion of an NVAC representative on the President's Advisory Council on Combating Antibiotic Resistant Bacteria to provide knowledge of vaccines and the immunization system to their discussions. Cross representation on Committees maximizes the use of subject matter expertise and stakeholder input to better harmonize Departmental efforts.
3. The NVAC strongly encourages the ASH to communicate to the HHS Secretary and the CARB Economic Incentives Working Group that incentives proposed to stimulate antibiotic development must also be evaluated for their utility to accelerate the development of vaccines and other novel prevention strategies. Proposed incentives must be flexible enough to apply to a range of diverse technologies to ensure that we continue to move towards long term solutions to antibiotic resistance. When incentives are not found to be cross-cutting, additional alternative incentives should be proposed and analyzed to promote a more robust and comprehensive pipeline that includes vaccines.

- 3.1. Once appropriate economic incentives are identified, NVAC recommends that the ASH work with relevant federal and non-federal stakeholders to prioritize promising vaccine candidates to ensure programmatic resources support vaccine candidates with the greatest potential impact for combating antibiotic resistance and reducing the use of antibiotics in healthcare and community settings.
4. The NVAC recommends that the ASH work with FDA and vaccine manufacturers (including pre-commercial stage biotechnology companies) to encourage early discussion of appropriate regulatory pathways and clinical trial design requirements for the development of vaccines targeting antibiotic resistant bacteria, and vaccines that decrease the use of antibiotics.
5. The NVAC requests that NVPO provide an annual update on the progress made in supporting the role of vaccines in strategies to combat antibiotic resistant bacteria.

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