

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

February 2017

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Executive Summary

The Assistant Secretary for Health (ASH) asked the National Vaccine Advisory Committee (NVAC) to conduct an independent mid-course review to evaluate the status of the National Vaccine Plan following and considering the findings of a separate mid-course review commissioned by the National Vaccine Program Office (NVPO). In March 2016, the NVAC formed a Mid-course Review Working Group to evaluate the status of progress on the goals of the National Vaccine Plan and develop recommendations to the ASH. The NVAC supports the NVPO Mid-course Review findings and its focus on the top 5 priority opportunity areas identified in its review to advance 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 routinely recommended vaccines; iv) Strengthen the science base for the development and licensure of vaccines; and v) Facilitate vaccine development. The NVAC similarly focused on these 5 opportunity areas, but also recommends that if additional funding or other resources become available, the ASH and other federal partners should continue to support the 2010 National Vaccine Plan objectives not included in the five opportunity areas described in this report, specifically to: 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.

This report outlines the indicators that the NVAC identified would constitute near-term success for each opportunity area, metrics to measure this success, and the challenges that could limit success. Within each opportunity area, the indicators would monitor progress between the baseline and target goal. However, the NVAC also recognized the need for additional metrics that would provide more appropriate measures of success for each indicator, and this report recommends the development of future metrics in some areas to improve tracking and analysis. The NVAC particularly highlighted the importance of improved tracking of vaccine innovation efforts.

The NVAC recommends the following:

- The ASH should charge the NVPO in coordination with relevant departments and agencies with the adoption of the existing metrics (e.g., Healthy People 2020 metrics) to track progress on the National Vaccine Plan goals and 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 metrics within each of the opportunity areas to ensure improved measurements for future use, including a metric to track and report on U.S. government annual financial investments in vaccine innovation that would support shared understanding of current investments in the development of (i) vaccines for established pathogens with no vaccines, (ii) vaccines for emerging pathogens, and (iii) improvements in existing vaccines. The metrics 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, to 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 that incorporates considerations of the findings from this report.
- The ASH should charge the NVPO in coordination with other relevant departments and agencies to begin the process of developing strategies to (i) prioritize U.S. government (USG) investments in vaccine-related innovations and (ii) identify and make recommendations to overcome barriers that inhibit innovation.

Introduction

Public health represents a collaboration of multiple sectors of society working together to prevent disease and promote health. These efforts include the tremendous impacts of the U.S. vaccine and immunization system, which represents one of the most significant public health achievements in the 20th century. Estimates suggest 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 trillion¹.

The Public Health Service Act §300aa–et. seq. created the National Vaccine Program as a cross-departmental effort to integrate the numerous federal agencies and offices, who work together and with non-federal stakeholders on numerous efforts related to vaccine development, production, and delivery². In addition to the creation of the National Vaccine Program, the legislation called 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”².

The National Vaccine Plan provides strategic direction for all U.S. vaccine and immunization related activities to create a robust and coordinated system to improve the health of Americans by achieving optimal prevention of infectious diseases through vaccination³. The 2010-2020 National Vaccine Plan represents a detailed 10-year roadmap to unify and strengthen all aspects of the U.S. vaccine and immunization enterprise through five over-arching goals, which include to: 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 strategies³.

The National Vaccine Implementation Plan, released in Spring 2012, outlined federal activities conducted in support of the National Vaccine Plan priorities⁴. However, to inherently build in the flexibility to adapt to changes in technologies, healthcare delivery models, and previously unidentified or

unpredicted needs to strengthen the National Vaccine Program, the National Vaccine Implementation Plan only included activities for the first five years of the Plan (2010-2015). Specifically, the National Vaccine Implementation Plan called for a formal mid-course review of the 2010 National Vaccine Plan, with guidance from the National Vaccine Advisory Committee (NVAC)⁴.

The National Vaccine Program Office Mid-course Review of the 2010 National Vaccine Plan sought to evaluate and define priorities to guide implementation activities for the remainder of the decade (2016-2020)⁵. It does not replace the National Vaccine Plan, but rather identifies and highlights the areas of greatest opportunity – either defined by continuing need or by efforts that will make a significant difference in strengthening the vaccine and immunization system in the near term (i.e., between 2017-2020). Opportunity areas represent a consensus from the broader stakeholder community to focus federal priorities in light of changing and/or uncertain budgetary and political environments. The NVPO mid-course review process consequently included asking stakeholders to define indicators for use as benchmarks of the success of current efforts and to inform the next iteration of the National Vaccine Plan in the coming decade (i.e., the 2020 National Vaccine Plan).

As requested by the Assistant Secretary for Health (ASH), this NVAC report provides an independent assessment of the findings from the federal midcourse review conducted by the NVPO⁵ and presents the evaluation by NVAC of the proposed opportunity areas for 2016-2020. This report also highlights nuances for the interpretation of the identified opportunity areas and explores metrics used to define success and monitor progress towards the opportunity areas. Finally, this NVAC report includes recommendations on broader considerations for the implementation of the 2010 National Vaccine Plan going forward, including the need for the development of new metrics.

Process

The NVAC received stakeholder input collected through the multipronged approach described in detail in the National Vaccine Program Office Mid-course Review of the 2010 National Vaccine Plan⁵. Briefly, non-federal and federal stakeholders provided input on the accomplishments and remaining gaps to evaluate and prioritize opportunities (identified as “opportunity areas”) for advancing the National Vaccine Program over the remaining five years of the National Vaccine Plan. The combined stakeholder

inputs identified nine consensus opportunity areas, which three separate focus groups conducted by the NVPO ranked according to priority (as shown in Box 1)⁵.

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

Opportunity Area (OA)	Rank
Strengthen health information and surveillance systems to track, analyze and visualize disease, immunization coverage and safety data both domestically and globally.	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 ^a
Support the strengthening of immunization systems globally through policies, practices and partnerships.	8 ^b

a – most focus group participants grouped this opportunity area into OA#4 (i.e., implicit in OA#4)

b – this opportunity area ranked similarly to OA#8

The NVAC independently evaluated the information collected during the focus groups to help clarify the findings and conclusions from these discussions. The NVAC also gathered information from non-federal stakeholders representing two consumer groups and from federal stakeholders in order to obtain additional input not included in the NVPO focus group discussions and to inform the findings and recommendations represented in this report. The NVAC findings in this report further define the activities needed to achieve success in the opportunity areas and the metrics needed to measure progress towards success during the remaining time horizon of the 2010 National Vaccine Plan.

General Findings

Overall, the NVAC agreed with the identification and prioritization of opportunity areas from the NVPO report⁵. The NVAC also agreed that the top five most highly ranked opportunity areas represented the efforts that the broad stakeholder community felt would yield the greatest impact over the next five years⁶. These top five 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 acknowledged the necessity of prioritizing efforts in the context of uncertain and limited resources and recognized that agencies would most greatly benefit from recommendations that optimize public health impact through a targeted use of resources. However, the NVAC recommends that the ASH and federal partners not lose the opportunity to support (or continue to support) the remaining opportunity areas (Box 1) in the event that additional funding or other resources become available.

The NVAC also voiced concerns that prioritizing U.S. domestic efforts may risk losing the momentum to advocate for U.S. global immunization efforts^{7,8}, which reduce the potential for importations of diseases into the U.S. The NVAC agreed that when possible global efforts should directly tie into any domestic implementation activities and incorporate into the five prioritized opportunity areas. In particular, the NVAC recognizes that indicators should reflect progress of both U.S. domestic and global immunization goals, as the expertise, technical support, and capabilities to achieve domestic and global objectives often overlap^{5,7}. Similar to conclusions made in NVPO report⁵, the NVAC supports the incorporation of appropriate existing or proposed indicators outlined in the Global Vaccine Action Plan (GVAP)⁹ as a reference to the U.S. commitment to those efforts. The NVAC notes that contributions to strengthening routine immunization systems both in the U.S. and abroad help ensure the access of all populations to safe and effective vaccines, which in turn further protects the U.S. population from the possible importation of vaccine-preventable diseases^{7,8}.

Finally, the NVAC recognizes that while NVPO stakeholder engagement throughout the mid-course review process included a diverse and comprehensive group of stakeholders, bias introduced by the participation of individual stakeholders represents a concern for any focus group. Therefore, the NVAC emphasizes that implementation activities going forward should consider all opportunity areas and regularly assess the impact of these efforts on different stakeholder groups and particularly on

populations at risk that 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 opportunity area, the NVAC discussed what it would mean to achieve success, considering what success would look like near term, possible challenges and/or barriers that could impede that success, and any other additional issues. The NVAC also discussed possible indicators to help benchmark progress towards that success by choosing existing metrics already tracked by the U.S. government agencies as its indicators to the extent possible (e.g., Healthy People 2020 metrics). However, the NVAC found that many of the existing metrics did not provide the flexibility to track emerging issues highlighted by the opportunity areas. Where existing metrics could not provide the nuances sought to mark progress on a specific issue, the NVAC provides suggestions for other more appropriate metrics. In some cases, no appropriate metrics currently exist and the NVAC identified the need for the development of new metrics. However, since the development of new metrics will most likely exceed the timeframe of the implementation plan and require additional resources to develop and validate, the NVAC included these as recommended actions for future implementation of 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

HHS efforts to use health information technologies and data from patient electronic health records (EHRs) for improving healthcare quality and supporting public health efforts continued to accelerate since the introduction of the 2010 National Vaccine Plan. Strong consensus among all stakeholders engaged by the NVPO review recognized that the use of health information systems represents the greatest opportunity to significantly advance the goals in the National Vaccine Plan over the coming years⁵. Broadening the use and interoperability of health information technologies across a variety of platforms, providers, and public health stakeholder agencies could provide near real-time data for surveillance to identify national trends in disease incidence, vaccination coverage, vaccine effectiveness, and vaccine safety monitoring. Improved data quality and sharing can also facilitate outbreak response efforts¹⁰ and improve patient access to recommended vaccines by preventing missed opportunities to vaccinate¹¹⁻¹⁴. Efforts to improve data systems should also include making the data easily and widely

accessible to broad groups of stakeholders in order to improve implementation of the 2010 National Vaccine Plan and future updates. In addition, emerging technologies such as 2-D barcoding may contribute to tracking vaccination coverage and safety and to better management of vaccine inventory and supply.

Ongoing NVAC discussions continue to focus on the opportunities to strengthen interoperability and data-exchange between patient EHRs, Immunization Information Systems (IISs), and different public health jurisdictions¹⁵. While a number of efforts at both the federal and non-federal levels included addressing barriers to interoperability and use of IISs^{16–19}, NVAC notes that success will depend on continued efforts to characterize the technical, legal, and policy challenges to cross-jurisdictional data-exchange¹⁵. Previous NVAC recommendations supported the implementation of policies and practices such as defining standardized data submission elements and the development of template legal agreements and Memoranda of Understanding between jurisdictions to facilitate the uniform, reliable, and secure exchange of immunization and health data^{15,20}.

At the patient care level, health information technologies can monitor vaccination coverage, vaccine effectiveness, and immunization safety signals. For example, the use of EHRs provided important information about seasonal influenza vaccine effectiveness and evidence to support the use of pertussis-containing vaccines in pregnant women for the protection of newborn infants^{21,22}. Federal vaccine safety monitoring systems such as PRISM and VSD use patient information from EHRs to identify and analyze potential adverse events that occur following immunization^{23,24}. In 2014, NVAC recommendations further encouraged federal partners to identify ways to optimize the use of EHR and IIS data for monitoring and surveillance of vaccination coverage and vaccine safety, particularly in mother-infant pairs following vaccination with recommended vaccines during pregnancy²⁵.

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

example, active surveillance of vaccine preventable diseases significantly improved monitoring of vaccine effectiveness and provides information about shifts in the prevalence of disease caused by vaccine-serotypes versus non-vaccine serotypes²⁶. For diseases such as Respiratory Syncytial Virus (RSV), surveillance data can provide better clarity on the disease burden among varying age groups to inform the design of clinical trials for the development and licensure of new vaccines. Currently, the lack of standards for data submission across EHRs and electronic laboratory reporting systems remain 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 data²⁷. Challenges also remain with respect to making the existing data easily and widely available. Box 2 summarizes characteristics of near-term success and challenges for achieving success for opportunity area 1 (OA#1) and 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
<p>OA#1 - Strengthen health information and surveillance systems to track, analyze and visualize disease, immunization coverage, and safety data, both domestically and globally.</p>	<ul style="list-style-type: none"> • 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 IT 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 	<ul style="list-style-type: none"> • 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

With the exception of the global indicator to track the number of countries with case-based surveillance against vaccine-preventable diseases (Box 3), the NVAC diverged from the NVPO report⁵ by designating indicators for success in this area. Moreover, the NVAC felt that several of the existing metrics proposed in the NVPO report⁵ did not fully encompass the many complexities of this opportunity area. For example, the NVPO report⁵ did 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 additional metrics currently tracked by known entities and proposed by the NVAC to more fully benchmark near-term success of the National Vaccine Plan.

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

Existing Metric	Responsible Entity	Baseline	Target
Percent of office-based physicians electronically sharing patient information with any providers outside their organization (domestic)	ONC	42% (2014)	Increasing trend
Percent of healthcare providers electronically sharing patient information with their state IIS (e.g., a meaningful use requirement)	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	CDC	67% (2014)	100%
Number of countries with case-based surveillance for vaccine-preventable diseases (e.g., invasive bacterial disease [IBD] and rotavirus).	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

For metrics that do not currently exist, the NVAC proposes the development of new metrics that may further inform the planning of implementation activities and potential allocation of resources going forward to achieve success in this opportunity area (Box 4).

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

Metric Proposed for Future Development	As a Measure of
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Number of operational MOAs between state and territorial IISs	Progress toward interoperability of IISs
Percent of providers utilizing 2D 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

In 2013, NVAC provided analyses highlighting remaining opportunities to strengthen vaccine-preventable disease surveillance efforts and pharmacovigilance at the global level²⁸. Few countries currently maintain the surveillance or laboratory capabilities to accurately measure the burden of vaccine-preventable diseases or the impact of vaccines on reducing morbidity and mortality in their populations. Even fewer countries created and maintain the infrastructure to monitor, assess, and respond to vaccine safety signals²⁸. Global surveillance activities outlined in the National Vaccine Plan play an important role in justifying the development and introduction of new and improved vaccines globally. 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 vaccination remains the social norm²⁹. 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, a fundamental reason may relate to the success of implementing routine vaccine schedules resulting in significant reductions in the prevalence and 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 2015 that originated in California and involved a disproportionately high proportion of intentionally 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 Canada³⁰, and resulted in significant morbidity and increased public health costs to mitigate this national outbreak.

In 2015, NVAC issued a report to ASH examining the determinants of vaccine acceptance among parents and recommending a number of strategies to improve parental confidence in vaccines¹⁴. The NVAC 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”*¹⁴. NVAC concluded that vaccine acceptance represents a very complex issue with nuances at the federal, state, and local levels. Additional research and evaluation efforts will need to better characterize the salient issues and develop evidence-based interventions related to increasing vaccine confidence in diverse populations.

In contrast to some albeit imperfect evidence about confidence regarding childhood and adolescent vaccinations, less evidence exists related to adult confidence about the vaccinations they receive. In general, vaccination coverage in adults remains very low for all recommended vaccines³¹. Some studies document misperceptions about vaccine safety and the effectiveness and/or benefits of vaccination for particular vaccines such as influenza vaccine³², 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 among all ages (e.g., access, awareness of recommendations, etc.) will require further investigation³³.

Vaccine confidence and consumer and healthcare provider trust in the entities involved in developing, licensing, recommending, and monitoring vaccines and in the vaccines themselves represent issues of global concern. The World Health Organization (WHO) Strategic Advisory Group of Experts (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) across different settings³⁴. Similar to the NVAC report, 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 subsequent low demand for immunization services. Box 5 summarizes characteristics of near-term success and challenges for achieving success 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
<p>OA#2 - Foster and facilitate efforts to strengthen confidence in vaccines and the immunization system to increase coverage rates across the lifespan</p>	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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

As noted in the NVAC report on *Assessing the State of Vaccine Confidence in the United States*, currently no validated methodologies exist for measuring and evaluating the complexities of vaccine confidence¹⁴. 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*)³⁵ tracks data to look for an annual increasing trend in children that remain completely unvaccinated. Although this metric does not reflect geographic differences between states, health care access disparities that may exist at local levels, or the multitude of factors that lead to unvaccinated children (e.g., access issues, poverty), it does help to confirm that overall vaccination acceptance remains the social norm. Until additional metrics exist, the NVAC suggests that this metric can help in understanding nation-wide trends (Box 6).

At the international level, the GVAP includes indicators for vaccine confidence⁹ to help benchmark progress towards the strategic objective that “individuals and communities understand the value of vaccines and demand immunization both as a right and a responsibility”⁹. The NVAC discussed the lack of standardized metrics and the nuances that exist between cultural attitudes toward vaccines and immunizations that make it difficult to interpret and extrapolate from broad, global data. While viewing

the global indicators as aspirational, the NVAC included them to reflect a unified commitment to developing standardized measurement tools and to creating a framework for better understanding of this issue globally (Box 6).

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

Existing Metric	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	HP2020 0.8% (2012)	Target not set (informational)
Number of states reporting kindergarten coverage data based on census	HHP2020 58% (2014)	Increasing trend
Percentage of un- and under-vaccinated for which confidence was a factor that influenced their decision	GVAP, SAGE none	Decreasing trend
Percentage of countries that assessed (or measured) the level of confidence at the subnational level	GVAP, SAGE none	Increasing trend

The NVAC underscores the importance of future activities including the development of metrics to better understand and accurately assess vaccine confidence in the U.S. (Box 7). The success of this opportunity area depends on a better understanding of this issue both at a national level and at the community level where attitudes and beliefs may vary by communities. The NVAC reiterates the recommendations detailed in its previous report described the characteristics of possible metrics for assessing vaccine confidence in the U.S. (Box 7)¹⁴.

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

Metric 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 intervention strategies and determine best practices
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*¹⁴

Additional Considerations for OA#2

The high number of measles cases in the 2014-2015 measles outbreak in California due to intentionally unvaccinated individuals led to important implications for state policies related to the types of exemptions considered permissible for school-entry laws. In September 2015, the NVAC meeting included discussions of data about 2014-2015 exemption rates among kindergarteners and the potential use of personal belief exemption percentages as an indicator for measuring vaccine confidence³⁶. Non-medical exemption data proved useful in correlating pockets of unvaccinated individuals to the incidence of vaccine-preventable disease outbreaks³⁷. However, a number of caveats to consider emerge when evaluating exemption rates and their correlation with vaccine confidence because states do not collect this information 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 method, some states continue to use a sample-based method or a combination of methods³⁸. Some states allowed or required exemptions if a child missed a single dose of vaccine, even for a child otherwise up-to-date on other vaccines³⁸. Exemptions 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 significantly 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 outbreaks³⁹. Non-medical exemptions may reduce coverage without mandating education on the risks of 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 also strongly encourages future activities to support the standardized collection of non-medical exemption rates across states to help improve the utility of this data, and NVAC specifically noted the important role that IISs may play in these efforts³⁶.

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

Similar to the NVPO report⁵, the NVAC appreciates the need to improve vaccination coverage across the lifespan by addressing access and financing issues that prevent patients from seeking and receiving recommended immunization services. Access to immunization services represents a multifaceted issue impacting vaccine coverage at both the domestic and global levels. Factors affecting access may include, but are not limited to, convenient access to immunization providers and/or the healthcare system, an adequate and available supply of vaccines, and financial barriers to vaccines and immunization services. Recent evidence suggests disparities in immunization represent an ongoing issue, with children living below the poverty level continuing to receive lower vaccination coverage⁴⁰. Despite the Vaccines for Children mandate, the U.S. still needs to address health disparities and correct inequities in immunizations.

As of August 2016, the passage of the Affordable Care Act (ACA) expanded health insurance coverage to greater than 16.4 million previously uninsured people in the U.S.⁴¹. While the ACA represents an important milestone for immunization in the U.S., it did not completely eliminate financial barriers to consumers, particularly for adults. The expanded access to immunizations increased demand for preventive services among adults, which creates the need for a more diverse array of provider types that can offer these services within their practices.

Provider ability and willingness to offer vaccines and immunization services lead to higher vaccination coverage. Multiple studies show patients as much more likely to receive vaccination if their provider offers them vaccine at the time of their healthcare visit^{31,42,43}. However, offering immunization services in the office requires up-front investments by providers, including the purchase of vaccine products, equipment for proper storage and handling, and payment of the costs required to manage vaccine inventories. These potentially significant costs factor into the decisions by providers to offer certain vaccines, along with concerns regarding fair and adequate payment from public and private health insurance payers for the administration of immunization services⁴⁴.

A number of NVAC reports document an urgent need to identify and improve upon current processes and discuss issues related to billing, coding, and subsequent payment for the provision of immunization services (including vaccine counseling and administration) across the lifespan^{25,45,46}. Changing models of compensation continue to impact immunization rates and incentives for different types of vaccine providers. In 2009, the NVAC provided guidance to HHS on strategies to address the financial pressures that impact pediatric and adolescent vaccination practices among private and public providers⁴⁶. However, these analyses did not characterize the challenges particular to the provision of immunizations to adult populations.

Recent NVAC discussions included representatives from different physician practices and private payers who articulated several issues that need further examination⁴⁷. Many stakeholders agreed that efforts should include additional analyses to build the business case for vaccines to share with providers. Tools, resources, and standardized billing codes and interpretations of these codes would help to optimize business practices (and payment) and improve efficiencies of immunization services. Finally, the NVAC appreciates the need for additional work to quantify the financial impact of provider issues and how these affect their willingness to offer vaccines in office, which would help in describing fair and adequate payment for immunization services^{46,47}. 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 in this OA	Challenges for Achieving that Success
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<p>OA#3 - Eliminate financial and systems barriers for providers and consumers to facilitate access to routinely recommended vaccines</p>	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 tract 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
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Proposed Indicators for OA#3

The NVAC largely concurred with the NVPO report⁵ on the choice of indicators to use for domestic efforts, as shown in Box 9. Globally, the NVAC suggested using WHO regional measles elimination achievement. The baseline for measles elimination reflects the remaining 5 WHO regions endemic with measles after the member countries of the Pan American Health Organization (PAHO) region successfully interrupted endemic measles transmission in 2002 and certified the region as measles-free in 2016⁴⁸. The NVAC also recommended using the drop-out rates between the first and third doses of vaccines containing diphtheria-tetanus-pertussis (DTP1 and DTP3, respectively) as an indicator of access to vaccines and immunization services. The NVAC also suggested including tracking the number of countries that reach high coverage levels through routine immunization programs (Box 9).

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

Metric	Baseline	Target
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Percentage of surveyed primary care providers who stock vaccines routinely recommended for adults	20% Internists and 31% FP (CDC, 2012)	60% (NAIP)
Percentage of state and territories that allow pharmacists to administer all routinely recommended vaccines for adults > 19 without a patient-specific prescription	85% (APhA, 2013)	100% (NAIP)
Percentage of state Medicaid programs that provide coverage of all ACIP/CDC-recommended vaccinations for adults and prohibit cost-sharing	20% (CMS, 2012)	100% (NAIP)
Number of WHO regions achieving measles elimination by 2020 (global metric of access)	GVAP, SAGE 0/5 WHO regions (2010)	6 WHO regions
Number of countries reaching vaccination coverage targets through routine services (global metric of access)	GVAP 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 dropout rates between DPT3 and DPT1, globally (global metric of access)	GVAP SAGE 18.6% Member States w/ dropout rates ≥10%	decreasing trend

The NVAC proposes the development of two additional metrics for consideration to inform the planning of implementation activities and potential allocation of resources going forward to achieve success in this opportunity area (Box 10).

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

Metric 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, Ob/Gyns)	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 acknowledges that changes to Medicare and Medicaid policies regarding costs to patients and providers may not resolve existing barriers in the remaining five years of the National Vaccine Plan. However, the NVAC suggests that federal and state programs 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 to the healthcare

system. Therefore, public payers should support the administration of all vaccines recommended by the CDC for routine use for all ages by working to minimize the financial burden to patients and providers.

The NVAC also supports the concept of the “immunization neighborhood,” a term used to describe coordinated efforts of healthcare and community immunizers to ensure patients receive recommended vaccines and to improve access to recommended vaccines. Several analyses provided by the NVAC called for strategies to understand and overcome the barriers to receiving recommended vaccines from non-physician vaccine providers (e.g., pharmacists) and/or at non-traditional locations (e.g., workplace, schools)^{12,13,25}. The NVAC recognizes the need to monitor how changing models of compensation impact the immunization neighborhood. The NVAC further reiterates that communities, especially rural communities, will continue to experience missed opportunities until convenient and affordable access to immunization services exists everywhere.

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

There are a number of reasons to explain the lack of currently available vaccines for infectious diseases that impact public health, both in the U.S. and globally⁴⁹. For example, developing vaccines for scientifically complex pathogens requires additional information about both the pathogen and the host immune response to optimally elicit a directed, protective response against specific antigens^{50,51}. This opportunity area aims to broadly encompass the many scientific questions that the NVAC and other stakeholders identified as pertinent to the development and licensure of new and improved vaccines to meet ongoing, emerging, and/or unmet public health needs. These scientific questions include, but are not limited to, better understanding of pathogen biology, better understanding of the host immune response, better understanding of why and among whom vaccine adverse events occur, correlates/surrogates of immune protection, and knowledge of additional factors that can help predict vaccine effectiveness and duration of protection⁵. In addition to recognizing the importance of improving our understanding, the NVAC emphasized the need to encourage data sharing among investigators related to optimizing the science base.

During the June 2016 meeting, the NVAC discussed how strengthening the science base around vaccinology and understanding of the human immune response to vaccines (and how induced immunity compares to natural infection) could help to foster innovation in tools and resources far beyond the timeline of the National Vaccine Plan⁵². Greater scientific knowledge about the immune response and

surrogates of immune protection may also aid in the vaccine development process by helping to more rapidly identify promising candidates and/or provide a possible pathway to licensure in the context of limited feasibility of large-scale efficacy trials due to unpredictable disease burden from year to year (e.g., development of new pertussis-containing vaccines for use in the U.S.). 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^{6,53} and to improve understanding of immune responses in the elderly. The NVAC further described success as making scientific breakthroughs that result in vaccine candidates for pathogens with historically unsuccessful development pathways, such as HIV, tuberculosis, or 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	<ul style="list-style-type: none"> • 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 (e.g., the Human Vaccines Project, NIH’s Human Immunology Project Consortium) 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 	<ul style="list-style-type: none"> • Better understanding of waning immunity and strategies to address duration of protection (e.g., pertussis-containing vaccines) • Difficulties associated with enrolling pregnant women in studies⁵⁴ • 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

Proposed Indicators for OA#4

Indicators to benchmark scientific progress remain very difficult to define and may not provide good information about success in increasing the scientific knowledge base critical to vaccine development. 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^{55,56}, but uncertainty remains about how to best use this information to aid in the development of improved vaccine candidates⁵⁷. The NVAC noted the general unpredictability of the ways that incremental steps forward in scientific knowledge will translate into longer term returns on investment. Similarly, the NVAC did not believe that metrics using the number of peer-reviewed journal articles on vaccine science would necessarily provide an accurate diagnosis of the systems in place to support scientific advances that lead to new vaccine development. For these reasons, the NVAC agreed with the NVPO report⁵ suggestion to combine indicators for OA#4 and OA#5 to reflect the inter-relatedness of these opportunity areas and their combined role in driving vaccine innovation and development.

Additional Considerations for OA#4

Substantial data exist to help inform knowledge about immune responses and approaches to identifying correlates/surrogates of protection. However, in addition to filling crucial knowledge gaps, harnessing the available data, and knowing how to best use them represents a significant challenge. The NVAC encourages the support of collaborative efforts and partnerships to optimize the use of existing data to inform vaccine science and further vaccine development efforts and the support of meetings that would review experience and catalyze efforts to identify and address gaps. The NVAC recognizes the importance of improving correlates of protection for vaccine development and suggests that development of a future metric to track their availability may represent an important opportunity for future updates to the National Vaccine Plan.

OA#5 - Facilitate vaccine development

Many unmet public health needs remain both within the U.S. and globally that 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 frequently discusses the need to better understand the drivers of vaccine innovation and development and how to best support those efforts going forward. Opportunity areas 4 and 5 both focus on drivers of vaccine development,

which makes them interconnected. Development barriers may include scientific challenges that require mechanisms to incentivize and/or support higher-risk research and development investments by biotechnology and pharmaceutical companies to pursue specific vaccine targets. The NVAC supports this opportunity area as a priority and emphasizes that the NVPO report⁵ metrics and activities defined to achieve success in this opportunity area require broad and more holistic interpretation and application to ensure optimal use of resources and knowledge gained.

The NVAC discussed a number of considerations it viewed as underrepresented in the NVPO report that future efforts should address. 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 smaller companies, while larger companies may care more about regulatory certainty, regulatory consistency, and/or a ready market that would drive final development.

The NVAC further recognized 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, which led the NVAC to suggest 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 disease that lack an effective vaccine (e.g., RSV, HIV, TB), the 2014-2015 Ebola outbreak and the unfolding 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 pathogens⁵⁸. 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 context⁵⁸. Activities include strengthening policies, partnerships, and capabilities both before and during an epidemic to minimize lives lost and economic disruptions due to infectious disease outbreaks⁵⁸. The NVAC encourages USG 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 Blueprint⁵⁸ to better understand the capabilities and infrastructure needed to respond to future emerging pathogens.

The NVAC also discussed 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 investment⁴⁹. In addition, newer vaccines may require complex manufacturing techniques that can impact production capacity and supply⁵⁹. 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 problems⁶⁰. The NVAC suggest 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 law and regulation pertaining to vaccine development and

evaluation, global efforts harmonize 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.	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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#5

The WHO recently developed a vaccine pipeline tracker limited to clinical-stage vaccines aimed at protecting against HIV-1, malaria, TB, 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.

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

Metric	Baseline	Target
A mechanism to track the vaccine development pipeline that includes a specific number of target, priority pathogens	WHO Pipeline tracker (and others)	Ongoing progression of candidates entering and advancing through the pipeline

While the WHO pipeline tracker represents a good existing metric and 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. However, tracking this metric 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 metric, 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.

The NVAC proposes the development of metrics 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 metric 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).

Box 14. Metrics Proposed for Future Development – OA#5

Metric 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
The number of vaccine delivery technologies (devices and equipment) that have received WHO pre-qualification compared to 2010	Progress toward improved administration and delivery of vaccines
Number of vaccines licensed for use in a controlled-temperature chain at temperatures above the traditional 2-8 °C range”	Improved thermostability of vaccines
Pipeline of candidates in development for emerging threats that passed Phase I with a clear regulatory path for efficacy studies in humans	Progress toward responding to emerging threats with new vaccine candidates ready for human clinical efficacy studies in a timely manner

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). In addition, 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 supported the development of the Strategic Multi-Attribute Ranking Tool for Vaccines⁶² (SMART-Vaccines) to facilitate decision-making around prioritizing vaccine candidates, a formal list of priority targets endorsed across the USG 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 exist⁶³. The pathogens included in this analysis represent targets with candidates previously identified as priority development targets in the GVAP⁹ 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 years⁶³.
- The 2013 CDC report on *Antibiotic Resistant Threats in the United States* describes antibiotic resistance as one of the most significant threats to public health⁶⁴. 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 action⁶⁴.

- 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 area⁶⁵. 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 an 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 ⁶³

b - CDC Antibiotic Resistance Threats Report, 2013 ⁶⁴

c - NIAID Emerging Infectious Diseases/Pathogens ⁶⁵

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 metrics 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 five 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 Mid-course Review Report findings⁵ 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 Mid-course Review⁵, particularly the 2015 NVAC report on *Assessing the State of Vaccine Confidence in the United States*¹⁴. 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.

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 metrics 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 metrics lies beyond the scope, timeline, and resources of its review and the next few years, we urge the ASH to consider prioritizing the development of these new metrics 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 with the adoption of the existing metrics (e.g., Healthy People 2020 metrics) to track progress on the National Vaccine Plan goals and 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 metrics within each of the opportunity areas to ensure improved measurements for future use, including a metric to track and report on U.S. government annual financial investments in vaccine innovation that would support shared understanding of current investments in the development of (i) vaccines for established pathogens with no vaccines, (ii) vaccines for emerging pathogens, and (iii) improvements in existing vaccines. The metrics 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, to 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 that incorporates considerations of the findings from this report.
- The ASH should charge the NVPO in coordination with other relevant departments and agencies to begin the process of developing strategies to (i) prioritize USG investments in vaccine-related innovations and (ii) identify and make recommendations to overcome barriers that inhibit innovation.

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