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August 31, 2017

Dr. Angela Shen
NVAC Designated Federal Official
Senior Advisor, National Vaccine Program Office
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Dr. Shen:

The Infectious Diseases Society of America (IDSAs) welcomes the opportunity to provide input on federal government efforts to promote vaccine innovation. Vaccines are considered one of the greatest accomplishments in public health and disease prevention, and also one of the most cost-effective. However, there are still significant opportunities for innovation to maximize the potential of vaccines. With many potential targets and limited resources, appropriately prioritizing vaccine research and development is both a highly important but complicated task. A summary of our recommendations can be found below:

- There are several existing methods of optimizing vaccine prioritization that may serve as a good start, but no method is perfect. A panel of experts is necessary to determine the optimal approach for the US government;
- Vaccines that have value from a public health standpoint may not have sufficient business value for pharmaceutical companies. Novel incentives and protections should be developed for companies developing less economically viable vaccines, including public private partnerships and innovative clinical trial designs;
- More robust surveillance is needed to accurately assess both economic and public health value of vaccines. In particular, there is a lack of epidemiologic data on vector-borne diseases. Additionally, the full value of community protection from high vaccination coverage is frequently underestimated;
- Lack of access to vaccines affects not just individuals but the entire population's health. Steps need to be taken to eliminate barriers preventing people from getting vaccinated. Vaccine hesitancy has also caused pockets of unimmunized populations, and more research and public engagement should be done to communicate the safety and efficacy of vaccines. This impacts innovation, because depressed vaccine uptake discourages investment in the development of new vaccines;
- Therapeutic vaccines provide distinct potential benefits compared to standard preventive vaccines and merit distinct criteria for evaluation and development;

- The differences between therapeutic and preventive vaccines necessitate having different criteria and development guidelines for each;
- Development of a universal influenza virus vaccine, which would obviate the need for annual immunization, would greatly reduce anticipated threat from an emerging pandemic; and
- Pregnant women and HIV infected persons are important and underrepresented targets for vaccine studies. More guidance on when these studies are necessary, and how to conduct them safely would greatly benefit these populations.

We thank you for allowing us to give input on this very important subject, and we would appreciate the opportunity to collaborate with the Department of Health and Human Services as you address these issues.

Processes for Optimizing Vaccine Prioritization:

The public health burden, presence or absence of effective treatment options, severity of disease, and capacity to spread are all important criteria to consider when prioritizing vaccine development. Global and domestic vaccine needs should also be given consideration for this country's public health security, as infectious diseases do not respect borders and an outbreak anywhere in the world can quickly become an outbreak at home.

Developing a strategic plan for vaccine innovation with a mechanism to review priorities on a regular basis would be a useful approach to guide US efforts. HHS could consider using existing expert bodies, such as the National Vaccine Advisory Committee and the Advisory Committee on Immunization Practices, in developing such a plan, or could convene a separate panel of experts to support the development of a strategy. The process for developing the strategic plan should also provide opportunities for public input. HHS should also utilize recent expert efforts to develop methods for prioritizing vaccine development in the last several years, including:

[The Strategic Multi-Attribute Ranking Tool for Vaccines \(SMART Vaccines\)](#) tool which was released in 2012 resulted from collaboration between the National Vaccine Program Office (NVPO) and the National Academy of Medicine. SMART Vaccines is a program that allows the user to input data and adjust a large number of variables to analyze the potential benefits and downsides of investing in vaccines for a variety of diseases.

[The National Academy of Medicine \(NAM\) also released its own list of vaccine priorities](#) in March of 2016, which ranked 26 diseases according to societal benefit, based on an estimation of how many dollars a vaccine would cost per Quality Adjusted Life Year (QALY) saved. The NAM states that the list is not exhaustive and explains the constraints the Academy placed on its recommendations.

While we believe both of the above systems are valuable for informing an effort to set vaccine priorities, no system is perfect. This effort would require a collaborative, multidisciplinary approach involving multiple governmental entities (Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health, Biomedical Advanced Research and Drug Authority, Department of Defense, Veterans' Affairs, and the National Vaccine Program Office), as well as clinicians, researchers, public health authorities, vaccine developers, and other stakeholder groups.

Obstacles to Vaccine Development and Potential Solutions:

One of the primary difficulties in prioritizing vaccine R&D is the difference between the “value” of a vaccine to a pharmaceutical company and the “value” of that vaccine to the population. Some vaccines that would be immensely beneficial to the target population will not be cost-effective to a vaccine company due to high research and development costs, small markets, or both. For example, vaccines being developed in response to public health emergencies or outbreaks are fraught with market uncertainty. If the scope of an outbreak is smaller than thought, or subsides by the time the vaccine is available, the financial return on investment in vaccine development may plummet. This high level of risk can decrease the likelihood that companies will work with the government on these types of projects and may leave us without necessary private sector partners to develop these essential vaccines. We urge the government to consider strategies to help mitigate some of the risks and costs associated with development of vaccines in response to public health emergencies and other vaccines of high public health value. Federal support, such as grants, public private partnerships, or other sources of funding will likely be needed. Further, HHS should seek to develop and advance innovative clinical trial designs to decrease cost and speed the path to licensure. The Ebola Phase III vaccine trial in Guinea – Ebola ça suffit—may be a useful model.

The lack of comprehensive epidemiologic and geographic distribution data for several vector-borne diseases makes it difficult to determine both the public health value and potential economic value of certain types of vaccines accurately. Investment in more complete vector-borne surveillance is essential to allow vaccine developers and public health leaders alike to ascertain the impact of these diseases and the value of potential vaccines. Better tools are also needed for determining the value of community protection through population immunization, as current economic studies often underestimate the value of community protection through vaccines. Many childhood vaccines, including hepatitis A and pneumococcal conjugate vaccines, have provided more public health and economic value than predicted. More accurately estimating such factors would also improve decision making on vaccine population targeting and development of recommendations.

Vaccines can only provide coverage to patients who receive them. Adult immunization rates in particular are far below recommended levels due to lack of awareness of vaccine recommendations and persistent barriers to access, including fragmented Medicare coverage of vaccines, incomplete immunization health records, as well as other financial and access barriers. Resolving [ongoing issues that hinder access](#) is vital. In addition, companies will be more likely to invest if there is a greater likelihood of more patients utilizing their vaccines.

Developing clear guidelines and pathways for ACIP recommendations would also help assuage pharmaceutical companies’ concerns about market size and accessibility. This could be done by constructing a list of target vaccines with achievable safety and efficacy profiles for companies to aim for in product development.

The occurrence of predicted and unpredicted adverse events have had an, arguably, disproportional influence on acceptance of vaccines and on industry decisions to continue developing or marketing them. We suggest the relevant government agencies and/or NAM to promote more thorough investigation into the frequency, nature, causes and

mechanisms of adverse events by encouraging clinical trial sponsors to collect especially detailed epidemiological information and appropriate biologic materials for future evaluation among trial participants and by supporting scientific studies that may explain and potentially help prevent those events. If the underlying causes of adverse effects can be elucidated in this manner, it will hopefully either help determine who is more or less at risk for these events or, reassure the public that vaccines were not the cause to begin with.

It would be useful to have separate criteria and development guidelines for therapeutic vaccines, (e.g. like for diabetes, multiple sclerosis, or arthritis) and preventive vaccines like influenza and pneumonia. This distinction is necessary because these vaccines are targeted toward significantly different populations. Therapeutic vaccines are designed to help people who already have a disease, while preventive vaccines are used to prevent an initial infection. The different uses and populations result in significant mechanistic differences such as how the vaccine affects the target's immune system.

Recommendations for Target Vaccines:

The NAM list mentioned in the opening section on vaccine prioritization is an excellent starting point for a federal effort to create a road map to vaccine research and development goals. Though their list omits an HIV vaccine due to the already high prioritization within government and industry, we feel it is necessary to emphasize the importance again here. An effective HIV vaccine will still require vast amounts of resources and has many technical barriers that must be overcome before clinical trials can begin, but the public health impact both domestically and globally cannot be overstated. We would also specifically like to highlight the following infectious diseases for which we believe new or improved vaccines would have a significant impact on patient safety and public health:

Influenza is still the most costly vaccine-preventable disease for which we currently have a vaccine, costing the U.S. healthcare system billions of dollars each year. A universal influenza vaccine with protection for at least 5 years without the need for boosters would significantly reduce this burden and lead to higher levels of community protection which would further enhance the vaccine's effectiveness. It is also important to evaluate the durability of such a universal influenza vaccine in persons with HIV infection who may demonstrate suboptimal responses and levels of protection.

Similar to influenza, Respiratory Syncytial Virus (RSV) poses the greatest threat to infants and older adults. RSV cause more pediatric hospital admissions than any other infectious etiology in the country, leading to significant stress for our health care system each year. It is another example of a respiratory virus for which a vaccine would significantly ease the public health burden.

Antimicrobial resistance (AMR) is a growing threat, causing over 23,000 deaths in the US and costing our healthcare system \$20 billion dollars a year. Vaccines for some of the most common and deadly resistant infections could significantly reduce their impact and provide a powerful tool in the battle against AMR. *Clostridium difficile*, *Staphylococcus aureus*, Carbapenem-resistant *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Neisseria gonorrhoeae* would all be worthy candidates. Pneumococcal conjugate vaccine (PCV13) has

already produced a decrease in drug resistance in pneumococci. When determining cost effectiveness of potential vaccines for these pathogens, it will be important to consider rising rates of antimicrobial resistance and the ability of vaccines to reduce our overall antibiotic use.

Additional viral diseases for which vaccines could significantly improve public health include Hepatitis C, Herpes simplex virus (HSV), and cytomegalovirus (CMV) infections. Hepatitis C infection rates have risen as the opioid crisis has taken place across the country. It has extremely high care costs and often occurs in vulnerable populations where targeted vaccinations could dramatically reduce both the public health and economic costs of the disease. HSV is one of the highest burden chronic diseases in the United States and increases the infected person's chances of contracting more serious infections like HIV. A vaccine to prevent HSV would not only impact herpes rates, but would also likely decrease infection rates of many other diseases including sexually transmitted infections and encephalitis. CMV is the most common cause of non-genetic childhood hearing loss in the United States. Like Zika virus infection during pregnancy, congenital CMV infection can also result in severe neurological abnormalities.

Amongst vector-borne diseases mosquito-borne diseases like West Nile virus infection and encephalitis caused by Arbo-viruses would be good targets, as well as tick-borne diseases such as Lyme disease, Babesiosis, and Powassan virus encephalitis. There has been emergence of new, and a steady increase in, many of these mosquito- and tick-borne infections for over 20 years, and the scope and breadth of the problem is still unclear. With a knowledge gap around the epidemiology of tick-borne illnesses across the country, and little to no research on how to prevent exposure to these diseases, developing vaccines now could limit the potential for them to become major public health concerns in the future. As these diseases have no known person-to-person transmission and the primary reservoirs are animals, a different or revised model from more traditional vaccine preventable diseases is needed to determine public health impacts.

For the purposes of global health, vaccines for the prevention of Chikungunya and Dengue fever, malaria, and tuberculosis would not only help prevent the spread of these diseases already in the U.S., they could greatly reduce cases in high burden countries. Vaccines for diseases such as Lassa fever, Nipah virus, Ebola virus, and Middle Eastern respiratory syndrome caused by a coronavirus (MERS-CoV) could help prevent the next outbreak before it starts. Chikungunya and Dengue are mosquito-borne viral infections that have been increasing in frequency in the U.S. and are expected to continue as mosquitos are able to move into geographic areas they previously were unable to inhabit, with the potential for them to become endemic in new locales. It is estimated that no other cause of death in the history of our world has claimed more lives than malaria. Though significant progress has been made, mosquitos that carry malaria are continually developing resistance to the pesticides and other substances used to deter them, and the Plasmodia that cause malaria have also been developing resistance to the primary course of treatment for the disease. A vaccine could reduce the devastatingly high disease burden that mostly occurs in African nations. *Mycobacterium tuberculosis* (TB) is the biggest infectious disease killer in the world, and has been identified by the World Health Organization as a priority for vaccine development. A recent Centers for Disease Control and Prevention (CDC) report also estimated that the disease burden of TB would continue to grow, and that an increasing percentage of new infections would be of the drug resistant strain.

We appreciate the opportunity to give input on these topics that are so important to our members and to public health. If you have any questions or would like to engage our membership on these important issues please reach out to our Program Officer for Public Health Policy, Colin McGoodwin, at cmcgoodwin@idsociety.org. Thank you again for your time and consideration.

Sincerely,

A handwritten signature in cursive script that reads "Bill Powderly". The signature is written in dark ink and is positioned above the typed name.

William G. Powderly, MD, FIDSA
President, IDSA