Evaluation of the 2010 National Vaccine Plan Mid-course Review: Recommendations from the National Vaccine Advisory Committee

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Acronyms

Abbreviation	Definition
2-D	Two-dimensional
ACA	Affordable Care Act
ACIP	Advisory Committee on Immunization Practices
APhA	American Pharmacists Association
ASH	Assistant Secretary for Health
CDC	U.S. Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
CTC	Controlled temperature chain
CRE	Carbapenem-resistant Enterobacteriaceae
DPT	Diphtheria, Pertussis, and Tetanus
EHR	Electronic Health Record
EV71	Enterovirus 71
GBS	Group B Streptococcus
GVAP	Global Vaccine Action Plan
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HP2020	Healthy People 2020
HPV	Human Papilloma Virus
IBD	Invasive Bacterial Disease
IIS	Immunization Information System
MOA	Memoranda of Agreement
NIAID	National Institute of Allergy and Infectious Diseases
NRA	National Regulatory Authority
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OA	Opportunity Area
ONC	Office of the National Coordinator
PQS	Performance, quality and safety system
R&D	Research and development
RSV	Respiratory syncytial virus
SAGE	Strategic Advisory Group of Experts
SMART	Strategic Multi-Attributable Ranking Tool
TB	Tuberculosis
USG	U.S. government
WHO	World Health Organization

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Executive Summary

In September 2014, the Assistant Secretary for Health (ASH) asked the National Vaccine Advisory Committee (NVAC) to conduct an independent mid-course review to evaluate the progress on the goals of the National Vaccine Plan and develop recommendations for the ASH. This NVAC review considers the findings of a parallel, separate mid-course review of the status of the National Vaccine Plan commissioned by the National Vaccine Program Office (NVPO) in August 2015 that included a broad stakeholder engagement process. This report provides the NVAC conclusions and recommendations. The NVAC supports the NVPO Mid-course Review report findings and its focus on the following 5 top priority opportunity areas for advancing U.S. vaccine and immunization efforts: i) "Strengthen health information and surveillance systems to track, analyze, and visualize disease, immunization coverage, and safety data, both domestically and globally; ii) Foster and facilitate efforts to strengthen confidence in vaccines and the immunization system to increase coverage rates across the lifespan; iii) Eliminate financial and systems barriers for providers and consumers to facilitate access to routine, recommended vaccines; iv) Strengthen the science base for the development and licensure of vaccines; and v) Facilitate vaccine development." The NVAC agrees with the focus in the NVPO report on these 5 opportunity areas, but also recommends that, if additional funding or other resources become available, the ASH and other federal agencies should continue to support the following other opportunity areas in the NVPO Mid-course Review report: i) "Increase coordination, collaboration and knowledge sharing among related parties and disciplines; ii) Improve the transparency of the vaccine safety system and the entire vaccine enterprise to policymakers, the public, and providers; iii) Improve scientific knowledge about why and among whom vaccine adverse events occur; and iv) Support the strengthening of immunization systems globally through policies, practices, and partnerships."

In this report, the NVAC outlines its assessment of what would constitute near-term success for each of the 5 opportunity areas and identifies indicators to use to measure success and monitor progress on the established target goals. Recognizing the limitations of existing indicators, the NVAC recommends the development of new indicators to improve tracking and analysis, especially for vaccine innovations.

The NVAC recommends the following:

- The ASH should charge the NVPO, in coordination with relevant departments and agencies, to adopt existing indicators (e.g., Healthy People 2020 indicators) to track progress on the National Vaccine Plan goals and to prepare an annual report to the ASH and the NVAC on progress.

- The ASH should charge the NVPO, in coordination with departments and agencies, to develop and validate new indicators within each of the 5 opportunity areas to ensure improved tracking of goals. The new indicators should include one that will track and report on U.S. government annual financial investments in vaccine innovation that support the development of (i) vaccines for established pathogens that have no vaccines, (ii) vaccines for emerging pathogens, and (iii) improvements in existing vaccines. The new indicators should also consider investments in vaccine delivery technologies.
- The ASH should continue to strongly support U.S. contributions to global immunization efforts and the integration of global immunization efforts into the opportunity areas as appropriate.
- The NVPO should continue to implement the recommendations from previous NVAC reports, such as the 2015 NVAC report on *Assessing the State of Vaccine Confidence in the United States*. By doing so, the NVPO can highlight NVAC recommendations related to implementing the priorities outlined in the NVPO 2010 Mid-course Review. The NVPO should use the framework defined in this report to make further advancements under the existing 2010 National Vaccine Plan for both domestic and global immunization outcomes.
- The ASH should charge the NVPO to develop the 2020 National Vaccine Plan, which should incorporate the findings in this report, and consider the impact of health care disparities on implementation and achievement of the objectives of the 2020 Plan.
- The ASH should charge the NVPO, in coordination with other relevant departments and agencies, to begin developing strategies to (i) identify priorities for U.S. government investments in vaccine-related innovations and (ii) overcome barriers that inhibit innovation.

Introduction

Preventing disease and promoting health depend on the collaboration of several sectors of society. Over decades of collaborative work, the U.S. vaccine and immunization system accomplished one of the greatest public health achievements in the 20th century.[1] Immunization provides significant health and economic benefits. A 2013 study performed by the U.S. Centers for Disease Control and Prevention (CDC) estimates that routine childhood immunizations prevented 322 million illnesses and averted 732,000 premature deaths from vaccine-preventable illnesses in children born between 1994-2013, with an estimated societal cost-savings of $1.38 trillion.[2] A 2016 study reports that investments in immunization in low- and middle-income countries for 2011-2020 will yield an estimated return of approximately 16 times the cost.[3]

In 1986, the Public Health Service Act §300aa–et. seq. created the National Vaccine Program as a way to integrate the numerous federal agencies and offices that work with each other and non-federal stakeholders on vaccine development, production, and delivery.[4] The legislation calls for the development of a strategic plan to "…*establish priorities in research and the development, testing, licensing, production, procurement, distribution, and effective use of vaccines, describe an optimal use of resources to carry out such priorities, and describe how each of the various departments and agencies will carry out their vaccine functions*."[4] The strategic plan, developed and maintained by the National Vaccine Program Office and called the National Vaccine Plan, provides strategic direction for all U.S. vaccine-and immunization-related activities.[5] It aims to create a robust and coordinated system to prevent infectious diseases through vaccination.[5] The most recent version, the 2010 National Vaccine Plan,[5] provides a detailed 10-year roadmap to unify and strengthen all aspects of the U.S. vaccine and immunization enterprise. It sets out five over-arching goals: 1) "Develop new and improved vaccines; 2) Enhance the vaccine safety system; 3) Support communications to enhance vaccine decision-making; 4) Ensure a stable supply of, access to, and better use of recommended vaccines in the U.S.; and 5) Increase global prevention of death and disease through safe and effective vaccination." The National Vaccine Plan further defines the five goals by providing additional supporting objectives and strategies.[5]

The National Vaccine Implementation Plan, released in Spring 2012, outlines federal activities conducted in support of the National Vaccine Plan priorities.[6] However, the National Vaccine Implementation Plan recognizes the need to incorporate flexibility that allows the plan to adapt to changes in vaccination

technologies and healthcare delivery models and to unforeseen contingencies that require changes to the National Vaccine Plan. Therefore, the National Vaccine Implementation Plan only encompasses activities for the first five years of the National Vaccine Plan (i.e., 2010-2015). The National Vaccine Implementation Plan calls for a formal mid-course review of the 2010 National Vaccine Plan, with guidance from the National Vaccine Advisory Committee (NVAC).[6]

The NVPO mid-course review, performed between September 2014 and September 2016, included an extensive stakeholder engagement process, and disseminated a report in November 2016.[7] The NVPO report does not replace the National Vaccine Plan. Instead, it aims to identify and highlight areas of greatest opportunity to make critical advancements in the vaccine and immunization enterprise, and it evaluates and defines priorities to guide implementation activities for the near-term (2016-2020).[7] The opportunity areas represent a consensus of stakeholders on how to focus federal priorities in light of changing and uncertain budgets and political environments. The NVPO report[7] also summarizes indicators identified by the stakeholders as the best measures of the success of current efforts and tools to inform the next iteration of the National Vaccine Plan (i.e., the 2020 National Vaccine Plan).

In March 2016, the Assistant Secretary for Health (ASH) requested that the NVAC provide an independent, parallel mid-course review of the National Vaccine Plan. This report presents the NVAC's conclusions and recommendations. The report also highlights nuances for the interpretation of the 5 opportunity areas and explores indicators used to define success and monitor progress. The report recommends broader considerations for the implementation of the National Vaccine Plan going forward, including the need for the development of new indicators.

Process

The NVAC builds on input collected during the stakeholder engagement process and the findings described in the NVPO report.[7] Briefly, between September and December 2015, non-federal and federal stakeholders provided input on the accomplishments and remaining gaps of the 2010 National Vaccine Plan, and they developed "opportunity areas" (OAs) for advancing the National Vaccine Program during the remaining five years of the Plan, 2016-2020. Between February and April 2016, federal and non-federal stakeholders participated in focus groups and interviews to prioritize the

opportunity areas.[7] The NVPO report[7] identifies 9 consensus opportunity areas that three focus groups ranked according to priority (Box 1).[7]

Box 1. Nine Opportunity Areas and Stakeholder Rankings (adapted from the NVPO Mid-course Review of the 2010 National Vaccine Plan)

Opportunity Area (OA)	Rank and OA Number
Strengthen health information and surveillance systems to track, analyze and visualize disease, immunization coverage and safety data both domestically and globally.[a]	1
Foster and facilitate efforts to strengthen confidence in vaccines and the immunization system to increase coverage rates across the lifespan.	2
Eliminate financial and systems barriers for providers and consumers to facilitate access to routinely recommended vaccines.	3
Strengthen the science base for the development and licensure of vaccines.	4
Facilitate vaccine development.	5
Increase coordination, collaboration and knowledge sharing among related parties and disciplines.	6
Improve the transparency of the vaccine safety system and the entire vaccine enterprise to policymakers, the public and providers.	7
Improve scientific knowledge about why and among whom vaccine adverse events occur.	8[b,c]
Support the strengthening of immunization systems globally through policies, practices and partnerships.	9[c]

a – a tenth opportunity area in the NVPO report[7] (i.e., "Improve surveillance for VPDs, and strengthen health information systems to monitor vaccine coverage, effectiveness, and safety both domestically and globally") overlaps with this opportunity area and does not appear in this table
b – most focus group participants grouped this opportunity area into OA#4 (i.e., implicit in OA#4)
c – these opportunity areas ranked similarly

Between March and October 2016, the NVAC independently evaluated the information collected during the NVPO focus groups and the findings in the NVPO report.[7] The NVAC also gathered information from non-federal stakeholders representing two consumer groups, and from federal stakeholders not included in the NVPO focus groups. In December 2016, the NVAC invited and received public comments on a draft of the report. The NVAC findings in this report should help to define the activities needed to achieve success in the opportunity areas and the indicators needed to measure progress during the remaining time horizon of the 2010 National Vaccine Plan.

General Findings

Overall, the NVAC agrees with the identification and prioritization of opportunity areas in the NVPO report.[7] The NVAC also agrees that the top 5 most highly ranked opportunity areas (see Box 1) correctly represent activities likely to yield the greatest impact over the next five years. These top five opportunity areas include:

1) Strengthen health information and surveillance systems to track, analyze, and visualize disease, immunization coverage, and safety data, both domestically and globally.
2) Foster and facilitate efforts to strengthen confidence in vaccines and the immunization system to increase coverage rates across the lifespan.
3) Eliminate financial and systems barriers for providers and consumers to facilitate access to routinely recommended vaccines.
4) Strengthen the science base for the development and licensure of vaccines.
5) Facilitate vaccine development.

The NVAC acknowledges the need to identify priorities for vaccination activities. Future funding remains uncertain and limited and the greatest public health impact will likely come from carefully targeting available resources. On the other hand, the NVAC also recognizes the importance of the other four opportunity areas (Box 1), and recommends that the ASH and federal partners not lose the opportunity to support them if additional funding or other resources become available.

The NVAC recognizes that highlighting U.S. domestic efforts may risk losing the momentum to advocate for U.S. global immunization efforts, which reduce the potential for importations of diseases into the United States. The NVAC notes that strengthening routine immunization systems in the United States and abroad helps protect the American population from the importation of vaccine-preventable diseases by ensuring access globally to safe and effective vaccines. The NVAC suggest that, when appropriate, domestic implementation activities related to the 5 prioritized opportunity areas should tie directly to global activities. The NVAC agrees with the NVPO report[7] that indicators used to measure progress should reflect progress of both U.S. domestic and global immunization goals, because the expertise, technical support, and capabilities needed to achieve domestic and global objectives often overlap. The NVPO report[7] includes global indicators developed for the Global Vaccine Action Plan (GVAP)[8] by the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE),[9] which the NVAC recognizes as supporting the importance the national commitment to global immunization.[10]

The NVAC highly values stakeholder engagement processes, like the one used to prioritize the opportunity areas in the NVPO report.[7] The NVAC also acknowledges that individual participants in focus groups may introduce bias and the results may not be representative. Accordingly, the NVAC suggests that future implementation activities should consider all of the opportunity areas and regularly assess the impact of the activities on all populations. The NVAC recognizes that the impact of health care

disparities among different stakeholder groups should be assessed regularly particularly among populations at risk. Notably, implementation activities should particularly consider populations at risk, because focusing on these potentially under-represented groups may help to address overarching health care and access disparities that may prohibit achieving the objectives of the 2010 National Vaccine Plan.

NVAC Analysis and Discussions of Individual Opportunity Areas

For each of the 5 prioritized opportunity areas, the NVAC discusses what it would mean to achieve success, including what success would look like in the near-term, and what challenges could impede success. The NVAC also discusses possible indicators to track progress. To the extent possible, the NVAC suggests the use of existing indicators, such as those already used by the U.S. government agencies like the Healthy People 2020 (HP2020) indicators.[11] However, the NVAC notes that many of the existing indicators do not provide the flexibility needed to fully track the opportunity areas. Where existing indicators do not provide the information needed to mark progress for an opportunity area, the NVAC provides suggestions for other more appropriate indicators. In some cases, no appropriate indicators currently exist and the NVAC suggests the development of new indicators. However, the time needed to develop new indicators will likely exceed the timeframe of the National Vaccine Plan and require additional resources. Accordingly, the NVAC includes these as recommended actions for future updates to the National Vaccine Plan.

OA#1 - Strengthen health information and surveillance systems to track, analyze, and visualize disease, immunization coverage, and safety data, both domestically and globally

The use of health information technologies and data from patient electronic health records (EHRs) for improving healthcare quality and supporting public health continues to increase.[7] The NVPO report[7] recognizes that the use of health information systems represents the greatest opportunity to significantly advance the goals of the National Vaccine Plan over the coming years. Broadening the use and interoperability of health information technologies across a variety of platforms, providers, and public health agencies may provide near real-time data for surveillance and allow the identification of trends in disease incidence, vaccination coverage, vaccine effectiveness, and vaccine safety. Improved data quality and sharing may also facilitate outbreak response efforts[12] and improve patient access to

recommended vaccines by preventing missed opportunities to vaccinate.[13–16] Efforts to improve data systems should include making the data easily and widely accessible to stakeholders that may improve implementation of the 2010 National Vaccine Plan and future updates. In addition, emerging technologies such as two-dimensional (2-D) barcodes, which contain scanable information about the product identifier, lot number, and expiration date, improve (i) tracking of vaccination coverage and safety and (ii) the management of vaccine inventory and supply.

Ongoing NVAC discussions continue to focus on the opportunities to strengthen interoperability and data-exchange among patient EHRs, Immunization Information Systems (IISs), and different public health jurisdictions.[17] While a number of efforts at both the federal and non-federal levels include addressing barriers to interoperability and use of IISs,[18–21] NVAC notes that success will depend on continued efforts to characterize the technical, legal, and policy challenges to cross-jurisdictional data-exchange.[17] Previous NVAC recommendations support the implementation of policies and practices that can facilitate the uniform, reliable, secure exchange of immunization and health data, such as defining standardized data submission elements and developing template legal agreements and memoranda of understanding between jurisdictions.[17,22]

Health information technologies can help monitor vaccination coverage, vaccine effectiveness, and immunization safety.[23,24] Federal vaccine safety monitoring systems, such as the Post-licensure Rapid Immunization Safety Monitoring and Vaccine Safety Datalink, use patient information from EHRs to identify potential adverse events following immunization.[25,26] A 2014 NVAC report on *Reducing Patient and Provider Barriers to Maternal Immunizations* encourages federal partners to identify ways to optimize the use of EHR and IIS data for monitoring and surveilling vaccination coverage and vaccine safety for mother-infant pairs following the administration of recommended vaccines during pregnancy.[27]

Important opportunities exist to strengthen infectious disease surveillance using EHR and electronic laboratory reporting. Advances in diagnostic technologies continue to improve our understanding of pathogens, and the collection and integration of these data represent an important opportunity to better track diseases and the value of vaccines. Currently, most disease surveillance depends on passive reporting of reportable diseases by states. Surveillance through automated processes that extract information from EHRs and electronic laboratory reports provides more complete data on infectious

disease trends. For example, electronic surveillance of vaccine preventable diseases significantly improves monitoring of vaccine effectiveness and provides information about shifts in the prevalence of disease caused by vaccine-serotypes versus non-vaccine serotypes of pneumococcal disease.[28] For diseases such as those caused by respiratory syncytial virus (RSV), electronic surveillance data may provide better clarity on the disease burden among varying age groups and inform the design of clinical trials of new vaccines. Currently, the lack of standards for data submission across EHRs and electronic laboratory reporting systems remains a significant barrier to collecting automated data for nation-wide surveillance. Despite some progress, barriers continue to exist due to variation among states in their capabilities, the electronic systems used for disease surveillance, and the inability to integrate and share public health data.[29] Challenges also remain with respect to making the existing data easily and widely available.

Box 2 summarizes characteristics of near-term success, and it identifies challenges to achieving success opportunity area 1 (OA#1) and to fully realizing the opportunities afforded by the availability of integrated electronic data.

Box 2. NVAC Characteristics of OA#1 Near-term Success and Potential Challenges

Opportunity Area	Characteristics of Near-term Success in this OA	Challenges for Achieving that Success

OA#1 - Strengthen health information and surveillance systems to track, analyze and visualize disease, immunization coverage, and safety data, both domestically and globally.	• Interoperable IISs across all US states and territories • Bidirectional, real time exchange of data between all IISs and all EHRs used by vaccine providers in the US • End-to-end tracking of vaccines across all sectors utilizing standardized, interoperable information technology solutions • Automated disease surveillance at the local, state, and federal levels that incorporates real-time data from EHRs and electronic laboratory reports to provide case-based information on vaccine-preventable diseases, diseases with vaccines under development, and infectious diseases with vaccine development efforts under consideration, and easy and wide access to these data for broad use by providers, parents, health departments, and other stakeholders • Vaccine post-marketing surveillance in all countries	• Legal barriers to sharing IIS data among jurisdictions • Lack of EHR standardization to facilitate bidirectional data sharing • Funding for health information technologies, such as 2-D barcoding across the immunization enterprise • Lack of a universal commitment to data sharing and resources required to make data easily and widely accessible • Absence of electronic case-based surveillance systems for many diseases (domestically and globally) • Lack of vaccine safety surveillance in many countries outside of the US

Proposed Indicators for OA#1

The NVPO report[7] provides three domestic and one global existing indicators for this opportunity area. The NVAC recommends the same global indicator for this opportunity area as the NVPO report (Box 3).[7] The domestic indicators in the NVPO report[7] include: (i) The number of Meaningful Use adopters that opt to fulfill the electronic reporting to IIS requirements to obtain Meaningful Use certification, (ii) Percentage of adults aged >19 years who have one or more immunizations recorded in an IIS, and (iii) Increase the percentage of children aged <6 years whose immunization records are in a fully operational, population-based IIS tracked by the Office of the National Coordinator (ONC) and the Centers for Medicare & Medicaid Services (CMS). The NVAC suggests that these do not fully address the many complexities of this opportunity area. For example, the NVPO report[7] does not capture any indicators to mobilize additional efforts around the use of health information technologies to support comprehensive, standardized, real-time, electronic laboratory reporting on the incidence of vaccine-preventable diseases. Box 3 outlines indicators currently tracked by the ONC, CDC, and GVAP that the NVAC proposes will provide benchmarks of near-term success for this opportunity area.

Box 3. Proposed Indicators for Tracking Success – OA#1

Existing Indicator	Baseline	Target
Percent of office-based physicians electronically sharing patient information with any providers outside their organization (domestic)	ONC 38% (2015)	Increasing trend
Percent of healthcare providers electronically sharing patient information with their state IIS (e.g., a meaningful use requirement) (domestic)	ONC 73% of eligible hospitals in the U.S. reported vaccination to their local IIS (2014)	Increasing trend
Percent of laboratory reports received electronically annually for notifiable conditions (domestic)	CDC 67% (2014)	100%
Number of countries with case-based surveillance for vaccine-preventable diseases (e.g., invasive bacterial disease [IBD] and rotavirus) (global)	GVAP, SAGE 67% Member States IBD; 52% Member States rotavirus (2013)	75% of low and middle-income countries with hospital-based sentinel site surveillance for IBD and rotavirus

The NVAC also proposes the development of new domestic indicators that may further inform the planning of implementation activities in this opportunity area (Box 4).

Box 4. Indicators Proposed for Future Development – OA#1

Indicator Proposed for Future Development	As a Measure of
Number of operational memoranda of agreement (MOAs) between state and territorial IISs	Progress toward interoperability of IISs
Percent of providers utilizing 2-D barcodes to populate EHRs and IISs	More accurate data collection on immunization safety, efficacy, and coverage
Number/percent of case reports received electronically by local/state health departments	Capability of states to collect data for surveillance and reporting
Number of disease surveillance systems interoperable with corresponding IISs	Capability to link information about vaccination status to disease surveillance information

Additional Considerations for OA#1

A 2013 NVAC report on *Enhancing the work of the Department of Health and Human Services National Vaccine Program in Global Immunization* provides analyses highlighting remaining opportunities to strengthen vaccine-preventable disease surveillance efforts and pharmacovigilance at the global level.[10] Unfortunately, few countries currently maintain the surveillance or laboratory capabilities needed to

accurately measure the burden of vaccine-preventable diseases or the impact of vaccines on reducing morbidity and mortality in their populations.[10] Most countries lack the critical infrastructure to monitor, assess, and respond to vaccine safety signals.[10] Global surveillance activities outlined in the 2010 National Vaccine Plan play an important role in justifying the development and introduction of new and improved vaccines. The NVAC continues to strongly encourage efforts to integrate health information technologies that facilitate quality data collection domestically and globally to further strengthen immunization programs and vaccine pharmacovigilance.

OA#2 - Foster and facilitate efforts to strengthen confidence in vaccines and the immunization system to increase coverage rates across the lifespan

National data continue to show that vaccination coverage among children 19-35 months of age remains high and in general among American parents childhood immunization remains the social norm.[30] However, national discussion continues to grow about the attitudes and beliefs people hold and express regarding their confidence in the recommended vaccines and schedule. While many reasons may explain shifts in vaccine confidence, the success of implementing routine vaccine schedules and the resulting significant reductions in incidence continue to reduce the visibility of vaccine-preventable diseases. Unfortunately, even small increases in concerns about vaccination may result in decreasing vaccination rates, delays in receipt of immunizations, and the accumulation of populations of susceptible individuals within U.S. communities. Under-immunization—including intentionally forgoing vaccines—can lead to serious public health consequences. For example, a nation-wide measles outbreak in 2014-2015 that originated in California and involved a disproportionately high proportion of unvaccinated individuals (i.e., 49 of 110 (45%) unvaccinated, 47% unknown or undocumented vaccination status) led to measles cases in 7 U.S. states, Mexico, and Canada.[31] Measles outbreaks in the United States, continue to cause significant morbidity and lead to substantial costs for control.[32]

A 2015 NVAC report on *Assessing the State of Vaccine Confidence in the United States* examines the determinants of vaccine acceptance among parents and recommends a number of strategies to improve parental confidence in vaccines.[16] That report defines vaccine confidence as "*the trust that parents or health-care providers have (1) in the recommended immunizations, (2) in the provider(s) who administers vaccines, and (3) in the process that leads to vaccine licensure and the recommended vaccination schedule*."[16] The NVAC recognizes that vaccine acceptance represents a very complex issue

with nuances that may play out differently at the federal, state, and local levels. Additional research and evaluation activities will need to develop evidence-based interventions to increase vaccine confidence in diverse populations and for different vaccines and vaccine formulations.

In contrast to the growing body of evidence about confidence regarding childhood and adolescent vaccinations, less evidence exists related to adult confidence in vaccinations. Vaccination coverage in adults remains very low for all recommended vaccines.[33] A 2012 NVAC report on *A Pathway to Leadership for Adult Immunization* highlights the lack of a "coordinated public health infrastructure to support an adult immunization program" (i.e., no effort for adults exists comparable to the Section 317 Program and Vaccines for Children), and recommends the development of a National Adult Immunization Program.[34] The 2016 National Adult Immunization Plan[35] includes 4 goals: "(i) Strengthen the adult immunization infrastructure, (ii) Improve access to adult vaccines, (iii) Increase community demand for adult immunizations, and (iv) Foster innovation in adult vaccine development and vaccination-related technologies." The NVAC emphasizes the need to further improve adult immunization. Some studies document misperceptions about vaccine safety and the effectiveness and benefits of vaccination, such as for influenza vaccine,[36] but the role vaccine confidence plays in the uptake of adult vaccines generally remains unclear. Vaccine confidence also represents only one component of overall vaccine acceptance across the life course, and understanding the cumulative factors that lead to high vaccination coverage at all ages (e.g., access, awareness of recommendations, etc.) will require further investigation.[37]

Vaccine confidence and consumer and healthcare provider trust in the entities that develop, license, recommend, and monitor vaccines, and in the vaccines themselves, represent issues of global concern. The SAGE issued a report to help characterize vaccine confidence (including the context of vaccine hesitancy and the consequences of hesitancy attitudes and beliefs on vaccine uptake) in different settings.[38] Similar to the NVAC report on *Assessing the State of Vaccine Confidence in the United States*,[16] the SAGE recommendations called for the development of standardized, validated tools to help national immunization programs better understand factors that can lead to low vaccine confidence and low demand for immunization services. Box 5 summarizes characteristics of near-term success and challenges for achieving it for opportunity area 2 (OA#2).

Box 5. NVAC Characteristics of OA#2 Near-term Success and Potential Challenges

Opportunity Area	Characteristics of Near-term Success in this OA	Challenges for Achieving that Success
OA#2 - Foster and facilitate efforts to strengthen confidence in vaccines and the immunization system to increase coverage rates across the lifespan	• Improved immunization rates among all age groups • Reduced number of exemptions for vaccination in all states • Robust vaccine communication tools available for healthcare personnel and community advocates	• Introduction of new vaccines and increasing complexity of the immunization schedules presents challenges to providers to explain the vaccines and the schedule and to patients to understand changes • Lack of standardized immunization coverage data reporting and tracking for non-pediatric age groups • Continued under-vaccination of adults and adult skepticism about the need for immunizations across the lifespan • Need for consistent and reliable methods to communicate with the public about the importance of vaccines and other strategies to bolster vaccine confidence

Proposed Indicators for OA#2

Currently no validated methodologies exist for measuring and evaluating vaccine confidence.[16] Healthy People 2020 objective IID-9 (i.e., *Decrease the percentage of children in the United States who receive zero doses of recommended vaccines by age 19 to 35 months)*[39] tracks data on children who remain completely unvaccinated. The NVPO report includes this as its only indicator for this opportunity area.[7] Although this indicator does not reflect geographic variations or the factors that lead to unvaccinated children (e.g., state and local policies and practices, access issues, poverty), until more precise indicators exist, the NVAC recognizes that this indicator may provide indirect evidence about nation-wide trends in vaccine confidence (Box 6). In addition, the NVAC suggests using the number of states reporting kindergarten coverage data based on census as an indication that may similarly provide indirect information about the quality of data available to track trends in vaccine confidence.

At the international level, the GVAP identifies the need for indicators for vaccine confidence[8] to help benchmark progress toward the strategic objective that "individuals and communities understand the value of vaccines and demand immunization both as a right and a responsibility."[8] The NVAC notes the lack of standardized indicators and challenges faced by the GVAP in the development of appropriate indicators.[9] The NVAC includes the GVAP indicators on vaccine hesitancy in Box 6 while emphasizing the need to create a framework for better understanding vaccine confidence globally.

Box 6. Proposed Indicators for Tracking Success – OA#2

Existing Indicator	Baseline	Target
Decrease the percentage of children in the United States who receive 0 doses of recommended vaccines by age 19 to 35 months of age (domestic)	HP2020 0.8% (2012)	Target not set (informational)
Number of states reporting kindergarten coverage data based on census (domestic)	HP2020 58% (2014)	Increasing trend
Number and percentage of countries that responded to the question on the top three reasons for vaccine hesitancy (Indicator 1) in 2014 (global)	GVAP, SAGE 73% (2014)	Increasing trend
Percentage of countries that have assessed the level of hesitancy in vaccination at the national or subnational level in the last 5 years (global)	GVAP, SAGE 29% (2014)	Increasing trend

The success of this opportunity area depends on a better understanding of vaccine confidence at national and community levels, because attitudes and beliefs vary. The NVAC underscores the importance of developing indicators to better understand and more accurately assess vaccine confidence in the United States (Box 7). The 2015 NVAC report on *Assessing the State of Vaccine Confidence in the United States*[16] describe the characteristics of possible indicators for assessing vaccine confidence in the U.S.

Box 7. Indicators Proposed for Future Development – OA#2

Indicator Proposed for Future Development[a]	As a Measure of
Track state legislation on non-medical exemptions to determine number of states that offer non-medical exemptions and ease of obtaining such exemptions in each state	Policies that influence vaccine confidence
Development of a validated index, composed of a number of individual and social dimensions, to measure vaccine confidence and capable of (1) rapid, reliable, and valid surveillance of national vaccine confidence; (2) detection and identification of variations in vaccine confidence at the community level; and (3) diagnosis of the key dimensions that affect vaccine confidence	Validated measures to evaluate vaccination confidence-related to intervention strategies and determine best practices for all ages and providing information about differences between different vaccines
Development of measures and methods to analyze the mass-media environment and social media conversations about vaccine confidence	Identified topics of concern to parents, health-care providers, and members of the public

a – language adapted from the NVAC report *Assessing Vaccine Confidence in the United States*[16]

Additional Considerations for OA#2

Events like the 2014-2015 measles outbreak in California, which included a relatively high fraction of intentionally unvaccinated individuals,[31] raise issues about state policies on exemptions to school-entry laws. Discussions about this outbreak and the 2014-2015 exemption rates among kindergarteners in California, motivate the NVAC to suggest the potential use of personal belief exemption rates as an indicator for measuring vaccine confidence.[40] Data on the rate of non-medical exemptions to school-entry laws may help public health authorities to correlate pockets of unvaccinated individuals with the incidence of vaccine-preventable disease outbreaks.[41] However, states may not collect information about exemptions in a standardized way, which limits generalizability. For example, while an increasing number of states (i.e., 32/51, 62%) collect data using a census-based methods (e.g., kindergartners in all schools), some states continue to use a sample-based method (e.g., some selected schools), voluntary response (e.g., convenience reporting from schools), or a combination of methods.[42] In addition, some states may allow or may require an exemption if a child missed a single dose of vaccine, even for a child otherwise up-to-date on other vaccines,[42] and these differences create challenges for cross-state comparisons. Exemption rates do not necessarily provide a good indication of coverage, as parents may opt to file an exemption for convenience and then later go on to fully vaccinate their child. The enforcement of school-entry laws also differs substantially between and within states, and home-schooled children often remain outside of these laws, further complicating the interpretation of the data. The impact of home-schooled children remains unknown, but un- and under-vaccinated individuals may cluster and can contribute to outbreaks.[43] Non-medical exemptions may also reduce coverage without requiring caregiver education on the risks of children remaining unvaccinated.

Data on immunization exemptions can help to inform schools, parents, and public health programs about possible pockets of susceptible children. A number of entities track exemption legislation across jurisdictions, and the NVAC recognizes that keeping apprised of this information could inform the development and testing of strategies to improve vaccine confidence. The NVAC strongly encourages future activities to support the standardized collection of non-medical exemption rates across states to help improve the utility of these data and highlights the important role that IISs may play in these efforts.

OA#3 - Eliminate financial and systems barriers for providers and consumers to facilitate access to routinely recommended vaccines

The NVAC appreciates the need to improve vaccination coverage across the lifespan by addressing access and financing issues that prevent patients from receiving recommended vaccines. Access to immunization services represents a multifaceted issue impacting vaccine coverage at both the domestic and global levels. Factors affecting access may include, for example, convenient access to immunization providers and the healthcare system, an adequate and available supply of vaccines, and freedom from financial barriers to vaccines and immunization services. Recent evidence suggests that disparities in immunization remain an issue, with children living below the poverty level reporting lower vaccination coverage.[44] Despite the 1994 Vaccines for Children mandate, which makes recommended, routine childhood immunizations available at no cost to children who might not otherwise be vaccinated because of inability to pay, the U.S. still needs to address health disparities and correct inequities in immunizations.

The Affordable Care Act (ACA) expands health insurance coverage and access to preventive services, including immunization, and it provides insurance to more than an estimated 16.4 million previously uninsured people in the United States as of August 2016.[45] While the ACA represents an important milestone for adult immunization in the U.S., it does not completely eliminate financial barriers to immunization for consumers, and as of early 2017, its future remains uncertain. Expanded access to immunizations should lead to increased demand by reducing financial barriers to vaccine providers, and it also creates the need for a more diverse array of provider types who can offer convenient immunization services.[46]

Provider ability and willingness to offer vaccines and immunization services lead to higher vaccination coverage. Multiple studies show patients are much more likely to receive vaccinations if their providers offer them at the time of their healthcare visit.[33,47,48] However, offering immunization services in the office requires up-front investments by providers, including the purchase of vaccine products and equipment for proper storage and handling, and the cost of managing vaccine inventories, counseling, and recording and reporting (e.g., to the IIS). These potentially significant costs factor into the decisions by providers to offer vaccines in the form of concerns about fair and adequate payment from public and private payers for the administration of immunization services.[46] Several NVAC reports document an urgent need to identify and improve upon current processes related to billing, coding, and payment for immunization services (including vaccine counseling and administration).[27,34,49] Changing models of

compensation continue to affect immunization rates and incentives for different types of vaccine providers. A 2009 NVAC report on *Financing Vaccination of Children and Adolescents* recommends strategies to address the financial pressures on pediatric and adolescent vaccination practices.[49] However, the recommendations do not cover challenges of providing immunizations to adult populations. The NVAC appreciates the need for additional work to quantify the financial impact of issues that affect providers' willingness to offer vaccines in their offices.

Box 8 summarizes characteristics of near-term success and challenges for achieving success for opportunity area 3 (OA#3).

Box 8. NVAC Characteristics of OA#3 Near-term Success and Potential Challenges

Opportunity Area	Characteristics of Near-term Success	Challenges for Achieving that Success
OA#3 - Eliminate financial and systems barriers for providers and consumers to facilitate access to routinely recommended vaccines	• Increased vaccination rates and increased offering of vaccines by providers • Increased number of providers that stock and administer vaccines • Better understanding of providers choosing to not offer vaccine services in their practices due to negative perceptions of business opportunities • Decrease in discrepancies in vaccination coverage by socioeconomic status and in rural areas	• Lack of standardized immunization coverage data reporting and tracking for non-pediatric age groups (see also OA#2) • Lack of granular data (e.g., census track level) for immunization coverage to identify local health care access or other population disparities • Mismatch in Medicare B/D payment for vaccines • Reimbursement for providers (private vs public payers) – specifically Medicaid reimbursements for vaccines administered through the Vaccines for Children program, payment methods, bundling, capitation • Grandfathered plans – not required to adhere to coverage of preventive care benefits (but going away) • Alternate vaccinators (not in-network but part of the immunization neighborhood) – concerns from pediatricians regarding medical home for children • Inventory and acquisition costs of newer, more expensive vaccines

Proposed Indicators for OA#3

The NVAC agrees with the indicators for this opportunity area in the NVPO report[7] and includes the same indicators from the American Pharmacists Association (APhA), CDC, CMS, GVAP and HP2020 for both domestic and global indicators in Box 9. In addition, the NVAC included a GVAP indicator that tracks vaccination coverage targets.

Box 9. Proposed Indicators for Tracking Success – OA#3

Indicator	Baseline	Target
Percentage of surveyed primary care providers who stock vaccines routinely recommended for adults (domestic)	CDC 20% Internists and 31% Family Practices (2012)	60%
Percentage of state and territories that allow pharmacists to administer all routinely recommended vaccines for adults > 19 without a patient-specific prescription (domestic)	APhA 85% (2013)	100%
Percentage of state Medicaid programs that provide coverage of all Advisory Committee on Immunization Practices (ACIP)/CDC-recommended vaccinations for adults and prohibit cost-sharing (domestic)	CMS 20% (2012)	100%
Increase the percentage of adults who are vaccinated against zoster (shingles) (domestic)	HP2020, CDC 6.7% (2008)	30%
Increase coverage with the recommended number of doses of HPV for females by 13 through 15 years of age (domestic)	HP2020, CDC 28.1% (2012)	80%
Percentage of pregnant women who report receiving influenza immunization during pregnancy (domestic)	HP2020, CDC 52% (2013)	Not defined
Number of WHO regions achieving measles elimination by 2020 (global)	GVAP, SAGE 0/5 WHO regions (2010)	6 WHO regions
Dropout rates between the first and third dose of diphtheria, pertussis, and tetanus (DPT), globally (global)	GVAP, SAGE 18.6% Member States w/ dropout rates ≥10% (2012)	decreasing trend
Number of countries reaching vaccination coverage targets through routine services (global)	GVAP, SAGE 129 countries vaccinated at least 90% of their children with DTP (2014)	By 2020, reach coverage of 90% national and 80% in every district for all recommended vaccines in national programs

The NVAC proposes the development of two additional indicators for this opportunity area (Box 10).

Box 10. Indicators Proposed for Future Development – OA#3

Indicator Proposed for Future Development	As a Measure of

Percentage of providers not providing immunization services for their patients (year on year trends for subgroups of provider types (i.e., pediatricians, obstetricians and gynecologists	Continuing barriers to providers to offer immunization services in their practices
Number of countries that eliminated rubella	Global measure of access, equity, and strength of routine immunization systems

Additional Considerations for OA#3

The NVAC suggests that in the context of the complex and dynamic payer environment, federal and state payers should increase their efforts to better align payment policies with public health priorities. Vaccination provides a well-recognized, cost-effective, and often cost-saving prevention strategy that yields significant benefits for pediatric and adolescent populations domestically[2] and globally,[3] and could prevent significant costs associated with vaccine-preventable diseases in adults.[50] Therefore, public payers should support the administration of all recommended vaccines for routine use for all ages by working to minimize the financial burden to patients and providers. At the global level, the Gavi Alliance and others should continue to support the expansion of immunization adoption and increased coverage.

The NVAC also supports more coordination of healthcare and community immunizer activities to ensure that patients receive recommended vaccines and to improve access to recommended vaccines. For example, increasing coverage rates for human papilloma virus (HPV) vaccine and expanding adult immunization coverage motivates greater consideration of opportunities in the "immunization neighborhood".[51] The NVAC continues to call for strategies to understand and overcome the barriers to receiving recommended vaccines from non-physician vaccine providers (e.g., pharmacists) and at non-traditional locations (e.g., workplace, schools).[14,15,27] The NVAC recognizes the need to monitor how changing models of compensation impact the immunization neighborhood. The NVAC further emphasizes that some communities, especially rural ones that lack convenient and affordable access to immunization services, continue to experience missed opportunities for immunization. State-to-state variability in immunization policies and practices further increases complexity in the current system.

OA#4 - Strengthen the science base for the development and licensure of vaccines

The world lacks vaccines against many infectious diseases that impact public health, both in the U.S. and globally.[52] Unfortunately, developing vaccines for poorly understood pathogens requires additional

information about both the pathogen and the host immune response to optimally elicit a directed, protective response against specific antigens.[53,54] This opportunity area aims at the development and licensure of new and improved vaccines to meet ongoing, emerging, and/or unmet public health needs. Scientific needs in this area include, for example, a better understanding of pathogen biology and host immune response, a better grasp of why vaccine adverse events occur, and identification of the correlates and surrogates of immune protection and other factors that can predict vaccine effectiveness and duration of protection among diverse populations.[7] In addition to recognizing the importance of improving our understanding of immune responses to vaccines and correlates of protection, the NVAC emphasizes the need to identify appropriate mechanisms that will encourage data sharing among investigators related to optimizing the science base.

The NVAC recognizes the importance of strengthening the science base around vaccinology and the human immune response to vaccines (and how induced immunity compares to natural infection) and how improved understanding could help to foster innovation in vaccines far beyond the timeline of the National Vaccine Plan.[55] Greater scientific knowledge about the immune response and surrogates of immune protection may aid in vaccine development by helping to more rapidly identify promising candidate vaccines. Greater knowledge may also provide a possible pathway to licensure in the context of limited feasibility of large-scale efficacy trials in some situations. For example, the unpredictable disease burden from year to year of pertussis makes it difficult to identify study populations for testing a new pertussis vaccine for use in the U.S., and emerging infectious diseases like Ebola spread unpredictably such that testing vaccines may require innovative strategies.[56] The NVAC highlights the importance of supporting translational research and its application to the development of vaccines for use in special populations such as pregnant women[57] and of improving knowledge of immune responses in the elderly. For this opportunity area, the NVAC defines success as making scientific breakthroughs that result in vaccine candidates for pathogens with historically unsuccessful development pathways, such as human immunodeficiency virus (HIV), tuberculosis (TB), malaria, and several priority antibiotic-resistant pathogens.

Box 11 summarizes characteristics of near-term success and challenges for achieving success for opportunity area 4 (OA#4).

Box 11. NVAC Characteristics of OA#4 Near-term Success and Potential Challenges

Opportunity Area	Characteristics of Near-term Success in this OA	Challenges for Achieving that Success
OA#4 - Strengthen the science base for the development and licensure of vaccines	• Ability to address more challenging disease targets with better understanding of natural immunity and correlates of protection • Development of vaccines for special subgroups (pregnant women, the elderly) • Clinical development for new vaccines moves more quickly through the development process • Full support of collaborative efforts and partnerships that produce high quality science and directly inform vaccine development and the overall understanding of human vaccinology • Increased use of new laboratory and analytical tools for characterizing pathogens	• Better understanding of waning immunity and strategies to address duration of protection (e.g., pertussis-containing vaccines) • Difficulties associated with enrolling pregnant women in studies[57] • The increasing cost and logistical challenges of conducting clinical trials and efficacy studies • Overcoming poorer T cell induction by vaccines in infants to address better boost and persistence of antibodies following booster doses in older children and adolescents

Additional Considerations for OA#4

New technologies continue to increase our knowledge and understanding of immune responses and correlates/surrogates of protection. Increasing the scientific knowledge base involves filling crucial knowledge gaps, harnessing the available data, and knowing how to best use them. The NVAC encourages the support of (i) collaborative efforts and partnerships to optimize the use of existing data to inform vaccine science and further vaccine development efforts and (ii) meetings that review experience and catalyze efforts to identify and address gaps. The NVAC recognizes the importance of improving knowledge about the correlates of protection for vaccine development and suggests the development of a future indicator to track the availability of useful immunological correlates of protection to support future updates to the National Vaccine Plan. Additionally, as vaccine science evolves, all stakeholders will need to incorporate new knowledge into curricula in a timely fashion to ensure that healthcare professionals remain on the forefront of immunization knowledge.

OA#5 - Facilitate vaccine development

Continuing unmet public health needs in the U.S. and globally motivate the development of new or improved vaccines (e.g., more effective, safer, higher-yield, etc.) and delivery strategies to support

immunization as a primary prevention strategy. The NVAC recognizes the need to better understand the drivers of vaccine innovation and development and how to best support them. Barriers to vaccine development may include the lack of mechanisms to incentivize or support higher-risk vaccine research and investments by biotechnology and pharmaceutical companies.

The NVPO report[7] notes the challenges associated with the lack of convergence of regulatory submission data requirements internationally, the need for funding and preparedness models for rapidly developing vaccines to address emerging diseases, the insufficient infrastructure to support clinical trials in low-resource settings, and inadequate support for crossing the "valley of death" between preclinical and clinical development. The NVAC emphasizes the importance of considering the entire vaccine development system in discussions related to providing incentives for vaccine development. For example, discussions around identifying barriers to vaccine development often center on mechanisms to incentivize innovation and vaccine development for larger pharmaceutical companies. However, different considerations may arise when discussing how to support translational research to bring vaccines to development from the perspective of smaller biotech companies. Financial incentives from governmental entities to minimize or share risk remain very important for supporting the success of some companies, while other companies may care more about regulatory certainty, regulatory consistency, and/or a ready market that would drive final development.

The NVAC further recognizes the importance of incentives that reward companies for the development of products with incremental, but significant, improvements over existing products (e.g., improved effectiveness, products for a special population such as high-dose influenza vaccine for the elderly). New technologies, including adjuvants, vaccine vial monitors, and novel delivery strategies, offer innovation opportunities that could improve the effectiveness of existing vaccines, lower vaccine production costs, decrease wastage, and make vaccines easier to deliver and administer. However, the lack of recognition or distinction for these products as incrementally improved vaccines makes this type of product development difficult for companies to justify, given little or no additional return on investment for providing these products. Understanding the impact of this barrier on vaccine development warrants additional characterization, the NVAC suggests retrospective case studies or prospective studies to follow new product launches and the uptake of incremental products.

In addition to creating incentives to develop vaccines for established diseases that lack an effective vaccine (e.g., RSV, HIV, TB), the 2014-2015 Ebola outbreak and the 2016 Zika outbreak further underscore the importance of the robustness of the vaccine development pipeline in the U.S. and international readiness levels to address emerging threats. In May 2016, the WHO released a *R&D Blueprint for Action to Prevent Epidemics* to provide technical guidance and coordination and to advocate for additional global resources to provide the necessary medical countermeasures to respond to and mitigate public health emergencies caused by emerging pathogens.[58] This Blueprint focuses on three main approaches: 1) improving coordination and fostering an enabling environment; 2) accelerating research and development processes; and 3) developing new norms and standards tailored to the epidemic context.[58] Activities include strengthening policies, partnerships, and capabilities both before and during an epidemic to minimize lives lost and economic disruptions due to infectious disease outbreaks.[58] The NVAC encourages federal agencies to continue working with the broader global community to support a preparedness research and development plan that includes platform technologies or other strategies that will help to minimize the barriers and the time needed for the development and delivery of vaccine products against emerging pathogens. Lessons learned from Ebola and Zika medical countermeasure response efforts should inform the implementation of the WHO R&D Blueprint[58] to better understand the capabilities and infrastructure needed to respond to future emerging pathogens.

The NVAC also appreciates the need to further explore the impact of vaccine pricing on vaccine manufacturing and supply. Vaccine development requires significant resource investments, and manufacturers must often choose between continuing vaccine development or focusing on products with a more certain return on investment.[52] In addition, newer vaccines may require complex manufacturing techniques that can impact production capacity and supply.[59] Manufacturers often build production facilities dedicated to the production of a single vaccine product to meet requirements for vaccine quality control and assurance, but this necessitates additional upfront costs that the producer must justify based on a reasonable expectation of multiple years of high vaccine demand. Lower vaccine prices impact investments in vaccine manufacturing and result in higher probabilities of vaccine shortages due to manufacturing problems.[60] The NVAC suggests that the contribution of these factors to vaccine development barriers warrants further investigation.

Other issues such as country-level differences in regulatory requirements for the testing, licensure, manufacturing, and distribution of vaccine products, while common across the development pipeline, may impact stakeholders differently. While National Regulatory Authorities (NRAs) must consider national needs and comply with applicable laws and regulations pertaining to vaccine development and evaluation, global efforts to converge regulatory guidance and reviews among different NRAs may streamline the development of vaccines and thus may facilitate broader and faster introduction of vaccines globally. Box 12 summarizes characteristics of near-term success and challenges for achieving success for opportunity area 5 (OA#5).

Box 12. NVAC Characteristics of OA#5 Near-term Success and Potential Challenges

Opportunity Area	Characteristics of Near-term Success in this OA	Challenges for Achieving that Success
OA#5- Facilitate vaccine development.	• Performance of a gap analysis for priority diseases to ensure enough vaccine candidates in the pipeline to lead to licensed vaccines • New products addressing incremental improvements for priority targets receive support to encourage further incremental development • Emerging pathogen threats quickly addressed by vaccination before outbreak ends • Facilitate global regulatory convergence, where feasible	• Building and maintaining a robust pipeline of vaccine candidates • Market or other incentives need to support the continued development of incremental improvement of existing vaccines • Identifying emerging pathogen threats and populations at-risk early enough to prepare vaccine candidates for proactive outbreak response • Identify opportunities for regulatory convergence among NRAs

Proposed Indicators for OA#4 and OA#5 (Combined)

The NVPO report[7] combines the indicators for opportunity areas 4 and 5 because "they speak to different challenges for the same issue: vaccine development." Regarding OA#4 (strengthening the science base for the development and licensure of vaccines), the NVAC recognizes that indicators to benchmark scientific progress remain very difficult to define and may not provide good information about success. Adequate, sustained funding levels represent a necessary but not sufficient requirement for attracting new talent, new ideas, and new innovations. Furthermore, the types of scientific questions that will lead to the development of new and improved vaccines represent "high-risk/high-reward" projects. The NVAC recognizes that tracking the total amount of funding towards specific scientific questions may not always translate into a direct path for the development of new vaccine candidates. For example, new evidence highlights that vaccine components in acellular versus whole-

cell vaccines may contribute differently to immune response pathways,[62,63] but uncertainty remains about how to best use this information to aid in the development of improved vaccine candidates.[64] The NVAC notes the general unpredictability of steps forward in scientific knowledge and how they translate into returns on investment. Similarly, the NVAC does not expect that indicators based on the number of peer-reviewed journal articles on vaccine science would necessarily provide an accurate indicator of scientific advances that could lead to new vaccine development.

The NVPO report[7] provides 3 indicators for OA#4 and #5 that focus on later stage vaccine development: "(i) Average vaccine development timeline from the preclinical phase to regulatory submission (domestic and global), (ii) Number of vaccines in phase I clinical trials for diseases for which no vaccines are currently on the market. The analysis will include the following infectious diseases: influenza (development of universal influenza vaccines), HIV/AIDS, malaria and tuberculosis, and (iii) Licensure and launch of at least one platform delivery technology or the number of vaccine delivery technologies (devices and equipment) that have received WHO prequalification against the 2010 baseline (global)." Unfortunately, the NVPO report[7] could not provide baseline values for the first two of these proposed indicators, which the NVAC views as not sufficiently established to represent current validated indicators. The NVAC proposes four global indicators developed by the GVAP[9] in Box 13, including one included in the NVPO report.[7]

Box 13. Proposed Indicators for Tracking Success – OA#4 and OA#5

Indicator	Baseline	Target
Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases (global)	GVAP, SAGE Not applicable (2015)	Progress towards licensure/launch of one or more such vaccines by 2020
Licensure and launch of at least one platform delivery technology (global)	GVAP, SAGE Not applicable (2015)	1 or more vaccines by 2020
Number of vaccines that have either been re-licensed or licensed for use in a controlled-temperature chain at temperatures above the traditional 2–8°C range (global)	GVAP, SAGE Not available	Increasing trend
Immunization programmes have sustainable access to predictable funding, high-quality supply and innovative technologies: number of vaccine delivery technologies (devices and equipment) that have received who prequalification (global)	GVAP, SAGE 284 products (2015)	Increasing trend

The NVAC proposes the development of a domestic indicator for OA#4 to improve tracking of vaccine research and development (R&D) funding, vaccine delivery and administration, vaccine thermostability and U.S. technical readiness to respond to emerging infectious disease threats (Box 14). The NVAC recommends that the NVPO begin a process to define and develop a validated indicator for estimating vaccine R&D funding across all of the U.S. government agencies. Longer-term efforts may then build on this to include vaccine R&D funding from non-U.S. government funding sources (e.g., pharmaceutical companies, private foundations). The NVAC also proposes to expand tracking of clinical-stage vaccines included in the NVPO report[7] (indicator ii above) to clinical phases beyond Phase 1 and to include a broader range of priority pathogens than the four cited in NVPO indicator. The WHO recently developed a vaccine pipeline tracker limited to clinical-stage vaccines aimed at protecting against HIV, malaria, tuberculosis, RSV, and enteric pathogens (e.g., enterotoxigenic *E. coli*, *Shigella* and norovirus).[61] The WHO intends to update the pipeline tracker every 6 months and expand beyond these vaccine targets. While the WHO pipeline tracker represents a tool that may work for tracking the progress of vaccine candidates against these targets, the U.S. could develop a similar clinical-stage pipeline tracker to include additional targets of national interest (Box 14). The NVAC recognizes, however, that developing an appropriate domestic indicator will likely require additional resources to define the specific inclusion and exclusion criteria, convene stakeholders to ensure consistent reporting and use of data, and extract and synthesize data into appropriate categories (e.g., by pathogen or disease category, by stage of clinical development, etc.). In defining and validating the indicator, the NVPO may benefit from review of inclusion and exclusion criteria used for the WHO pipeline tracker and/or by commercial services that track product development (e.g., PharmaProjects, BioMedTracker). Pipeline tracking should provide valuable information about the number of candidates entering clinical development and pressure points in the pipeline, at least in part by providing information about attrition rates at particular phases in development, but this depends on the data collection process.

Box 14. Indicators Proposed for Future Development – OA#4 and OA#5

Indicator Proposed for Future Development	As a Measure of
U.S. government annual spending on vaccine research and development	U.S. government investments in vaccine research and development

A mechanism to track the vaccine development pipeline that includes a specific number of target, priority pathogens	The robustness of the clinical pipeline to support eventual approval of vaccines against priority pathogens

Additional Considerations for OA#5

Although vaccine innovation discussions often focus on the development of new and improved vaccines (both for existing disease candidates and emerging pathogens), investments in innovation should include new platforms for the efficient presentation of antigens (e.g., new vectors, nanoparticle technologies). The GVAP indicator to support the development of vaccine delivery technologies includes improvements to cold-chain equipment, vaccine thermostability, and delivery mechanisms (e.g., nasal-administration, vaccine patch technology). The NVAC recognizes innovation in these areas as critically important to facilitate access and efficient delivery of safe and effective vaccines.

Tracking the clinical-stage pipeline of vaccine candidates for some disease targets can occur with limited on-going efforts due to the relatively slow pace of vaccine development and the availability of pipeline tracking data. However, establishing a consensus on a limited list of "priority" vaccine targets to track remains challenging. While the NVPO report[7] supports the development of the Strategic Multi-Attribute Ranking Tool for Vaccines[65] (SMART-Vaccines) to facilitate decision-making around prioritizing vaccine candidates, a formal list of priority targets endorsed across the federal government does not exist. In the absence of such a list, the NVAC proposes using existing prioritization lists to inform the selection of vaccine targets and to measure the robustness and diversity of the vaccine development pipeline. These existing lists may help to determine a finite number of targets that would satisfy the needs of several public health initiatives, both globally and domestically.

- The WHO Product Development for Vaccines Advisory Committee recently published recommendations focusing on a list of 24 pathogens of high public health importance for which effective licensed vaccines do not currently exist.[66] The pathogens included in this analysis represent targets with candidates previously identified as priority development targets by the GVAP[8] and others with the potential to substantially impact disease burden in low and middle-income countries. Future activities by this Committee will include focusing on targets that represent a significant unmet public health need and for which vaccines will probably show clinical proof of concept data within the next three years.[66]

- The 2013 CDC report on *Antibiotic Resistant Threats in the United States* describes antibiotic resistance as one of the most significant threats to public health.[67] While this report does not focus on vaccines or vaccine development, it categorizes antibiotic-resistant pathogens by threat level (i.e., urgent, serious, concerning) according to factors such as clinical impact, economic impact, incidence, 10-year projection of incidence, transmissibility, availability of effective antibiotics, and barriers to prevention. Antibiotic-resistant bacteria classified as urgent threats represent immediate public health threats that require urgent and aggressive action.[67]

- The National Institute of Allergy and Infectious Diseases (NIAID) provides a list of emerging infectious disease pathogens considered priority pathogens due to their recent emergence and/or their ability to rapidly spread in incidence or geographic area.[68] Pathogens on this list include emerging infectious disease threats as well as pathogens potentially used as bioweapons. Their categorization depends on their threat to public health (and to national health security) and their ability to disseminate widely to the public.

Table 1 shows the overlap of pathogens from each of the different prioritization lists constructed based on the following inclusion criteria:

1) All pathogens listed by the WHO Product Development for Vaccine Advisory Committee;
2) Priority pathogens in the CDC 2013 report on *Antibiotic Resistant Threats in the United States*, especially pathogens classified as 'urgent threats'
3) Priority pathogens in NIAID list of priority emerging infectious disease
4) Pathogens already included in WHO Pipeline tracking tool

These potential target vaccine candidates represent just one example of how the USG agencies may approach developing a list of target pathogens for the purpose of tracking candidates in the vaccine development pipeline.

Table 1. Compiled List of Clinical-stage Priority Vaccine Candidates to Track

Pathogen	WHO List[a]	CDC AMR List[b]	NIAID List[c]	WHO Pipeline Tracking[d]
Campylobacter jejuni	X	X	X	
Carbapenem-resistant Enterobacteriaceae (CRE)		X (URGENT)	X	
Chikungunya virus	X		X	X

Clostridium difficile		X (URGENT)	X	
Dengue	X		X	X
Enterotoxigenic Escherichia coli	X		X	X
Enterovirus 71 (EV71)	X		X	
Group B Streptococcus (GBS)	X	X		
Herpes Simplex Virus	X		X	
HIV-1	X		X	X
Malaria	X			X
MERS-CoV	X		X	X
Neisseria gonorrhoeae		X (URGENT)		
Nipah virus	X		X	X
Non-typhoidal Salmonella Disease	X	X	X	
Norovirus	X			X
Respiratory Syncytial Virus (RSV)	X			X
Rift Valley Fever virus			X	X
Shigella	X	X	X	X
Staphylococcus aureus	X	X	X	
Streptococcus pneumonia	X	X		
Tuberculosis	X	X	X	X
Universal influenza vaccine	X		X	
Ebola virus			X	
Zika virus				X

a - WHO Product Development for Vaccines Advisory Committee Target List[66]
b - CDC Antibiotic Resistance Threats Report, 2013[67]
c - NIAID Emerging Infectious Diseases/Pathogens[68]
d - WHO Pipeline Tracker[61]

While the priorities identified in Table 1 provide some guidance, the NVAC believes that further efforts should seek to develop tools and strategies to prioritize USG investments in innovation for (i) vaccines for established pathogens with no vaccines, (ii) vaccines for emerging pathogens, and (iii) improvements in existing vaccines. The indicators should also consider investments in vaccine delivery technologies. The NVPO plays an important role in convening stakeholders, and NVAC encourages further efforts to support vaccine development prioritization decisions.

Conclusion and Recommendations

For the past six years, the 2010-2020 National Vaccine Plan provided overarching strategic direction for a wide range of stakeholders collectively involved in the immunization enterprise, both in the U.S. and internationally. In this Mid-course Review, the NVAC carefully evaluated opportunity areas and defined priorities for strengthening our vaccine and immunization system based on progress made over the past half-decade and the changing immunization environment. The NVAC overall supports the NVPO report findings[5] and its focus on the five priority opportunity areas but recommends that with the availability of additional funding or other resources, federal partners should continue to support the 2010 National Vaccine Plan objectives not included in the five opportunity areas described in this report. The NVAC also makes several additional recommendations.

The NVAC recommends giving strong consideration to previous NVAC reports to highlight recommendations for implementing the priorities outlined in the NVPO report,[5] particularly the 2015 NVAC report on *Assessing the State of Vaccine Confidence in the United States.*[16] The NVAC also recommends that its findings should inform the NVPO as the NVPO develops the 2020 National Vaccine Plan. While many of the activities described for these five opportunity areas lay the groundwork for improving our national and international immunization infrastructure, the NVAC suggests that real advances in these areas will take both near-term and longer term strategies and resources to realize the full potential of these efforts. These strategies and resources must also be assessed within the context of new and existing population health care access disparities.

Although the 2010-2020 National Vaccine Plan focuses on domestic priorities, Goal 5 seeks to "increase global prevention of death and disease through safe and effective vaccination." The NVAC strongly supports the U.S. commitment to global immunization efforts and acknowledges that strengthening immunization systems throughout the world will improve access to safe and effective vaccines and ultimately protect the U.S. population from travel-related exposure and importation of vaccine-preventable diseases. For this reason, the NVAC recommends that the ASH continue to support and integrate global immunization efforts into the five opportunity areas highlighted in this review.

In the process of developing criteria for success within each opportunity area, the NVAC noted that some of the existing indicators lacked the detail, specificity, and/or flexibility to adequately measure progress or track emerging issues. In these cases, the NVAC recommends the development of other more appropriate indicators to better evaluate implementation of the National Vaccine Plan. While the

NVAC appreciates that development of these new indicators lies beyond the scope, timeline, and resources of its review and the next few years, the NVAC urges the ASH to consider prioritizing the development of these new indicators in preparation for the next update of the National Vaccine Plan in 2020.

Finally, the NVAC recommends that the ASH take into account the additional considerations outlined in this report when informing decisions regarding resources and activities to fulfill the goals and objectives in the current National Vaccine Plan and to support the development of priorities for the next one. The confluence of emerging vaccine science and increasingly sophisticated data systems creates unprecedented opportunities for real-time disease surveillance and effective control of an ever-expanding portfolio of vaccine-preventable diseases. At the same time, we face growing challenges to vaccine access and confidence, both in the U.S. and abroad. Overcoming these challenges and building efficient systems for the development and delivery of new or improved vaccines must receive the highest public health priority. The NVAC hopes that this document will serve as a useful tool in refining our collective strategies for shaping the future of the U.S. immunization enterprise, both domestic and global.

In summary, the NVAC recommends the following:

- The ASH should charge the NVPO, in coordination with relevant departments and agencies, to adopt existing indicators (e.g., Healthy People 2020 indicators) to track progress on the National Vaccine Plan goals and to prepare an annual report to the ASH and the NVAC on progress.
- The ASH should charge the NVPO, in coordination with departments and agencies, to develop and validate new indicators within each of the 5 opportunity areas to ensure improved tracking of goals. The new indicators should include one that will track and report on U.S. government annual financial investments in vaccine innovation that support the development of (i) vaccines for established pathogens that have no vaccines, (ii) vaccines for emerging pathogens, and (iii) improvements in existing vaccines. The new indicators should also consider investments in vaccine delivery technologies.
- The ASH should continue to strongly support U.S. contributions to global immunization efforts and the integration of global immunization efforts into the opportunity areas as appropriate.

- The NVPO should continue to implement the recommendations from previous NVAC reports, such as the 2015 NVAC report on *Assessing the State of Vaccine Confidence in the United States*. By doing so, the NVPO can highlight NVAC recommendations related to implementing the priorities outlined in the NVPO 2010 Mid-course Review. The NVPO should use the framework defined in this report to make further advancements under the existing 2010 National Vaccine Plan for both domestic and global immunization outcomes.
- The ASH should charge the NVPO to develop the 2020 National Vaccine Plan, which should incorporate the findings in this report, and consider the impact of health care disparities on implementation and achievement of the objectives of the 2020 Plan.
- The ASH should charge the NVPO, in coordination with other relevant departments and agencies, to begin developing strategies to (i) identify priorities for U.S. government investments in vaccine-related innovations and (ii) overcome barriers that inhibit innovation.

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