

NATIONAL VACCINE ADVISORY COMMITTEE
DRAFT WHITE PAPER
ON THE
UNITED STATES VACCINE SAFETY SYSTEM

September 2011

Version 3.0

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EXECUTIVE SUMMARY

INTRODUCTION

The U.S. Department of Health and Human Services (HHS) Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) in July 2009 "to review the current federal vaccine safety system and develop a White Paper describing the infrastructure needs for a federal vaccine safety system to fully characterize the safety profile of vaccines in a timely manner, reduce adverse events whenever possible, and maintain and improve public confidence in vaccine safety." This White Paper provides the findings and recommendations of this two-year review of the federal vaccine safety system.

BACKGROUND

The foundation of the modern vaccine safety system infrastructure in the United States is the National Childhood Vaccine Injury Act of 1986 (NCVIA). The NCVIA authorized the creation of the National Vaccine Injury Compensation Program (VICP) and the Vaccine Adverse Event Reporting System (VAERS), and authorized the establishment of the National Vaccine Program (NVP) and the NVAC. The HHS ASH was appointed Director of the NVP, and the National Vaccine Program Office (NVPO) was created to coordinate and integrate the efforts of the NVP as the agent of the ASH. The NVPO is responsible for coordinating and ensuring collaboration among the many federal agencies involved in vaccine and immunization activities. Additionally, the NVPO staffs the NVAC.

The NVAC advises and makes recommendations to the Director of the NVP on matters related to program responsibilities. Specifically, the NVAC recommends ways to achieve optimal prevention of human infectious diseases through vaccine development, and provides direction to prevent adverse reactions to vaccines. One of the functions of the NVAC is to recommend research priorities and other measures the Director of the NVP should take to enhance the safety and efficacy of vaccines, which is the subject matter of this White Paper.

FORMATION OF THE VACCINE SAFETY WORKING GROUP

The NVAC Vaccine Safety Working Group (VSWG) was created in 2008 to undertake and coordinate a scientific review of the draft Centers for Disease Control and Prevention (CDC) Immunization Safety Office (ISO) Scientific Agenda, which was its first charge from the ASH. The Working Group completed this charge in May 2009. Two months later, in July 2009, it began work on its second charge to review the federal vaccine safety system, which had not been reviewed since 1998. Keeping this in mind, the charge to the NVAC from the ASH recognizes the importance of vaccinations and vaccine safety to the American public. With the advances in the scientific, social, and fiscal landscape since the last review of the vaccine safety was undertaken in 1998, the NVAC believes a thorough review of the system is needed.

1 The VSWG was originally comprised of 18 members, nine of whom were current or past NVAC
2 members. (Four members subsequently agreed to take on non-voting consultant status after the
3 first year of the committee's deliberation due to time constraints.) The VSWG has a broad range
4 of expertise including pediatric and adult infectious diseases, genomics, immunology,
5 epidemiology, public health, maternal and child health, pharmacoepidemiology, and biostatistics.
6 Additionally, current or past consumer representatives from each of four federal advisory
7 committees with a role in vaccine safety (the NVAC, the Advisory Committee on Immunization
8 Practices [ACIP], the Vaccines and Related Biological Products Advisory Committee (VRPAC),
9 and the Advisory Commission on Childhood Vaccines [ACCV]) are members.

11 **METHODS FOR ADDRESSING ITS CHARGE**

12 To address its second charge of reviewing the national vaccine safety system and developing this
13 White Paper, the NVAC VSWG looked at prior reviews of the vaccine safety system by external
14 agencies and by the VSWG itself, conducted meetings in person and by telephone, created
15 subgroups to focus on specific information and processes, and developed initial
16 recommendations for improvement to the national vaccine safety system.

17
18 The VSWG also conducted meetings in person and by telephone. The Working Group's kickoff
19 meeting was held on July 15–16, 2009, and was followed by two more in-person meetings.
20 Additionally, 18 conference call meetings were held.

21
22 The VSWG also created three subgroups to focus on specific information and processes and to
23 develop initial recommendations for improvement to the national vaccine safety system. These
24 subgroups were the Biomechanisms Subgroup, which focused on biological mechanisms of
25 vaccine adverse events; the Surveillance and Epidemiology Subgroup, which focused on the
26 epidemiology to detect, quantify, and examine the cause of vaccine adverse events; and the
27 Structure and Governance Subgroup, which focused on topics related to the structure, oversight,
28 resources, and processes for the vaccine safety system.

29
30 Stakeholder and public input also was solicited during the VSWG's work on its charge.
31 Stakeholders were engaged in a meeting in April 2010. When version 2.0 of the draft White
32 Paper was available in May 2011, the public was invited to comment, and a meeting to obtain
33 stakeholder input was held on June 12, 2011 (Appendix 9), and a full NVAC meeting was held
34 the following day to discuss version 2.0. Following the NVAC discussion, the final version 3.0
35 of the White Paper presented at the September 2011 NVAC meeting was developed under the
36 direction of the NVAC chair by a technical writer under contract to the NVPO, with assistance
37 from the NVPO and the VSWG co-chairs.

41 **OVERVIEW OF THE NATIONAL VACCINE SAFETY SYSTEM**

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The key federal departments and agencies with a role in vaccine safety activities include the HHS—encompassing the CDC, the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), the National Institutes of Health (NIH), the Centers for Medicare and Medicaid Services (CMS), the Indian Health Service (IHS), and the National Vaccine Program Office (NVPO)—and the U.S. Department of Defense (DoD) and the U.S. Department of Veterans Affairs (VA). These components provide multiple levels of focus and assurance of the safety of vaccines in the United States.

The NVAC's review of the federal vaccine safety system concentrated on these aspects of the system to determine where opportunities for improvement exist:

- Coordination of the system – Coordination and integration of federal efforts relevant to immunization safety.
- Basic biomedical research – Basic research on the immunologic and physiologic effects of vaccines and vaccine ingredients. Also, research on the biological mechanisms that drive a successful immune response to a vaccine as well as the mechanisms underlying vaccine adverse reactions, how quality of the antigen affects the response, how adjuvants enhance the response to vaccines, and how their use may affect the vaccine safety profile.
- Pre-licensure activities – Vaccine discovery, early phase clinical evaluation, and pre-licensure vaccine clinical trials.
- Vaccine licensure – Vaccine approval and licensing processes.
- Role of the Advisory Committee on Immunization Practices (ACIP) – The process for reviewing and recommending a vaccine.
- Post-licensure activities
 - Adverse event surveillance – Surveillance systems currently in use in the United States.
 - Vaccine signal validation and hypothesis testing – Systems currently in place for testing hypotheses in vaccine safety.
 - Biological mechanisms research – Research into the biological mechanisms behind the human immune response to a vaccine or a confirmed adverse event following immunization (AEFI).
 - Causality assessment – Existing systems and methods for determining causes of AEFI.
 - Vaccine injury compensation – The VICP.
 - Public health response – The process for mobilizing federal, state, and local public health systems to participate in the response to acute concerns about the safety of a vaccine.

- 1 ○ Communication and information dissemination – The manner in which information is
- 2 communicated to the public and to healthcare providers regarding vaccine safety
- 3 issues.
- 4 ○ Reduction of vaccine administration errors – Mechanisms for tracking vaccine
- 5 administration errors.
- 6 ○ Management of vaccine adverse events in clinical practice – Clinical guidance to
- 7 evaluate and manage the severity of a vaccine adverse reaction.
- 8 ● Feedback mechanisms – Communication and collaboration between basic scientists
- 9 conducting laboratory research, epidemiologists conducting population-based research,
- 10 and other partners, such as scientists within the vaccine industry.

12 **STRENGTHS OF THE CURRENT VACCINE SAFETY SYSTEM**

13 The overall strength of the federal vaccine safety system is its ability to monitor the development
14 and administration of vaccines and potential adverse events through a framework involving
15 federal, state, and local departments and agencies, drug and vaccine manufacturers, private
16 enterprise, and the general public. Oversight is in place to ensure the safety of vaccines, to detect
17 adverse events, and to take steps to diminish and rectify impacts of AEFI. Examples of identified
18 strengths of the components of the system described above include the following:

- 19 ● Coordination of the System – The system has the ability to coordinate prompt, cross-
- 20 agency responses to specific issues (e.g., the H1N1 influenza pandemic response, the
- 21 ISFT as a coordinating body).
- 22 ● Basic Biomedical Research – Multiple new research methods have been developed and
- 23 utilized to evaluate the safety of vaccines and their components.
- 24 ● Pre-licensure Activities – Pre-licensure assessment is rigorous, including basic science
- 25 evaluation, animal testing, and randomized control trials of individual vaccines, and in
- 26 combination to evaluate safety, immunogenicity, and efficacy.
- 27 ● Vaccine Licensure – The FDA has successfully kept up with an expanding number of
- 28 licensure applications for new vaccines while their budget has not expanded accordingly.
- 29 ● Post-licensure Activities – The ACIP provides advice that leads to a reduction in the
- 30 incidence of vaccine preventable diseases in the United States and an increase in the safe
- 31 use of vaccines and related biological products.
- 32 ● Feedback Mechanisms – A mechanism exists for establishing vaccine related adverse
- 33 events and compensation for injury (i.e., the VICP).

35 **GOALS OF AN IDEAL VACCINE SAFETY SYSTEM**

36 During its review of the national vaccine safety system, the NVAC concluded that an ideal
37 vaccine safety system should consist not only of a responsive arm, but also a long-range,

1 proactive research arm. The NVAC also determined that the United States vaccine safety system
2 should be able to:

- 3 • Accurately detect AEFI with high sensitivity and specificity.
- 4 • Accurately quantify the risk of AEFI to allow benefit/risk comparisons.
- 5 • Assess whether an AEFI is causally linked to vaccination.
- 6 • Conduct an appropriate public health response to emerging vaccine safety issues.
- 7 • Appropriately communicate results between the scientific community and the public.
- 8 • Ensure that system processes and results are transparent.
- 9 • Better understand AEFI to develop proactive research into AEFI occurrence and
10 prevention.
- 11 • Perform these tasks in a timely manner.

12
13 The NVAC used these ideal vaccine system goals as a guide to develop the recommendations
14 made below.

15 16 **FINDINGS AND RECOMMENDATIONS**

17 18 **OVERVIEW**

19 The NVAC determined that the NVP includes all the requisite functions for a vaccine safety
20 system (i.e., research, regulation, post-licensure surveillance, guidance for immunization
21 programs, guidance for clinicians, injury compensation, and oversight) and that the
22 organizational placements of these functions are consistent with the missions of the respective
23 participating agencies and offices. The NVAC also determined that, while fundamentally sound,
24 the leadership, coordination, and ongoing assurance of the current vaccine safety system can be
25 improved.

26
27 For some of the recommendations below, the NVAC went beyond simply stating the objective to
28 include details regarding either how the objective should be achieved or what the completed
29 objective should include. This approach was taken for three reasons: First, the NVAC seeks to
30 avoid ambiguity regarding its thinking; absent the associated details, a reader could reasonably
31 interpret the recommendation substantially differently than does the NVAC. Second, in response
32 to a recent RAND Corporation study commissioned by the NVPO that found many previous
33 NVAC recommendations to be lacking sufficient details to guide implementation and called for
34 future NVAC recommendation to be "actionable," the NVAC sought to make its intended actions
35 clear. Third, the NVAC recognizes that the HHS may wish to consider alternative approaches to
36 implementing the recommendations below; therefore, the NVAC believes that the details it

1 offers will provide a valuable benchmark against which to compare any given alternative
2 approach and determine whether it is more or less superior to that recommended here.

4 **RELATIONSHIP OF WHITE PAPER TO THE NATIONAL VACCINE PLAN**

5 One of the goals of the Strategic Plan portion of the National Vaccine Plan, released in February
6 2011, is to enhance the nation's vaccine safety system. The vision of this goal is to "address
7 safety-related issues, strengthen the system that monitors the safety of vaccines throughout
8 production and use, and advance the safety profile of vaccines." The plan states that,
9 "Specifically, this goal aims to prevent adverse events and fully characterize the safety profile of
10 vaccines in a timely manner."

11
12 The National Vaccine Plan was released over a year and a half after the VSWG began work on
13 its second charge of reviewing the national vaccine safety system; therefore, the Working Group
14 did not have access to the Plan for much of the work on its second charge. However, the findings
15 and recommendations made within this White Paper do align with and will help to inform
16 implementation of this particular goal of the National Vaccine Plan.

18 **1. LEADERSHIP FINDINGS AND RECOMMENDATIONS**

20 **Findings**

21 The NVAC found the following areas where enhancements could be made to the leadership
22 component of the vaccine safety system:

- 23 • The leadership within the HHS Office of the Secretary to exercise its inherent authorities
24 to improve coordination among United States government agencies and offices could be
25 clarified and improved. This improved leadership should be able to fully engage all of
26 HHS and the other federal agencies that should be involved in the national vaccine safety
27 system. Enhanced collaboration on vaccine-safety initiatives between agencies could
28 improve the overall system.
- 29 • Public advisory committees and their related subcommittees/working groups could
30 benefit from enhanced, expert representation to address vaccine safety issues by inclusion
31 of subject matter experts in areas such as understanding, preventing, and treating vaccine-
32 associated adverse events.

34 **Recommendations**

35 **Leadership Recommendation 1.1 – Reaffirmation of the System Structure**

36 As the federal vaccine safety system incorporates 21st century science and technology, the
37 Secretary of HHS should affirm the commitment of the Department to vaccine safety by issuing
38 a policy statement that reaffirms the following components of the system:

- 1 • The NVP is a coordinated effort among the Food and Drug Administration (FDA), the
2 Centers for Disease Control and Prevention (CDC), the National Institutes of Health
3 (NIH), the Health Resources and Services Administration (HRSA), and the Centers for
4 Medicare and Medicaid Services (CMS), and the Departments of Defense (DoD) and the
5 VA and the United States Agency for International Development (USAID).
- 6 • The ASH, having been designated as Director of the NVP, is responsible for the direction
7 of the NVP activities related to coordination of vaccine safety.
- 8 • The NVPO is charged with advising the ASH regarding implementation of the
9 responsibilities of the NVP and coordinating the vaccine safety-focused activities of the
10 NVP¹ (see related recommendation in Coordination Recommendation 2.1).
- 11 • The NVAC is responsible for reviewing vaccine safety policy and the vaccine safety-
12 focused activities, developing recommendations based on these reviews, and transmitting
13 its recommendations to the ASH and to the Secretary pending implementation of
14 Leadership Recommendation 1.3.

15

16 **Leadership Recommendation 1.2 – Structural Organizational Changes in the National** 17 **Vaccine Program**

18 Include the IHS and the Agency for Healthcare Research and Quality (AHRQ) as participants in
19 the NVP. Also, direct HHS agencies coordinated under the NVP—accompanied by a request to
20 the DoD, the VA, and the USAID—to do the following:

- 21 • Fully participate in NVPO vaccine-safety coordination efforts.
- 22 • Identify and pursue opportunities for collaborative projects relevant to NVP vaccine
23 safety objectives with other NVP-coordinated agencies.
- 24 • Regularly obtain the advice of appropriate subject matter experts and consumers to guide
25 initiatives related to vaccine safety.
- 26 • Provide other governmental agencies, vaccine manufacturers, appropriate stakeholder
27 organizations, and representatives of the public the opportunity to provide feedback
28 regularly during the planning and implementation of initiatives related to vaccine safety,
29 and tell them about initiatives and outcomes related to vaccine safety
- 30 • Define performance expectations related to vaccine safety for NVP-coordinated agencies.

31 **Leadership Recommendation 1.3 – National Vaccine Advisory Committee Charter**

32 The charter of the NVAC should be modified to reflect the following changes:

- 33 • Specify that the NVAC advises the Secretary as well as the ASH, thereby defining a
34 relationship between the NVAC and the Secretary akin to that which already exists for

¹ Note that this includes NVPO being the central coordinating office of the Immunization Safety Task Force, an entity that did not exist in 1986 at the time the NCVIA was written.

1 the Advisory Committee on Immunization Practices (ACIP) and other major HHS public
2 advisory committees.

- 3 • Specify additional federal *ex officio* representation from the IHS and the AHRQ.

4
5 The NVAC should help evaluate the progress of the NVP-coordinated agencies toward
6 enhancing vaccine safety both in response to requests from the Secretary and at its own initiative.
7 This task could prove especially beneficial to evaluating NVP-wide initiatives to enhance
8 research, post-licensure surveillance, public information, and stakeholder engagement. The ASH
9 should charge the NVAC to create a Standing Working Group on Vaccine Safety. Members of
10 this Working Group should be selected using a similar approach as used for the H1N1 Vaccine
11 Safety Risk Assessment Working Group. Membership also should include representatives from
12 entities such as ACIP, the Advisory Commission on Childhood Vaccines (ACCV), the Vaccines
13 and Related Biological Products Advisory Committee (VRPAC), and others, as appropriate, and
14 should address issues of conflict of interest as they arise. This Working Group would, at a
15 minimum, be charged with reviewing the following long-term goals and activities:

- 16 • Implementation of these and other related NVAC safety recommendations through
17 regular reports from the Immunization Safety Task Force (ISTF), Immunization Safety
18 Coordinating Group (ISCG) (see Coordination Findings and Recommendations below),
19 or other similar coordinating body as described in Assurance and Accountability
20 Recommendation 3.2.
- 21 • Agencies' vaccine safety plans and progress in implementing them.
- 22 • Response to emerging vaccine safety issues as they arise.

24 **2. COORDINATION FINDINGS AND RECOMMENDATION**

25 **Findings**

26
27 The NVAC found the following areas where enhancements could be made to coordination of the
28 vaccine safety system:

- 29 • The ASH and the NVPO Director could increase the scope of the ISTF's vaccine safety
30 coordinating activities and expand its membership to include agencies with roles in
31 immunization delivery and vaccine safety or the ASH and the NVPO Director could
32 create a new Immunization Safety Coordinating Group (ISCG) or other similar
33 coordinating body to fulfill the recommendations made herein (i.e., the ISTF could be
34 expanded or a new group that includes the ISTF could be formed).
- 35 • Enhanced collaboration on vaccine-safety initiatives between agencies is needed. A
36 formalized, visible coordinating body for vaccine safety within the federal government
37 could enhance this collaboration and provide assurance and accountability of the vaccine
38 safety system.

1

2 **Recommendation**

3 **Coordination Recommendation 2.1 – Expanded Role and Composition for the ISTF, ISCG,** 4 **or Other Similar Coordinating Body**

5 The ISTF, the ICSG, or a similar coordinating body should make regular reports, in accordance
6 with the structure described in Assurance and Accountability Recommendation 3.2. The scope of
7 the ISTF's or ICSG's vaccine safety coordinating activities, under the leadership of the ASH and
8 the NVPO Director, should specifically include focused effort involving subcommittees of the
9 ISTF, ISCG, or a similar coordinating body in the following areas: research, post-licensure
10 surveillance, clinical practice, communications, and stakeholder and public engagement. This
11 may best be carried out by establishing a subcommittee or some other body.

12

13 The NVPO should expand the membership of the ISTF or create the ISCG or other similar
14 coordinating body to ensure representation from the agencies and departments specified as
15 contributing to the NVP components outlined in the NCVIA, or subsequently redesignated or
16 renamed agencies, including the CMS, the AHRQ, and the USAID.

17

18 **3. ASSURANCE AND ACCOUNTABILITY FINDINGS AND RECOMMENDATIONS**

19

20 **Findings**

21 The NVAC found the following area where enhancements could be made to the assurance and
22 accountability of the vaccine safety system:

- 23 • As with most important governmental functions, an ongoing, publically accessible
24 process of external review of the work the United States vaccine safety system could help
25 assure the effective functioning of the system and may increase confidence in its work.

26

27 **Recommendations**

28 **Assurance and Accountability Recommendation 3.1 – Enhanced Role of the NVAC**

29 The Secretary of HHS should assign the NVAC a broader and stronger role regarding
30 independent, periodic review and evaluation of the NVP. The NVAC, through the Standing
31 Working Group on Vaccine Safety (see Leadership Recommendation 1.3), should assess (1)
32 whether NVP-coordinated agencies are coordinating their efforts effectively and creating
33 appropriate NVP-wide agendas, (2) whether these agendas are being implemented and their
34 objectives met, and (3) whether NVP-coordinated agencies are complying with performance
35 expectations defined by the Secretary and other Secretarial guidance. The NVAC, consistent
36 with advisory functions, should communicate the outcomes of its assessments in a transparent
37 manner to the Secretary through the ASH.

38

1 **Assurance and Accountability Recommendation 3.2 – Relationship between the ISTF,**
2 **ISCG, or Other Similar Coordinating Body and the NVAC**

3 The ISTF, ISCG, or a similar coordinating body should meet at least annually with the NVAC
4 Standing Working Group on Vaccine Safety (see Leadership Recommendation 1.3) and file an
5 annual progress report, with an associated presentation at an NVAC meeting, on processes
6 undertaken to monitor and evaluate vaccine safety, including, but not limited to, meeting the
7 recommendations specified in the recommendations for research and post-licensure surveillance
8 of this White Paper. These regular meetings with the NVAC Standing Working Group on
9 Vaccine Safety may occur through means other than in-person meetings (e.g., teleconferences).

10

11 **Assurance and Accountability Recommendation 3.3 – External Assessment of Adverse**
12 **Event Causality**

13 To resolve difficult scientific questions through external scientific review of available evidence
14 and provide regular updates to the National Vaccine Injury Compensation Program (VICP)
15 Vaccine Injury Table, a mechanism should be developed to conduct causality evaluation of
16 selected vaccine adverse events. On an annual basis, the ISTF, ISCG, or other similar
17 coordinating body, in consultation with the NVAC Standing Working Group on Vaccine Safety
18 (see Leadership Recommendation 1.3), will conduct a review of potential topics for examination,
19 based on AEFI for which a review of causality is warranted and for which there is scientific
20 literature addressing the topic. If serious adverse events that meet these criteria are identified, the
21 Secretary of HHS should continue using the IOM method to assess the causal relationship
22 between the identified vaccine(s) and suspected adverse event(s). Results of assessments should
23 be reported to the NVAC, the ACCV, and other entities as determined by the NVAC.

24

25 **Assurance and Accountability Recommendation 3.4 – Progress in Enhancing the Vaccine**
26 **Safety System**

27 To assure progress in enhancing the vaccine safety system, as highlighted in the
28 recommendations in this White Paper, a formal mechanism for review and accountability is
29 needed. The NVAC should continue to be the advisory entity primarily responsible for
30 evaluating the NVP programs and commissioning vaccine-specific investigations. Opportunities
31 exist for the HHS to enhance the NVAC's standing and authorities, as described in Leadership
32 Recommendations 1.1 and 1.3, Assurance and Accountability Recommendations 3.1 and 3.2, and
33 Stakeholder and Public Engagement Recommendation 8.1. Additionally, NVAC should
34 periodically review and report to the ASH on its assessment of progress toward implementation
35 of the recommendations of this report. Consideration should be given to charging another entity,
36 such as the IOM, to undertake a review in 3 to 5 years to assess progress toward vaccine safety
37 system assurance as defined in this report. As with all recommendations made in this White
38 Paper, assurance and accountability mechanisms will need to be in place for proper oversight of
39 the NVAC as they fulfill this recommendation.

40

4. RESEARCH FINDINGS AND RECOMMENDATIONS

Findings

The NVAC found the following areas where enhancements could be made to the research component of vaccine safety:

- A federal government-wide vaccine safety research agenda for enhancing research in critical subject matters, including both pre-licensure research activities and post-licensure surveillance, needs to be created.
- Research into the molecular and cellular mechanisms that may be involved in vaccine-associated adverse events is occurring but could benefit from increase coordination, planning, and resources.
- Coordinating research efforts into the molecular and cellular mechanisms that may be involved in vaccine-associated adverse events such research and more clearly identifying their possible application to vaccine safety potentially could enhance prevention and treatment of vaccine adverse events.
- A consistent funding mechanism for vaccine safety research could support program project grants and investigator-initiated research into vaccine safety under the scope of a national vaccine safety scientific agenda.
- The CDC could use the findings from its data collection of public opinions to assist in the implementation of the vaccine safety agenda and recommendations made in this White Paper.
- Clinical guidance and other support related to identification, evaluation, treatment, management, and coping with AEFI could be improved and widely disseminated to vaccination providers, patients, and caregivers.
- Formalized data sharing could inform a coordinated scientific agenda that includes biological mechanisms, which is critical to ensure that the biological basis behind vaccine adverse events is properly understood.
- Expansion into a larger-scale repository, such as a National Vaccine Safety Biospecimen Repository, could increase the ability of the vaccine safety system to perform necessary biological mechanisms research.
- Increased support for training for the vaccine safety research workforce is needed.
- Greater accessibility to existing vaccine safety data could enhance current vaccine safety research and foster additional research.

Recommendations

Research Recommendation 4.1 – Development of a Vaccine Safety Research Agenda

1 The ISTF, ISCG, or other similar coordinating body should develop and update on a regular
2 basis, approximately every 3 to 5 years, an NVP-wide vaccine safety research agenda.
3 Development and updating this agenda should use the ISTF, ISCG, or other similar coordinating
4 body Subcommittees specified in Coordination Recommendation 2.1, under the direction of the
5 ISTF, ISCG, or other similar coordinating body Subcommittee on Research. This agenda should
6 address research in both vaccine safety science (e.g., epidemiological, clinical, and laboratory
7 studies) as well as post-licensure surveillance for adverse events. Key focus areas of this agenda
8 should include, but not be limited to, identifying and addressing the following:

- 9 • Needs and opportunities for eliminating unnecessary redundancy across these activities to
10 make these research activities more effective and efficient.
- 11 • Needs and opportunities for new or redirected studies toward reducing or eliminating
12 gaps in knowledge relevant to vaccine safety.
- 13 • Needs and opportunities to assess the potential risks of vaccines currently in use.
- 14 • Strengths and limitations of the processes for assessing vaccine safety before and after
15 licensure.
- 16 • Existing basic research programs and findings that may have applicability in the broader
17 scope of vaccine safety research, to create linkages between these research programs to
18 improve the broader knowledge of vaccine safety science.

19

20 **Research Recommendation 4.2 – Building a Vaccine Safety Research Community**

21 Given that research into vaccine safety is broadly defined to contain a variety of fields and
22 disciplines, including, but not limited to, immunology, clinical practice, epidemiology, and
23 pathophysiology, the NVP, with the assistance of the ISTF, ISCG, or other similar coordinating
24 body Subcommittee on Research (see Coordination Recommendation 2.1), should implement the
25 following coordination efforts:

- 26 • Facilitate a community of vaccine safety researchers that crosses the boundaries from
27 basic research, clinical research, and epidemiology to ensure continuity of research from
28 different arenas, entities, and disciplines.
- 29 • Share vaccine safety-related research findings with all members of the ISTF, ISCG, or
30 other similar coordinating body at regular monthly Task Force meetings.
- 31 • Leverage existing infrastructure and investments for vaccine safety research, such as
32 CISA and the National Children's Study.
- 33 • Engage vaccine manufacturers to capitalize on their expertise, large preclinical and
34 clinical databases, specimen repositories, and scientific resources to inform further
35 vaccine safety studies.
- 36 • Coordinate the development, implementation, and periodic update of the National
37 Vaccine Safety Scientific Agenda, as described in Research Recommendation 4.1.

- Ensure feedback between stakeholders within the vaccine safety enterprise so that research findings translate into safer products and guidelines for their use when appropriate.

Research Recommendation 4.3 – Research Funding and Investigator Training

- The NIH should identify and link multidisciplinary, internal and external vaccine safety research programs and funding, including encouragement of researchers to highlight research that may have a potential application to vaccinology and vaccine safety through targeted applications of keywords and requested reviewers, and through appropriate revisions of "PA-08-256: Research to Advance Vaccine Safety" to ensure a wide range of applicability across multiple disciplines.
- The HHS and its related agencies, along with academic partners and professional organizations, should develop training programs for scientists and medical professionals in basic vaccinology and in related sciences that will contribute to informing vaccine safety research.
- The HHS and its related agencies, along with academic partners and professional organizations should support training in vaccine safety for scientists in non-biomedical research areas (e.g. cost/benefit analyses, quality assurance, and policy analysis).

Research Recommendation 4.4 – Ascertainment of Public Concerns and Perceptions

The CDC should evaluate the usefulness of rapidly deployed and analyzed public opinion polling and active monitoring of electronic media to ascertain public concerns and perceptions about vaccine safety. Findings should be used to inform both the vaccine safety research agenda and communications programs.

Research Recommendation 4.5 – Research Directed to Clinical Practice

- The NVP, working through the ISTF, ISCG, or other similar coordinating Body Subcommittee on Research and Clinical Practice (see Coordination Recommendation 2.1) and relevant non-governmental partners (e.g., the CISA Network) should coordinate research to improve clinical guidance and methods for the identification, evaluation, clinical management, and reporting of adverse events, including information on clinical follow-up for individuals who experience AEFI. Best practices identified from sources such as the DoD VHC Network, AHRQ, and the Brighton Collaboration should be utilized to the greatest possible extent.
- The CDC and the FDA should develop a consistent and systematic approach using VAERS or another related reporting mechanism to characterize the extent to which vaccine administration errors occur. The CDC and the FDA also should implement

1 strategies for reducing these errors as appropriate for quality improvement and patient
2 safety. The long-term goal of this approach is to establish a standard mechanism for
3 surveillance of administration errors.
4

5 **Research Recommendation 4.6 – Data Access**

6 The NVPO should establish a temporary expert committee, such as the IOM, to look at the
7 feasibility of and mechanisms for providing researchers access to preclinical, clinical, and post-
8 licensure vaccine safety data. This committee should consider the strengths and weaknesses of
9 developing a data center that may include the following:

- 10 • Final data that were used for decisions about vaccine safety (following "reproducible
11 research" strategies).
- 12 • General data that have not been used for a specific adverse event, such as VSD, CISA,
13 and associated specimen banks, to the extent possible.
- 14 • Preclinical, clinical, and post-licensure data that are part of the application process.
15

16 **Research Recommendation 4.7 – Biological Specimens**

17 The CDC and the CISA Network should complete the planning and implementation of
18 recommendations for the enhancement of a National Vaccine Safety Biospecimen Repository
19 linking biological samples to clinical data for unusual AEFI to accelerate studies of biological
20 mechanism and subpopulations at increased risk for adverse events.
21
22

5. POST-LICENSURE SURVEILLANCE FINDINGS AND RECOMMENDATIONS

Findings

The NVAC found the following areas where enhancements could be made to the post-licensure surveillance mechanisms of vaccine safety:

- Programs for post-licensure surveillance and hypothesis testing for AEFI could be enhanced regarding the quality and timeliness of reports and scope of coverage, while balancing the resources required for such efforts with the potential benefits. New data analysis technologies can assist in improving the timeliness of these findings.
- Even well-developed epidemiological studies of actual or potential vaccine-associated adverse events could benefit from increased sample sizes to be able to more quickly detect rare adverse events.
- Calculation of background rates of potential AEFI in subpopulations would assist in vaccine safety risk assessment.
- Efforts to educate physicians and the public about the uses and limitations of the VAERS may increase their understanding of the system.
- Strategies are needed to enhance the quality of data reported to the VAERS. Some potential examples are outreach to individuals who make reports encouraging more complete data reporting and utilization of technology and data abstraction methods from electronic health records to enhance reporting.
- For an increasingly proactive way to measure AEFI, the vaccine safety enterprise needs an expanded array of surveillance approaches to ascertain early concerns through public opinion polling and active monitoring the "new media," such as blogs.
- Causality assessment, as performed by the IOM, is a useful and robust process. Institutionalizing a standing causality assessment group is needed.
- Acute investigations have worked, but the broader responsibilities of federal departments and agencies involved in causality assessments may benefit from improved coordination to maximize available data and expertise.
- The timeframe for updating the vaccine injury compensation table could be improved commensurate to the pertinent and existing knowledge base.
- Provider and public awareness of the VICP could be increased.
- Recognizing the work of the CDC in vaccine safety-related public health response, best practices and collaborative efforts could be promulgated among federal departments and agencies that may be involved in these types of public health response activities.

- Future public health response could benefit from increased data linkages between sources of immunization data, both from traditional and non-traditional immunization settings, and sources of health outcomes data.

Recommendations

Post-licensure Surveillance Recommendation 5.1 – Plans for New Vaccines

The ISTF, ISCG, or other similar coordinating body Subcommittee on Post-licensure Surveillance (see Coordination Recommendation 2.1) should convene relevant federal agencies and departments at appropriate times to perform the following tasks:

- Review established proactive action plans for post-licensure vaccine safety evaluations.
- Ensure coordination of activities.
- Develop a systematic, integrated approach to post-marketing surveillance plans that includes FDA requests for post-licensure monitoring, CDC commitments to VSD data analysis, and participation from other federal agencies and departments that may contribute to coordinated post-licensure surveillance.

Post-licensure Surveillance Recommendation 5.2 – Data Considerations

The ISTF, ISCG, or other similar coordinating body Subcommittee on Post-licensure Surveillance should incorporate the following components into the plans reviewed in Post-licensure Surveillance Recommendation 5.1:

- Ensure vaccine safety data are collected on ACIP-recommended vaccine usage not covered by FDA-approved labeling.
- Utilizing coordination efforts detailed in Coordination Recommendation 2.1 and research coordination efforts detailed in Research Recommendation 4.2, post-licensure vaccine safety surveillance activities should be informed by manufacturer's expertise and experience with pre-licensure clinical trials.
- Utilize and fully take advantage of the FDA Sentinel Project for expanding the population under active surveillance to 100 million by 2012 to do signal detection, validation and confirmation. Special attention should be given to federal initiatives on electronic health, medical, and immunization records and alternative ways to link data, and under-represented groups, such as minority populations.

Post-licensure Surveillance Recommendation 5.3 – Implementation of Programs

The ISTF, ISCG, or other similar coordinating body, representing the NVP-coordinated agencies and departments, should lead efforts to implement the national agenda to enhance post-licensure surveillance (see Research Recommendation 4.1) and the post-licensure surveillance plans for

1 new vaccines or vaccine formulations/combinations (see Post-licensure Surveillance
2 Recommendation 5.1).

4 **6. CLINICAL PRACTICE FINDINGS AND RECOMMENDATIONS**

6 **Findings**

7 The NVAC found the following areas where enhancements could be made to the clinical practice
8 component of vaccine safety:

- 9 • Clinical guidance and other support related to identification, evaluation, treatment,
10 management and coping with AEFI could be improved and widely disseminated to
11 vaccination providers, patients, and caregivers.
- 12 • The use of barcode systems for identifying and tracking the immunizations provided
13 could ensure proper vaccine administration.

15 **Recommendations**

16 **Clinical Practice Recommendation 6.1 – Utilizing Improvements**

17 The ISTF, ISCG, or other similar coordinating body Subcommittee on Clinical Practice should
18 ensure dissemination of information on the following topics:

- 19 • Improved clinical guidance to clinicians on the identification, evaluation, clinical
20 management, and reporting of adverse events, particularly when advances in clinical
21 practice, as described in Research Recommendation 4.5, are made and published. An
22 example of this type of guidance is the CISA hypersensitivity algorithm.
- 23 • Clinical practice activities that can prevent adverse events associated with vaccine
24 administration errors, particularly when advances are made in examining the occurrence
25 of these errors, as described in Research Recommendation 4.5.

27 **Clinical Practice Recommendation 6.2 – Barcode Labeling of Vaccines**

28 Acknowledging efforts currently underway at the FDA, the NVAC is supportive of efforts to
29 create a routine system of barcode labeling of vaccine vials and pre-filled syringes that is
30 compatible, ideally, with international standards.

32 **7. COMMUNICATION FINDINGS AND RECOMMENDATION**

34 **Findings**

35 The NVAC found the following areas where enhancements could be made to the communication
36 mechanisms of vaccine safety:

- The provision of a one-stop source of comprehensive information about vaccine safety for the public and providers, such as how to report adverse events, how the vaccine safety system has successfully identified previous actual adverse events following immunizations, how the vaccine injury compensation program works, what safety-related research is underway, could improve communications to the public on these topics. Vaccines.gov is a good start to providing this type of comprehensive information but could be improved upon.
- Coordination between the different federal departments and agencies (e.g., the CDC, the FDA, the DoD, the VA) with respect to their outreach about the safety of vaccines could be improved.

Recommendation

Communication Recommendation 7.1

The ISTF, ISCG, or other similar coordinating body Subcommittee on Communications (see Coordination Recommendation 2.1) should ensure development and maintenance of a unified program of public information about vaccines, vaccine safety, and the vaccine safety system that can serve as a resource to the public and health professionals. This information should be available, at a minimum, through a publicly accessible website, such as Vaccines.gov. This program, and associated dissemination tools, should focus on establishing and maintaining links to specific agencies information about the safety, efficacy and effectiveness of each licensed vaccine, including:

- The Vaccine Information Statement.
- The official package insert, as prepared and issued by the FDA, and the FDA's analysis provided to VRBPAC.
- Summaries of the design, scope, and results of the key clinical trials that supported licensure.
- Summaries of the design, scope, and results of any post-licensure clinical trials required by the FDA or being conducted under the auspices of one or more of the other NVP-participating agencies.
- Abstracts of product-specific peer-reviewed research reports published after licensure.
- Abstracts of ongoing product-specific research studies funded by the HHS or other departments of the federal government.
- A clearer public explanation of each agency's role in post-licensure vaccine safety.

This communications plan also should focus on utilizing existing mechanisms, and where

1 necessary, establishing mechanisms and publicizing means by which members of the public can
2 obtain information about vaccines.

3
4 The CDC should utilize and disseminate findings from research into public concerns (see
5 Research Recommendation 4.4) to develop communications tools applicable to address public
6 concerns and perceptions.

7
8 The CDC and the FDA should improve methods for communication about the extent to which
9 follow-up to individual VAERS reports may be conducted.

11 **8. STAKEHOLDER AND PUBLIC ENGAGEMENT FINDINGS AND RECOMMENDATION**

13 **Findings**

14 The NVAC found the following areas where enhancements could be made to the stakeholder and
15 public engagement component of vaccine safety:

- 16 • The national vaccine safety system could benefit from the input of stakeholders and the
17 general public and through the enhanced assurance, accountability, and transparency that
18 engaging these groups provides.
- 19 • Vaccine safety-focused engagement activities could benefit from expert advice
20 representing all pertinent scientific and technical disciplines.

22 **Recommendation**

23 **Stakeholder and Public Engagement Recommendation 8.1**

- 24 • The ASH should direct the NVPO to work with the NVAC and the ISTF, ISCG, or other
25 similar coordinating body Subcommittee on Stakeholder and Public Engagement (see
26 Coordination Recommendation 2.1) to develop and maintain an ongoing and meaningful
27 program of appropriate stakeholder engagement around vaccine safety. This program
28 should focus on ensuring that appropriate stakeholders and the public have the
29 opportunity to regularly provide feedback, through routine stakeholder and public
30 engagement processes, during planning and evaluation of major NVP activities, such as
31 the development of the vaccine safety research agenda (see Research Recommendation
32 4.1) and the NVAC reviews of NVP activities.
- 33 • This program also should publicize various means by which members of the public can
34 share concerns and recommendations about vaccine safety not related to a specific
35 occurrence of a specific AEFI, as would be reported through the VAERS.

- 1 • The ASH should direct the NVPO to continue working with the NVAC and NVP-
2 coordinated agencies to ensure that all vaccine safety-focused engagement activities
3 benefit regularly from expert advice representing all pertinent scientific and technical
4 disciplines.
5

6 **9. COST EVALUATION OF RECOMMENDATIONS FINDINGS AND** 7 **RECOMMENDATION**

8 **Findings**

9 The NVAC found the following areas where enhancements could be made to the stakeholder and
10 public engagement component of vaccine safety:
11

- 12 • Resources, including fiscal support and staffing, provided to vaccine safety activities
13 could be increased at levels commensurate with the needs and opportunities that exist.
14

15 **Recommendation**

16 **Cost Evaluation of Recommendations Recommendation 9.1**

17 The NVPO should coordinate, across the relevant departments and agencies, a cost evaluation of
18 the recommendations in this report approved by the NVAC. This evaluation should be presented
19 to the NVAC at a regularly scheduled NVAC meeting.
20
21

INTRODUCTION

Vaccines are one of the most effective public health interventions. [1] Vaccines have greatly reduced morbidity and mortality from diseases that were formerly major killers in this country (see Table 1). In recent years, new vaccines against infectious agents such as rotavirus have been successful at reducing circulating disease [2], and high rates of vaccine coverage [3] continue to protect the majority of individuals and communities from vaccine-preventable diseases in the United States. In addition to reducing morbidity and mortality, routinely recommended pediatric vaccines have been estimated to save \$9.9 billion in direct costs and \$43.3 billion in societal costs over the lifetime of a single-year birth cohort [4], for the seven-vaccine series routinely recommended as of 2001. An updated economic analysis of the current vaccination schedule is underway. (page 5, lines 18-26)

No medical product can be proven to be 100% safe, and vaccines can carry some risks. Possible adverse reactions vary by vaccine and population vaccinated, and can include both minor but common side effects, such as fever, to very rare but life-threatening illnesses, such as anaphylaxis (approximately 0.5-1.5 cases / 1,000,000 vaccinations). [5] (page 5, lines 28-31) It is important to have in place a comprehensive system to assess and understand the benefits and risks of vaccines, including the risks of adverse events following immunization (AEFI). The United States has such a system, which is the subject of this White Paper. (new)

The United States vaccine safety system is a large, multifaceted system comprised of many components spanning the entire life-cycle from basic vaccine research, development, testing, licensure, and widespread use (see Figure 1). The goal of this system is to identify in a timely manner and minimize the occurrence of adverse events from vaccines. It is through this multifaceted framework that the national vaccine safety system has proven to be a sound system for identifying, evaluating, and responding to vaccine safety issues that have emerged. (page 6, lines 8-12)

As with any system, opportunities for improvement always exist. Previous federal efforts have been undertaken to review and enhance the nation's vaccine safety system, with the broadest reaching and most recent being in 1998. This White Paper comes 13 years after last review of the national vaccine safety system and builds upon those recommendations by identifying strategies for ongoing continuous improvement of the system and providing new recommendations more applicable to 21st century science, technology, social, and fiscal settings. (new)

Table 1. Impact of vaccines on vaccine-preventable diseases in the United States compared to the pre-vaccine era.

Disease	Reported Illness before Vaccine	Reported cases 2009 ¹⁴⁷	Percent Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Polio (paralytic)	16,316	1	> 99%
Measles	530,217	71	> 99%
Rubella	47,745	3	> 99%
Congenital Rubella Syndrome	152	2	99%
Haemophilus influenzae (Hib)	20,000	213	99%
Mumps	162,344	1,991	99%
Tetanus	580	18	97%
Pertussis (whooping cough)	200,752	16,858	92%

BACKGROUND

The foundation of the modern vaccine safety system infrastructure in the United States is the National Childhood Vaccine Injury Act of 1986 (NCVIA). [63] The NCVIA authorized the creation of the National Vaccine Injury Compensation Program (VICP) and the Vaccine Adverse Event Reporting System (VAERS), and authorized the establishment of the National Vaccine Program (NVP) and the National Vaccine Advisory Committee (NVAC). Additionally, the NCVIA mandated Institute of Medicine (IOM)-led studies of the relationship between vaccination and adverse events as well as requiring the development of "vaccine information materials" by the Centers for Disease Control and Prevention (CDC), leading to the development and distribution of Vaccine Information Statements. (page 15, lines 7-10)

The U.S. Department of Health and Human Services (HHS) Assistance Secretary for Health (ASH) was appointed Director of the NVP, and the National Vaccine Program Office (NVPO) was created to coordinate and integrate the efforts of the NVP as the agent of the ASH. (page 15, lines 14-15) The NVPO is responsible for coordinating and ensuring collaboration among the many federal agencies involved in vaccine and immunization activities. Additionally, the NVPO staffs the NVAC. (new)

The NVAC advises and makes recommendations to the Director of the NVP on matters related to program responsibilities. Specifically, the NVAC recommends ways to achieve optimal prevention of human infectious diseases through vaccine development, and provides direction to prevent adverse reactions to vaccines. One of the functions of the NVAC is to recommend research priorities and other measures the Director of the NVP should take to enhance the safety and efficacy of vaccines, which is the subject matter of this White Paper. (new)

FORMATION OF THE VACCINE SAFETY WORKING GROUP

In 2005, an IOM committee published *Vaccine Safety Research, Data Access, and Public Trust*. One of the recommendations of the IOM committee was that "a subcommittee of the NVAC that includes representatives from a variety of stakeholders (such as advocacy groups, vaccine manufacturers, the FDA [Food and Drug Administration], and the CDC) review and provide advice to the National Immunization Program on the Vaccine Safety Datalink research plan annually." In response to the IOM review and recommendation, the CDC Immunization Safety Office (ISO) developed a 5-year research agenda for all of their vaccine safety research activities, referred to as the draft ISO Scientific Agenda. (new)

The CDC ISO requested that the NVAC address the following charge: undertake and coordinate a scientific review of the draft ISO Scientific Agenda, and provide advice on its content (e.g., Are the topics on the Agenda appropriate? Should other topics be included?), the prioritization of scientific topics, and possible scientific barriers to implementing the Scientific Agenda and suggestions for addressing them. (new)

To address this charge, the NVAC formed the Vaccine Safety Working Group (VSWG), which deliberated on the draft ISO Scientific Agenda from April 2008 through May 2009. The Working Group identified gaps in the ISO Scientific Agenda and developed prioritization criteria for research topics. The Working Group made 32 recommendations in three general categories: general recommendations, capacity recommendations, and research needs recommendations. These recommendations were approved by the NVAC on June 2, 2009. (new)

CURRENT CHARGE TO THE VACCINE SAFETY WORKING GROUP

One month later, the VSWG began work on its second charge of obtaining expert advice on utilizing 21st century science and technology to enhance the federal vaccine safety system. In July 2009, the HHS ASH asked the NVAC VSWG "to review the current federal vaccine safety system and develop a White Paper describing the infrastructure needs for a federal vaccine safety system to fully characterize the safety profile of vaccines in a timely manner, reduce adverse events whenever possible, and maintain and improve public confidence in vaccine safety."

Review the current federal vaccine safety system and develop a White Paper describing the infrastructure needs for a federal vaccine safety system to fully characterize the safety profile of vaccines in a timely manner, reduce adverse events whenever possible, and maintain and improve public confidence in vaccine safety.

– U.S. Department of Health and Human Services
Assistant Secretary for Health

This NVAC White Paper reports NVAC's findings and recommendations based on a review of the current federal vaccine safety system by the VSWG and a draft it provided the NVAC. The charge to the NVAC from the ASH recognizes the importance of vaccinations and vaccine safety to the American public. With the advances in the scientific, social, and fiscal landscape since the

1 last review of the vaccine safety was undertaken in 1998, the NVAC believes this review of the
2 system is timely. (new)

4 **MAKEUP OF THE VACCINE SAFETY WORKING GROUP**

5 The VSWG was originally comprised of 18 members, nine of whom were current or past NVAC
6 members (Appendix 3). (Four members subsequently agreed to take on non-voting consultant
7 status after the first year of the committee's deliberation due to time constraints.) The VSWG has
8 a broad range of expertise including pediatric and adult infectious diseases, genomics,
9 immunology, epidemiology, public health, maternal and child health, pharmacoepidemiology,
10 and biostatistics. Additionally, current or past consumer representatives from each of four federal
11 advisory committees with a role in vaccine safety (the NVAC, the Advisory Committee on
12 Immunization Practices [ACIP], the Vaccines and Related Biological Products Advisory
13 Committee (VRPAC), and the Advisory Commission on Childhood Vaccines [ACCV]) were
14 members. (page 11, lines 22-27)

15
16 Ten federal ex officio members (Appendix 4) also provided information about aspects of the
17 existing safety system. The federal ex officio members did not participate in development of the
18 VSWG's findings and recommendations, and the findings and recommendations in this report do
19 not reflect their or their agencies' points of view. (page 11, lines 29-32)

21 **METHODS FOR ADDRESSING ITS CHARGE**

22 To address its second charge of reviewing the national vaccine safety system and developing a
23 draft of this White Paper, the NVAC VSWG looked at prior reviews of the vaccine safety system
24 by other agencies and by the VSWG itself, conducted meetings in person and by telephone,
25 created subgroups to focus on specific information and processes, and developed initial draft
26 recommendations for improvement to the national vaccine safety system. (new)

27 **PRIOR REVIEWS OF THE VACCINE SAFETY SYSTEM**

28 **HHS Activities and Related Reviews by the NVAC**

29 There have been several previous federal efforts to enhance the nation's vaccine safety
30 system. The broadest reaching of these reviews was the *Final Report of the Task Force on*
31 *Safer Childhood Vaccine* [44] released in 1998. This task force, convened by the National
32 Institutes of Health (NIH), made four recommendations on greater assessment of concerns
33 about vaccine safety, strengthened research into developing safer vaccines, increased
34 surveillance related to vaccine safety and efficacy, and coordinated review and assurance
35 related to federal vaccine safety efforts. (page 11, lines 43-48)

36
37 In 1999, the NVAC reviewed and strongly endorsed the Vaccine Safety Action Plan, which
38 is the formal implementation plan for the 1998 Task Force report. [60] In the intervening
39 years, there has been partial implementation of these recommendations, though the lack of a

1 sufficient budget process has hampered full implementation of this Action Plan. [61] (page
2 11, lines 48-51; page 12, line1)

4 **Reviews by the Institute of Medicine**

5 The Institute of Medicine's (IOM's) *Priorities for the National Vaccine Plan* released in
6 December 2009 identified four high priority vaccine safety actions that were largely
7 consistent with NIH's recommendations: [46]

- 8 1. Establish a process for identifying potential vaccine safety hypotheses for further
9 study from annual reviews of data from the VAERS, the Vaccine Safety Datalink
10 (VSD), the Clinical Immunization Safety Assessment (CISA) Network, the National
11 VICP, and from information from outside of the United States.
- 12 2. Develop a framework for prioritizing a national research agenda.
- 13 3. Create a permanent vaccine safety subcommittee in the NVAC for ongoing review
14 and guidance on vaccine safety issues.
- 15 4. Expand and enhance vaccine safety science research through the CDC ISO, the FDA,
16 and the NIH. (page 12, lines 8-14)

18 **Review of CDC ISO Scientific Agenda**

19 The NVAC VSWG was established in April 2008 with a charge to review the CDC ISO
20 Draft Scientific Agenda (Charge 1). Specifically, the VSWG was asked to provide advice on
21 the content of the ISO draft research agenda, the prioritization of research topics, and
22 possible scientific barriers to implementing the research agenda, with suggestions for
23 addressing them. (page 12, line 18-21)

24
25 The NVAC VSWG review [62] of the CDC ISO research agenda [53] provided the
26 opportunity for a coordinated review of vaccine safety research activities, though it was
27 confined to activities occurring only through the ISO. The Working Group was challenged to
28 limit discussion of vaccine safety only to the ISO, acknowledging that "many other
29 governmental agencies and departments have important roles in vaccine safety research" and,
30 as a result, suggested that there is a "strong need for a federal vaccine safety research agenda
31 that encompasses research undertaken by non-ISO CDC offices, FDA, and the NIH and
32 requires increased collaboration and coordination between all federal agencies with a stake in
33 vaccine safety." (page 12, lines 23-34)

34
35 The VSWG's recommendations were approved by the full NVAC on June 9, 2009, and
36 transmitted to the ASH and the CDC. Following this approval, the VSWG began work on its
37 review of the federal vaccine safety system (Charge 2). (new)

39 **VSWG MEETINGS AND SUBGROUP ACTIVITIES**

1 The VSWG also conducted meetings in person and by telephone. The Working Group's kickoff
2 meeting was held on July 15–16, 2009, and was followed by two more in-person meetings.
3 Additionally, 18 conference call meetings were held. (new)

4
5 The VSWG also created three subgroups to focus on specific information and processes and to
6 develop initial recommendations for improvement to the national vaccine safety system. These
7 subgroups were the Biomechanisms Subgroup, which focused on biological mechanisms of
8 vaccine adverse events; the Surveillance and Epidemiology Subgroup, which focused on the
9 epidemiology to detect, quantify, and examine the cause of vaccine adverse events; and the
10 Structure and Governance Subgroup, which focused on topics related to the structure, oversight,
11 resources, and processes for the vaccine safety system. (new)

12
13 Stakeholder and public input also was solicited during the VSWG's work on its charge.
14 Stakeholders were engaged in a meeting in April 2010. When version 2.0 of the draft White
15 Paper was available in May 2011, the public was invited to comment, and a meeting to obtain
16 stakeholder input was held on June 12, 2011 (Appendix 9). (new)

17
18 A more detailed explanation of the VSWG's methods for addressing Charge #2 is provided in
19 Appendix 2. (new)

20
21 At the June 13, 2011, full NVAC meeting, version 2.0 of the draft White Paper was discussed
22 along with a summary of public comment and the results of the prior day's Stakeholder Meeting,
23 which the majority of NVAC members had attended. Following the NVAC discussion, the final
24 version 3.0 of the White Paper presented at the September 2011 NVAC meeting was developed
25 under the direction of the NVAC chair by a technical writer under contract to the NVPO, with
26 assistance from the NVPO and the VSWG co-chairs. (new)

27

OVERVIEW OF THE NATIONAL VACCINE SAFETY SYSTEM

The United States vaccine safety system is overseen and coordinated by federal departments and agencies, and vaccine safety activities occur both pre-licensure and post-licensure. Pre-licensure activities include basic biomedical research, vaccine development, and application for licensure. Post-licensure activities include adverse event surveillance, vaccine signal validation and hypotheses testing, biological mechanisms research, causality assessment, vaccine injury compensation, public health engagement, communication and information dissemination, reduction of vaccine administration errors, and management of vaccine adverse events in clinical practice. (new)

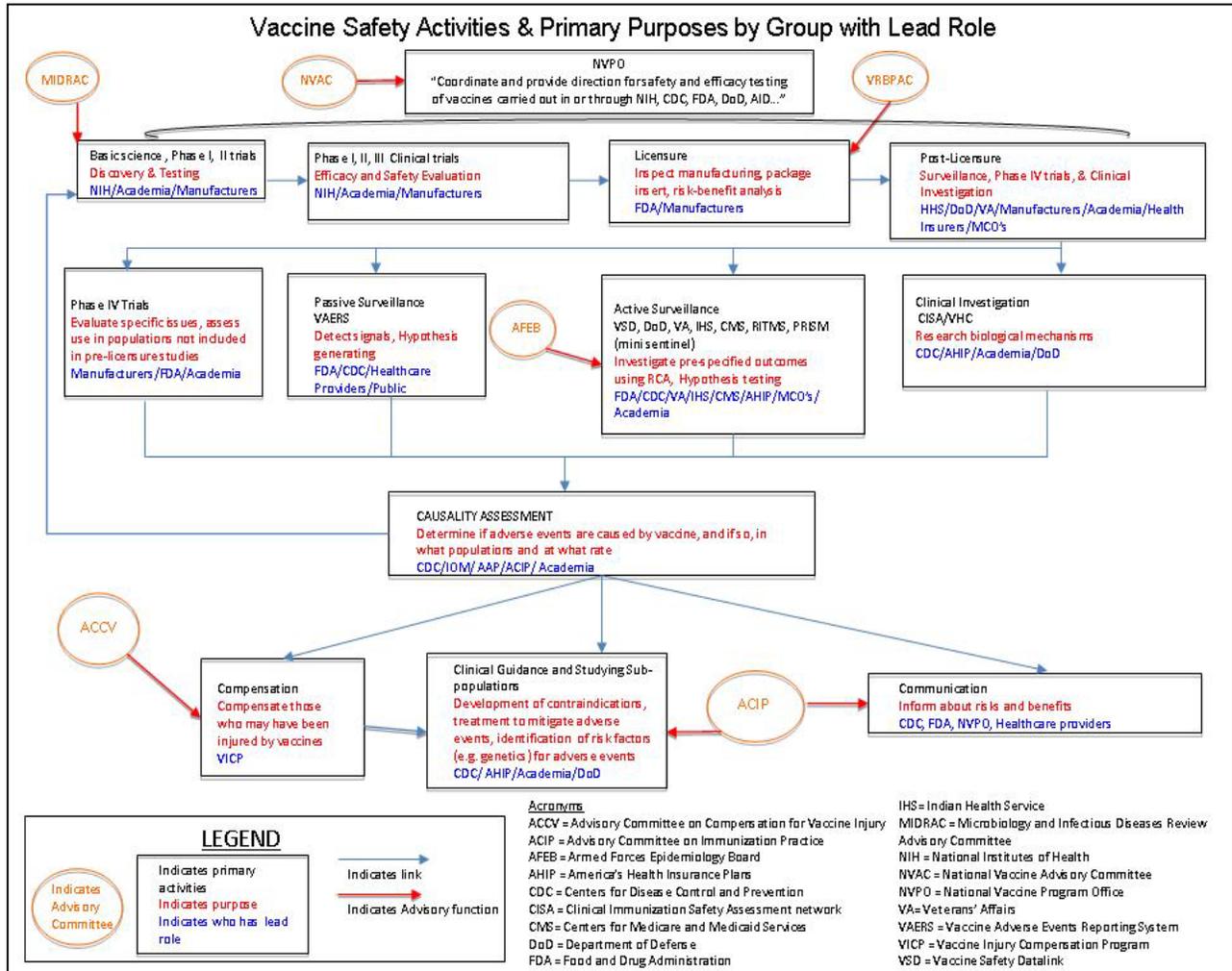
THE CURRENT VACCINE SAFETY SYSTEM

The key federal departments and agencies with a role in vaccine safety activities include the U.S. Department of Health and Human Services (HHS)—encompassing the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), the National Institutes of Health (NIH), the Centers for Medicare and Medicaid Services (CMS), the Indian Health Service (IHS), and the National Vaccine Program Office (NVPO)—and the U.S. Department of Defense (DoD) and the U.S. Department of Veterans Affairs (VA). The relationships between these federal components of the vaccine safety system are illustrated in Figure 1. (page 15, lines 23-27) The components of this system provide multiple levels of focus and assurance of the safety of vaccines in the United States. (new)

Coordination of the System

The federal Immunization Safety Task Force (ISTF) was established in 2008 to ensure that all federal efforts relevant to immunization safety are coordinated and integrated and that opportunities to enhance synergies across the federal government in immunization safety are identified. (page 15, lines 43-44) This cross-government task force is led by the HHS and is jointly chaired by the Assistant Secretary for Health (ASH) and the Assistant Secretary for Preparedness and Response (ASPR). The Task Force includes participation from the VA and the DoD. All three departments are responsible for vaccine research and safety monitoring. (new)

1 **Figure 1. Design of the current United States federal vaccine safety system.**
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Basic Biomedical Research

While knowledge of immune system function has increased dramatically in recent years, much basic research needs to be done on the actual biological mechanisms that drive a successful immune response to a vaccine as well as the mechanisms underlying vaccine adverse reactions, how quality of the antigen affects the response, how adjuvants enhance the response to vaccines, and how their use may affect the vaccine safety profile. The Institute of Medicine (IOM) Immunization Safety Review Committee has cited a need for more information on the biology underlying vaccine adverse reactions. [51] [52] One potential pathway for basic biomedical research related to vaccine adverse reactions is to study triggers of more common, less severe reactions (e.g., fever, allergy) to identify common mechanisms that may help focus research into rarer reactions while also helping to identify means to ameliorate these reactions. In addition, with the increasing availability of new

1 research technologies, an achievable goal may be to define mechanisms that tip the balance
2 toward a detrimental adverse response to immunization; in particular, why certain individuals
3 may react adversely while others respond positively to a given vaccine. (page 16, lines 18-
4 29)

5
6 Basic research on the immunologic and physiologic effects of vaccines and vaccine
7 ingredients is typically funded by the National Institutes of Health (NIH) and vaccine
8 manufacturers, and conducted by academia and industry. Much of the work of the NIH is
9 organized on a disease-specific basis; applicable funding has been dedicated to a program of
10 novel adjuvant discovery and development program through targeted contracts, such as the
11 Human Immune Phenotyping program, and a recent vaccine safety program announcement.
12 [64] (page 16, lines 31-35)

13
14 Basic research, including immunology research, which may not be vaccine-focused, is
15 critical to advance knowledge. By considering the biologic role of the antigenic and the non-
16 antigenic components of a vaccine, one can generate useful hypotheses about the cause of an
17 adverse reaction to the vaccine that can be tested in well-designed non-clinical, clinical and
18 epidemiological studies. The National Vaccine Advisory Committee (NVAC) has previously
19 recommended that "ISO should evaluate cumulative levels of non-antigen component
20 exposure possible through the schedule of recommended vaccinations . . . a carefully
21 designed screening process that places ingredients into groups that are of: (1) minimal
22 concern, (2) potential for concern and deserving of research, and (3) in need of further risk
23 analysis and consideration for risk management." [62] While the NVAC has no specific
24 concerns regarding non-antigen components of vaccines, this approach to screening is more
25 transparent and allows targeting of research efforts to specific components based on scientific
26 assessment. (page 16, lines 37-47)

27
28 Basic research can also be vaccine-focused/targeted. An example of this type of targeted
29 research involves the concerns raised in 1999 regarding infant exposure to ethyl mercury as a
30 result of thimerosal used as a preservative in some vaccines, with subsequent
31 epidemiological studies including outcomes associated with (methyl) mercury. [65] [66]
32 However, a lack of basic research on the comparative biological effects of and clearance of
33 ethyl mercury and methyl mercury impacted the public health response to concerns regarding
34 the safety of thimerosal in 1999. The identified need for these targeted biomedical studies led
35 to research done since 1999 on the metabolism of ethyl mercury. [67] [68] [69] CDC studies
36 examining thimerosal-containing vaccines and neurodevelopmental outcomes, including
37 autism, have not found evidence to support an association between thimerosal-containing
38 vaccines and autism. [65] [66] These types of feedback mechanisms between basic biomedical
39 research and epidemiologic research are critical to identifying priority study areas in both
40 fields. (page 16, lines 49-51; page 17, lines 1-8)

1 **Pre-licensure Activities**

2 The NIH also plays a role in vaccine discovery and in early phase clinical evaluation through
3 the Vaccine and Treatment Evaluation Units (VTEUs), a group of National Institute of
4 Allergy and Infectious Diseases (NIAID)-funded medical research institutions. Before
5 biologics, such as vaccines, are licensed for marketing, they must undergo extensive clinical
6 trials for efficacy and safety. The FDA Center for Biologics Evaluation and Research
7 (CBER) is responsible for working with industry from preliminary application through
8 clinical trials leading to licensure. A key area of vaccine development and pre-licensure
9 activities is animal and toxicology studies conducted prior to beginning clinical trials. One
10 example of these extensive tests was the studies on Madin-Darby Canine Kidney cells
11 proposed for use in cell-culture influenza vaccine development. [70] (page 17, lines 12-18)

12
13 Modern pre-licensure vaccine clinical trials commonly involve tens of thousands of
14 participants and are a model for clinical trials of other medicines. However, they have some
15 limitations. Even these large sample sizes are too small to detect rarer adverse events
16 following immunization (AEFI). Additionally, follow-up monitoring for safety related events
17 during pre-licensure clinical trials is usually time limited by the duration of the trial, meaning
18 that delayed onset adverse events may not be detected. Finally, clinical trials are generally
19 conducted in healthy individuals that may not be representative of the population to be
20 vaccinated. Those excluded from clinical trials may have unique immunological responses
21 that increase or decrease the risk of AEFI. These limitations can be overcome with enhanced
22 monitoring after the vaccine is licensed (see below). Even with a reduced capacity to identify
23 all vaccine-associated adverse reactions, clinical trial data are useful to indicate the more
24 common AEFI as well as potential AEFI signals to monitor following licensure. (new)

25 **Vaccine Licensure (new)**

26
27 Successful completion of pre-licensure activities and clinical trials are followed by the
28 submission of a Biologics License Application (BLA). To be considered, the license
29 application must provide a multidisciplinary FDA review team (e.g., medical officers,
30 microbiologists, chemists, biostatisticians) with the efficacy and safety information necessary
31 to make a risk/benefit assessment and to recommend or oppose the approval of the vaccine.
32 Also during this stage, the proposed manufacturing facility undergoes a pre-approval
33 inspection during which production of the vaccine as it is in progress is examined in detail.

34
35 Following the FDA's review of a license application for a new indication, the sponsor and the
36 FDA may present their findings to the FDA's Vaccines and Related Biological Products
37 Advisory Committee (VRBPAC). This non-FDA expert committee (scientists, physicians,
38 biostatisticians, and a consumer representative) provides advice to the Agency regarding the
39 safety and efficacy of the vaccine for the proposed indication.

40

1 Vaccine approval also requires the provision of adequate product labeling to allow healthcare
2 providers to understand the vaccine's proper use, including its potential benefits and risks, to
3 communicate with patients and parents, and to safely deliver the vaccine to the public. ([URL](#))
4

5 **Role of the Advisory Committee on Immunization Practices**

6 Vaccine licensure does not guarantee that a vaccine will be recommended for use. Such a
7 recommendation comes from the Advisory Committee on Immunization Practices (ACIP).
8 The ACIP consists of 15 experts in fields associated with immunization, who have been
9 selected by the Secretary of the HHS to provide advice and guidance to the Secretary, the
10 ASH, and the CDC on the control of vaccine-preventable diseases. In addition to the 15
11 voting members, ACIP includes 8 *ex officio* members who represent other federal agencies
12 with responsibility for immunization programs in the United States, and 30 non-voting
13 representatives of liaison organizations that bring related immunization expertise.
14

15 The role of the ACIP is to provide advice that will lead to a reduction in the incidence of
16 vaccine preventable diseases in the United States, and an increase in the safe use of vaccines
17 and related biological products. The Committee develops written recommendations for the
18 routine administration of vaccines to children and adults in the civilian population;
19 recommendations include age for vaccine administration, number of doses and dosing
20 interval, and precautions and contraindications. The ACIP is the only entity in the federal
21 government that makes such recommendations. ([URL](#))
22

23 **Post-licensure Activities**

24 Adverse Event Surveillance

25 Surveillance systems are the primary source for the outcome data used in the post-
26 licensure vaccine safety research system. Their usefulness is defined by the quality of the
27 data collected and the ability to use these data to perform appropriate analyses. (page 18.
28 **Lines 23-25**) In the United States, the Vaccine Adverse Event Reporting System
29 (VAERS) is the primary surveillance system for detecting AEFI. The VAERS is a
30 voluntary, post-licensure, national passive reporting surveillance system jointly managed
31 by the CDC and the FDA, and serves as an early-warning system to detect adverse events
32 that may be related to vaccines. As a passive system, all reports are made voluntarily and
33 without active, targeted outreach by surveillance system operators. The main utility of the
34 VAERS is the identification of rare and severe AEFI, as evidenced by the rapid
35 identification of increased intussusceptions following administration of the first
36 generation rotavirus vaccine. [75] (page 18, lines 42-48)
37

38 The VAERS receives reports of possible vaccine adverse events from a wide variety of
39 sources, including parents, providers, manufacturers, pharmacists, and the military.

1 Healthcare providers and manufacturers are required to report two types of adverse
2 events to the VAERS within a seven-day period: (1) those that the vaccine manufacturer
3 has identified as contraindicating reactions to the vaccine as specified within the
4 manufacturer's package insert and (2) any adverse events present on the National Vaccine
5 Injury Compensation Program (VICP) Vaccine Injury Table. [100] Healthcare providers
6 and manufacturers also are encouraged to report any other adverse event they believe to
7 be clinically important. (page 18, lines 48-51; page 19, lines 1-4) From 2006-2010,
8 approximately 61% of all domestic reports came from either healthcare providers or
9 vaccine manufacturers, and approximately 10% came from vaccine recipients or their
10 parent/guardian. In addition, approximately 5% came from State Health Coordinators
11 (CDC, personal communication, 2010). (page 19, lines 4-7)

12
13 The strength of the VAERS is its ability to detect potential signals for followup; this was
14 demonstrated through the identification of an increase in cases of intussusception
15 following receipt of the first licensed rotavirus vaccine. The identification of this signal
16 led to further vaccine safety studies, ultimately resulting in the removal of the vaccine
17 from the market and the development of safer rotavirus vaccines. [76] (page 19, lines 8-
18 11)

19
20 While the VAERS serves as a national spontaneous reporting system that enables the
21 early detection of signals (potential vaccine safety concerns) and is particularly suited to
22 detect potential rare adverse events that can be more rigorously investigated, there are
23 several key limitations of this system. [77] [78] First, there are not precise denominator
24 data (number of vaccine doses administered/persons vaccinated) to put the number of
25 adverse event reports into context; only the number of doses manufactured or delivered is
26 available. Without denominator data and without information on non-vaccinated
27 individuals, vaccine-associated rates and background rates for comparison cannot be
28 calculated. Second, reporting to the VAERS is not always consistent or complete, and
29 underreporting is often cited as a significant problem for some AEFI. [79] [80] Reports
30 that are made to the VAERS may not always be complete, and even a fully completed
31 VAERS report form may lack the full range of information needed for epidemiologic
32 analysis. Additionally, increased reporting related to one particular vaccine or adverse
33 event can be stimulated by increased awareness or media reporting of that event. [81]
34 Newer vaccines often have higher VAERS reporting rates than older vaccines due to
35 heightened awareness of these vaccines and concern over their novelty. [78] Because of
36 these limitations, VAERS reports alone cannot be used to make population-level
37 causality assessments. If it appears as though a vaccine might be causing a health
38 problem, CDC and FDA will do additional studies or investigations. (page 19, lines 13-
39 28)

1 While information regarding the VAERS is on the Vaccine Information Statements
2 provided with every vaccination, immunizing physicians and nurses may not spend
3 adequate time discussing specific elements of vaccine safety, the vaccine safety system,
4 or the VAERS with their patients or their parents. [82] [83] (page 19, lines 31-35)
5 Improved education of and communication to physicians may decrease inaccurate
6 perceptions of the system, such as inability to perform causality studies or the perception
7 that VAERS reports trigger public health or medical responses to individual adverse
8 events. (new)

9
10 In addition to the VAERS, there are other surveillance systems in the United States to
11 detect AEFI:

- 12 • Adverse Drug Event Report System (ADERS) – A VA system that standardizes
13 adverse event reporting at the facility level, centralizes adverse drug event data
14 analysis, and improves the efficiency of adverse drug event report coding used to
15 categorize and classify symptoms associated with the event. (new)
- 16 • Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) – A
17 collaboration between the American Academy of Asthma, Allergy and
18 Immunology, the Organization of Teratology Information Specialists, and the
19 Pregnancy Health Interview Study at the Slone Epidemiology Center, Boston
20 University ([URL](#)). (page 23, lines 5-8)
- 21 • FDA Sentinel Initiative – Developed after the passage of the FDA Amendments
22 Act of 2007 [54] to create an additional mechanism to acquire information on
23 vaccine safety. The Sentinel Initiative is intended to create the Sentinel System, a
24 large surveillance system that will be used for medical product safety evaluations,
25 including devices, drugs, and vaccines. Currently, development and refinement of
26 the system is being conducted through the Mini-Sentinel Pilot Project ([URL](#)). [95]
27 Mini-Sentinel provides a systematic means to interrogate a distributed network of
28 independent healthcare databases, and is intended to include access to data of at
29 least 100 million patients by July 1, 2012. The Mini-Sentinel Pilot Project
30 incorporates, and is expanding on, the vaccine safety-related systems of the
31 PRISM System (described below) to provide infrastructure that will permit
32 evaluation of the full range of adult and pediatric vaccines. (page 23, lines 34-43)

33
34 Two surveillance systems were developed to detect AEFI during the 2009 H1N1
35 influenza pandemic:

- 36 • Real Time Immunization Monitoring System (RTIMS) – Implemented through
37 the Institute for Vaccine Safety at the Johns Hopkins Bloomberg School of Public
38 Health. RTIMS used web-based queries to identify adverse events at 1 day, 1
39 week, and 6 weeks following immunization, and was used for targeted follow-up

1 for nearly 10,000 H1N1 immunizations. Most AEFI identified through RTIMS
2 were reported to VAERS. (page 22, lines 47-51; page 23, lines 1-2)

- 3 • Post-licensure Rapid Immunization Safety Monitoring System (PRISM) – A near
4 real-time active surveillance system for monitoring the safety of the H1N1
5 influenza vaccine. Vaccine exposure and adverse event outcome data from large
6 health plans were merged with vaccine exposure data from state Immunization
7 Information Systems (IIS) to evaluate H1N1 vaccine doses given by both public
8 and private providers. (new)

9
10 Active surveillance (i.e., close and regular monitoring) is a tool used to detect AEFI when
11 new vaccine development for an emerging, widespread disease, such as the 2009 H1N1
12 influenza vaccine, is ramped up. (new) During this event, the DoD implemented active
13 surveillance for AEFI in active duty military through examination of electronic health
14 records. (page 22, lines 35-36) Additionally, the CDC Emerging Infections Program
15 (EIP) and CMS conducted enhanced surveillance for Guillain-Barre Syndrome (GBS)
16 during the pandemic. (page 22, lines 42-44)

17
18 Surveillance data alone usually cannot prove causation. (page 18, line 26) Instead,
19 VAERS data and data from other surveillance system detect vaccine signals that need to
20 be validated. Also, this data is used to generate hypotheses for further study and testing
21 by laboratory, clinical, and epidemiologic methods. (page 18, lines 26-27 + new)

22 23 Vaccine Signal Validation and Hypothesis Testing

24 Once a vaccine signal has been identified and validated, generated hypotheses are tested.
25 The Vaccine Safety Datalink (VSD) is the primary system for testing of hypotheses in
26 vaccine safety and is used to determine adverse event rates, assess associations, complete
27 population-based epidemiological studies to address a hypothesis, and contribute to
28 causality assessment. The VSD is a collaborative effort between the CDC, 10 managed
29 care organizations (MCOs) (facilitated by America's Health Insurance Plans [AHIP]), and
30 academic researchers. The VSD links databases, including vaccination and medical
31 records, from approximately 9 million children and adults (approximately 3% of the
32 United States population) and allows for testing of hypotheses and rapid cycle analysis
33 (RCA) for "near real-time" surveillance. Data are actively gathered; since the whole
34 population is known, the denominator is known. Because VSD data are obtained based
35 on MCO medical records databases, it is possible to define the population under study,
36 including direct calculations of denominator data. (page 21, lines 31-40)

37
38 RCA is an analytical technique whereby data from medical care encounters is monitored
39 and analyzed continuously to examine the potential association between selected health
40 outcomes and vaccination. By making these comparisons repeatedly—often on a weekly

1 basis—as new immunization and adverse event occurrence data are collected, researchers
2 have the ability to quickly assess potential associations between a particular vaccine and
3 adverse event. [93] (page 21, lines 42-46)
4

5 While the VSD does cover a large number of individuals, it may still be difficult to detect
6 very rare adverse events and AEFI potentially related to vaccines recommended for a
7 smaller population (e.g., meningococcal vaccine recommended for adolescents) which
8 would only constitute a subset of the total VSD population. (page 22, lines 4-7) Multi-
9 year studies may overcome this limitation. (new) Additionally, the VSD sites typically
10 have a very small population of Medicaid patients, which may impact socio-economic
11 diversity in the population under study. (page 21, lines 7-8)
12

13 Biological Mechanisms Research

14 Understanding the biological mechanisms behind the human immune response to a
15 vaccine or a confirmed adverse event may lead to (1) improved safety monitoring and
16 assessment by defining which populations or sub-populations should be monitored, (2)
17 identification of individuals at increased risk for experiencing adverse events (genetic
18 risk factors, previous or concurrent illness), (3) better clinical approaches to
19 treating/ameliorating adverse events that occur, (4) development of improved vaccines
20 that avoid the biological mechanism in question (as appropriate), and (5) improved risk
21 communication about the safety of vaccines, particularly with regard to groups identified
22 as higher risk for vaccine adverse reactions. (page 23, lines 50-51; page 24, lines 1-6)
23

24 Targeted clinical research into biological mechanisms of AEFI is essential. One locus of
25 this work is the Clinical Immunization Safety Assessment Network (CISA). The CISA is
26 comprised of six academic centers funded by the CDC. Its mission is to conduct clinical
27 research about adverse events and the role of individual variation, counsel clinicians on
28 vaccine safety issues, and assist policy makers in recommendations for exclusion criteria.
29 The CISA investigates the pathophysiological basis of adverse events, identifies risk
30 factors, and develops evidence-based guidelines. The CISA has the potential to rapidly
31 develop protocols and implement studies using multi-disciplinary research teams by
32 capitalizing on the diverse expertise available in its academic centers. These academic
33 centers also have a diverse range of specialty clinics that can be used for recruitment of
34 patients. The CISA and the VSD have sponsored a Vaccine Safety Fellowship Program to
35 train new investigators in the important area of vaccinology, which will encourage further
36 interest and expertise in evaluating vaccine safety. (page 24, lines 32-45)
37

38 The CISA also manages a biospecimen repository for samples collected from patients
39 experiencing unusual AEFI, which holds great promise for studying a variety of vaccine
40 safety questions. Inherent challenges in specimen collection as well as lack of resources

1 have limited the use of the repository except for specific studies that include specimen
2 collection in the protocol. Federal efforts are underway to identify opportunities for
3 enhancing the biospecimen repository, which are critical to maximizing its utility for
4 biological mechanisms research. (page 24, lines 47-50; page 25, lines 1-2)
5

6 There are other federal research programs addressing the clinical components of vaccine
7 adverse reactions. The FDA has been active in this arena. One example is the FDA
8 initiative to use VAERS data on cases of post-Lyme Disease vaccination arthritis to
9 facilitate a case-control study of the underlying genetics of this adverse event. [97] More
10 recently, the FDA CBER Office of Biostatistics and Epidemiology established the
11 Genomics Evaluation Team for Safety to examine the genomics of vaccine adverse
12 reactions. [98] Additionally, the Vaccine Healthcare Centers (VHC) Network is a DoD
13 organization that performs clinical consultation, conducts research into vaccine adverse
14 events research, and develops and disseminates educational materials about clinical
15 vaccine safety concerns in the military. [99] The VHC Network collaborates with other
16 research and healthcare related entities, such as the CISA and the Military Vaccine
17 Agency (page 25, lines 6-18), which supports DoD vaccination programs protecting
18 military service members and their dependents and beneficiaries and provides educational
19 support and training resources for DoD healthcare providers and clinicians. (URL) (new)
20

21 On a final note, it is important to recognize the role that manufacturers play in biological
22 mechanisms research. The vaccine industry has a strong incentive to ensure that their
23 products are safe and effective, and, thus, has invested significant resources into
24 determining the biological mechanisms of adverse reactions, not only during the pre-
25 licensure phase, but also post-licensure. (page 27, line 27-30)
26

27 Causality Assessment

28 On the population level, causality assessments often use set standards, and include factors
29 such as: the strength and consistency of the association; the specificity of the outcome of
30 interest; a clear temporal relationship between the vaccine and the adverse health
31 outcome; whether there is a biological mechanism to cause the adverse event; a dose
32 response relationship; experimental evidence; coherence between studies; and analogies
33 to other causal relationships. Population level causality assessments are done by many
34 individuals and groups, such as academics publishing in peer reviewed literature,
35 advisory groups such as the ACIP and the American Academy of Pediatrics (AAP) who
36 make vaccine recommendations, and most notably the IOM. (new)
37

38 The IOM was initially charged by Congress in the National Childhood Vaccine Injury
39 Act (NCVIA) in 1986 to review the evidence for causality assessments. Since then,
40 the IOM has done 11 reviews, with the most comprehensive review being completed in

1 August, 2011. These IOM causality assessments have been hindered by an inadequate
2 understanding of potential biologic effects elicited by immunization. Because 60% of the
3 IOM causality assessments have found "inadequate evidence to make a determination,"
4 [50] further research into this area may lead to more definitive causality assessments.

5 (new)

6 7 Vaccine Injury Compensation

8 No vaccines or any other medications can be proven to be 100% safe; therefore, adverse
9 reactions or vaccine-related injuries could occur in some individuals. While there are
10 societal benefits from vaccination, costs following vaccine adverse reactions are borne by
11 the injured individual or their family. Recognizing that monetary compensation does not
12 fully address the hardship created by vaccine adverse events in all cases, the NCVIA
13 created the VICP, which is administered by the HRSA. The VICP uses causality
14 assessment information to establish a Vaccine Injury Table, which lists and explains
15 injuries or conditions that are presumed to be caused by vaccines. It also lists time
16 periods in which the first symptom of these injuries or conditions must occur after
17 receiving the vaccine. If the first symptom of these injuries or conditions occurs within
18 the listed time periods, it is presumed that the vaccine was the cause of the injury or
19 condition unless another cause is found. If an injury or condition is not on the Table or if
20 an injury or condition did not occur within the time period on the Table, the injured
21 person must prove that the vaccine caused the injury or condition. Such proof must be
22 based on medical records or opinion, which may include expert witness testimony. After
23 reviewing the injury claim, a "special master" (an appointed lawyer) decides if the claim
24 will be paid and, if so, how much will be paid for the claim. [100] A review is currently
25 underway to address changes in the Table regarding more recently recommended
26 vaccines and adverse events potentially associated with them.² (page 25, lines 42-51;
27 page 26, lines 1-5)

28 29 Public Health Response

30 When an acute concern arises about the safety of a vaccine, elements of the federal, state
31 and local public health systems may be mobilized to participate in the response. The
32 CDC has both proactive and reactive public health response capabilities. The agency
33 develops and disseminates clinical guidelines and recommendations for safe vaccination,
34 provides education to healthcare providers on safe vaccination practices, and participates
35 in and coordinates public health responses when vaccine safety questions arise. For
36 example, in 1999, when intussusception was suspected to be occurring following

² On August 25, 2011, the Institute of Medicine released *Adverse Effects of Vaccines: Evidence and Causality* which presents a comprehensive review of the scientific evidence about the potential risks of eight vaccines covered by the VICP. The report identifies some risks that are linked to vaccines as well as some effects that are not caused by immunization. This report was released after this NVAC White Paper was developed.

1 vaccination with the first licensed rotavirus vaccine, identified through VAERS reports,
2 the CDC mobilized its Epidemic Intelligence Service (EIS) officers, and state and local
3 health departments participated in case finding as part of a large multistate, case-control
4 study. The findings from these activities led to the halting of the use of this vaccine
5 shortly after identification of the intussusception case cluster in the VAERS. (page 26,
6 lines 9-18)

8 Communication and Information Dissemination

9 An important component of the public health response is the manner in which
10 information is communicated to the public and to healthcare providers regarding vaccine
11 safety issues. The CDC and the FDA have been responsible for rapid communication and
12 outreach following identification of potential vaccine safety issues as well as preemptive
13 efforts to inform the public about the safety of coming vaccines (e.g., 2009
14 H1N1 influenza vaccine). (page 26, lines 22-26) There is much publicly available
15 information on vaccines and vaccine safety, particularly through publicly available
16 websites (e.g., www.cdc.gov, www.fda.gov), as well as through information distributed
17 through the CDC Health Alert Network (HAN) ([URL](#)), which is a national program that
18 provides vital health information and the infrastructure to support the dissemination of
19 information at the state and local levels, and beyond. Efforts at coordinated public
20 communication on vaccines more broadly, through websites such as www.flu.gov and
21 www.vaccines.gov, have proven beneficial. (page 26, lines 33-29)

23 Reduction of Vaccine Administration Errors

24 Another area of safety concerns related to vaccination is vaccine administration errors.
25 Common identified administration errors are administration of the wrong vaccine, the
26 wrong dose of the vaccine, or administration at an incorrect timeframe relative to the
27 recommended vaccination schedule. [102] [103] One way to address these errors is through
28 the "five rights" framework: Right Vaccine, Right Time, Right Dose, Right Route, and
29 Right Patient. [102] (page 26, lines 44-48)

31 The IOM, in *To Err is Human*, referenced five questions recommended by the National
32 Patient Safety Partnership for patients to ask to reduce the possibility of medication error.
33 While these are directed more towards prescription medications, the intent is similar for
34 vaccines. (page 26, lines 49-51; page 27, line 1)

36 There is no central reporting mechanism for tracking vaccine administration errors. If an
37 administration error results in injury (e.g., shoulder injury related to incorrect vaccine
38 administration) [104], it should be reported to the VAERS, but errors for which no injury
39 occurs are not required to be reported to the VAERS. Other databases and reporting
40 systems that track vaccine administration errors include MEDMARX [105], the

1 Medication Error Reporting Program at the Institute for Safe Medication Practices [106],
2 and the FDA MedWatch Program [107]. (page 27, lines 1-6)

3
4 One way to help ensure proper vaccine administration is the use of barcode systems for
5 identifying and tracking the immunizations provided. The FDA currently is developing
6 processes and guidance for expanded use of barcode labeling systems. [108] (page 27,
7 lines 8-10)

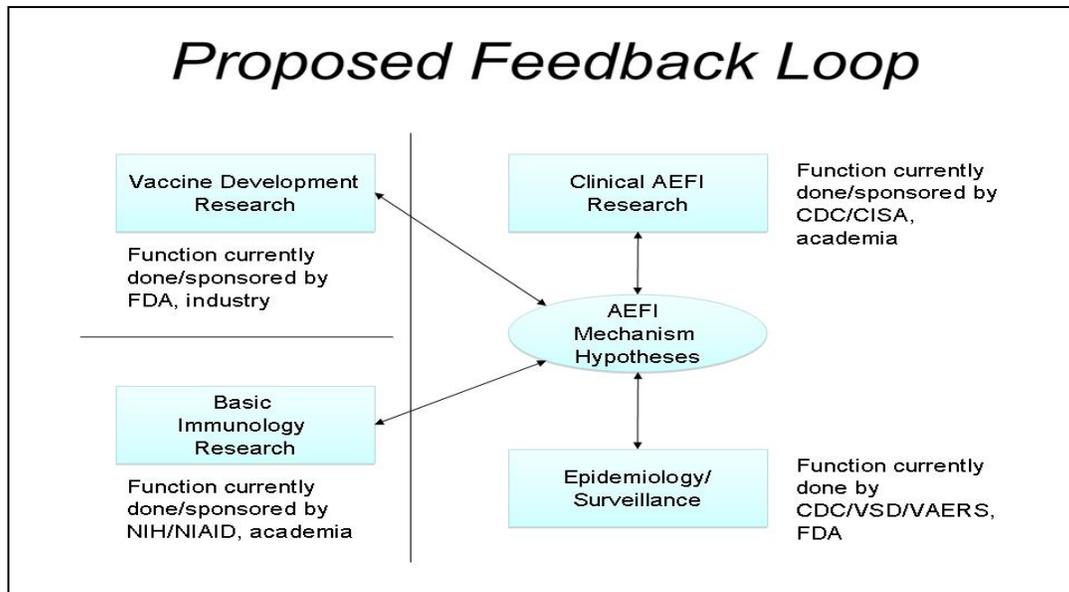
8 9 Management of Vaccine Adverse Events in Clinical Practice

10 Once a vaccine adverse reaction is identified in a patient, the clinician must be able to
11 evaluate and manage the severity of the reaction through clinical guidance. The CDC
12 "Pink Book" contains information on identifying and managing AEFI, with a focus on the
13 more common, and typically less severe, AEFI. [109] The CDC ISO Scientific Agenda,
14 previously reviewed by the NVAC VSWG, contains a call for the development of
15 evidence-based clinical guidance protocols for managing AEFI [53], but there does not
16 currently appear to be a central repository of such clinical guidance. (page 27, lines 15-
17 20)

18 19 **Feedback Mechanisms**

20 To improve our understanding of the biological mechanisms underlying adverse events,
21 robust communication and collaboration is needed between basic scientists conducting
22 laboratory research, epidemiologists conducting population-based research, and other
23 partners, such as scientists within the vaccine industry. (page 27, lines 24-27) When a
24 significant adverse reaction is observed in epidemiological/surveillance studies,
25 communication with laboratory scientists may help to understand potential underlying
26 mechanisms; similarly, if laboratory research uncovers mechanisms through which a severe
27 adverse event may be triggered, targeted surveillance and epidemiologic studies may be
28 helpful to assess whether there is an actual association of immunization with the event. This
29 two-way communication between epidemiologic and basic biomedical science research is
30 critical to ensuring that all parties involved in studies related to vaccine safety are aware of
31 concurrent research that may impact their own studies. A model for the flow of information
32 and collaboration among these various scientific disciplines is the Clinical and Translational
33 Science Awards (CTSA), now awarded to 46 institutions nationally, with a mission to
34 accelerate technology development from the lab to the clinic. Investigator initiated research
35 is an important mechanism for innovation and enhancing scientific understanding. The
36 general format for this flow and feedback of information is displayed in Figure 2 below.
37 (page 27, lines 32-43)

Figure 2. Proposed feedback loop between research, surveillance, and response functions of the vaccine safety system.



STRENGTHS OF THE CURRENT VACCINE SAFETY SYSTEM (new)

The overall strength of the federal vaccine safety system is its ability to monitor the development and administration of vaccines and potential adverse events through a framework involving federal, state, and local departments and agencies, drug and vaccine manufacturers, private enterprise, and the general public. Oversight is in place to ensure the safety of vaccines, to detect adverse events, and to take steps to diminish and rectify impacts of AEFI.

Coordination of the System

The identified strengths of the coordination of the vaccine safety system include the following:

- The system has the ability to coordinate prompt, cross-agency responses to specific issues (e.g., the H1N1 influenza pandemic response, the ISFT as a coordinating body).
- Multiagency program coordination has been demonstrated by the VAERS and the Vaccine Analytics Unit (VAU), a collaboration among the CDC, the FDA, and the DoD.
- The system includes agencies that serve high-risk patients in the vaccine safety system (e.g., the IHS, the CMS, and the VA).

- 1 • NVPO has the ability to capitalize on opportunities for innovation (e.g., the PRISM
2 System, the Biospecimen Repository Meeting held in April 2010) through its role and
3 broad view of agency and departmental activities.
- 4 • Prior independent and external reviews of safety issues have been conducted by the
5 NVAC, such as was done in the 2009 NVAC report on the CDC ISO Scientific
6 Agenda.
- 7 • Advisory committees (e.g., the NVAC, the ACIP, the VRBPAC, the MDRAC, the
8 Advisory Committee on Childhood Vaccines [ACCV], the Armed Forces
9 Epidemiological Board [AFEB]) play a role in decision making processes (i.e.
10 licensure alone is not sufficient for incorporation into the recommended vaccine
11 schedule).

12 13 **Basic Biomedical Research**

14 The identified strengths of basic biomedical research in the federal vaccine safety system
15 include the following:

- 16 • Current vaccines have an excellent safety profile. Numerous studies have been
17 conducted to address outstanding safety issues. ([URL](#))
- 18 • The updated ISO scientific agenda is a key step for the direction of vaccine safety
19 research
- 20 • Multiple new research methods have been developed and utilized to evaluate the
21 safety of vaccines and their components.

22 23 **Pre-licensure Activities**

24 The identified strengths of pre-licensure activities in the federal vaccine safety system
25 include:

- 26 • Code of Federal Regulations (CFR) standards for Good Laboratory Practices, Good
27 Manufacturing Practices, and Good Clinical Practices.
- 28 • IRB standards for clinical trial approval and monitoring.
- 29 • The FDA CBER process for review of Investigative New Drug (IND) applications.
- 30 • Peer review process for underlying science and clinical results of IND applications.
- 31 • Rigor of pre-licensure assessment, including basic science evaluation, animal
32 testing, and randomized control trials of individual vaccines, and in combination to
33 evaluate safety, immunogenicity, and efficacy.

1 **Vaccine Licensure**

2 The identified strengths with regard to vaccine licensure in the federal vaccine safety system
3 include the following:

- 4 • The FDA has successfully kept up with an expanding number of licensure
5 applications for new vaccines while their budget has not expanded accordingly.
- 6 • Clinical trials for licensure include minorities, women, and other disadvantaged
7 groups.
- 8 • The FDA has developed methodologies and laboratory capacity to ensure adequate
9 evidence is available for licensure decisions.
- 10 • The FDA has been quick in addressing new technologies and urgent needs, such as
11 the H1N1 influenza vaccine.

12

13 **Post-licensure Activities**

14 There are many strengths of the post-licensure activities of the federal vaccine safety system,
15 including the following:

- 16 • The ACIP provides advice that leads to a reduction in the incidence of vaccine
17 preventable diseases in the United States and an increase in the safe use of vaccines
18 and related biological products.
- 19 • Multimodal post marketing surveillance is in place, such as the VAERS, the VSD, the
20 Real Time Immunization Monitoring System (RTIMS), and the CDC EIP.
- 21 • Population-focused monitoring is conducted on vulnerable subgroups by departments
22 and agencies, such as the IHS, the DoD, the VA, and the CMS.
- 23 • Ongoing prospective reviews of safety are conducted on newly licensed vaccines.
- 24 • Safety signals have been picked up rapidly (i.e., intussuption in rotavirus vaccine),
25 and the VSD has conducted large number of studies examining possible associations.
- 26 • Public health investigations are responsive to potential safety concerns.
- 27 • The system has an ad hoc ability to mount larger scale studies or studies of special
28 populations (e.g., the PRISM and the Vaccines and Medications in Pregnancy
29 Surveillance System [VAMPSS]).
- 30 • VAERS and VSD budgets are modest in comparison to the costs of vaccination
31 programming.
- 32 • Numerous studies have been conducted among subpopulations, including racial and
33 ethnic minorities.

- 1 • VSD is considered a model for drug safety surveillance, and has pioneered numerous
2 new study methodologies.
- 3 • The IOM has a long history of conducting efficacious and rigorous causality
4 assessments.
- 5 • IOM reviews exclude persons with prior vaccine funding, and have strict protocols in
6 place to ensure objectivity.
- 7 • The ACIP, the AAP, and the American Academy of Family Physicians (AAFP) have
8 procedures for addressing conflicts of interest.
- 9 • CISA has used innovative methods for their individual level causality assessment
10 studies.

11 **Feedback Mechanisms**

12 The identified strengths with regard to feedback mechanisms in the federal vaccine safety
13 system include the following:
14

- 15 • Established mechanisms for feeding back information and changing decisions are in
16 place.
- 17 • A mechanism exists for establishing vaccine related adverse events and compensation
18 for injury (i.e., the VICP).
- 19 • Petitioner attorneys are reimbursed regardless of outcome, ensuring that petitioners
20 have representation.

21 **GOALS OF AN IDEAL VACCINE SAFETY SYSTEM** (page 38 – lines 6-36, edited)

22 During its review of the national vaccine safety system, the NVAC concluded that an ideal
23 vaccine safety system should consist not only of a responsive arm, but also a long-range,
24 proactive research arm. The NVAC also determined that the United States vaccine safety system
25 should be able to:
26

- 27 • Accurately detect AEFI with high sensitivity and specificity.
- 28 • Accurately quantify the risk of AEFI to allow benefit/risk comparisons.
- 29 • Assess whether an AEFI is causally linked to vaccination.
- 30 • Conduct an appropriate public health response to emerging vaccine safety issues.
- 31 • Appropriately communicate results between the scientific community and the public.
- 32 • Ensure that system processes and results are transparent.

- 1 • Better understand AEFI to develop proactive research into AEFI occurrence and
2 prevention.
- 3 • Perform these tasks in a timely manner.

4

5 The NVAC identified nine functions (Appendix 11) of a vaccine safety system and 10 attributes
6 (Appendix 12) by which these functions could be best performed. Attributes are defined as
7 qualities or characteristics the NVAC hopes to maximize for each essential system function.

8 Each of these attributes is important for all functions of the vaccine safety system, and each was
9 considered on a continuum. The NVAC identified three attributes that should be prioritized:
10 evidence-based decision making, objectivity, and transparency.

11

12 The NVAC used these ideal vaccine system goals as a guide to develop the recommendations
13 made in the next section. (new)

14

15

16

17

FINDINGS AND RECOMMENDATIONS

Overview

The charge of the National Vaccine Advisory Committee (NVAC) Vaccine Safety Working Group (VSWG), in the most distilled sense, is to review the current vaccine safety system, identify possible opportunities for improvement within the current system, and suggest potential steps to meet those opportunities. (page 28, lines 5-7) This review was called for because, in the 13 years since the last review of the system was undertaken, the scientific, social, and fiscal landscape has changed substantially. There have been significant advances in science that have and can enhance the vaccine safety system. The public has become more "socially aware" and interested in governmental activities. This calls for more transparency and accountability in the system. Finally, economic times in the United States are uncertain. Coordinating and streamlining the system can make sure that it is operating as efficiently and effectively as possible. Keeping these factors in mind, the VSWG successfully responded to its charge by conducting on behalf of the NVAC a two-year review of the current vaccine safety system, identifying opportunities for clarity and improvement, and developing draft recommendations to address these opportunities. (new)

As reflected in the review of the current system, the NVAC finds that the United States vaccine safety system is a fundamentally sound system for monitoring vaccine safety that has functioned well since the enactment of the National Childhood Vaccine Injury Act of 1986 (NCVIA), and believes that current system components should be maintained, even in times of federal funding uncertainty. (new) This does not, however, preclude additional efforts to coordinate the vaccine safety system or to utilize continuous quality improvement (CQI) approaches. Given recent advances in technology and research methodology, it is appropriate to look for and pursue opportunities to make this good system better. (page 28, lines 22-24) The NVAC believes further that, as resources are available, the federal vaccine safety system should be enhanced in response to these recommendations. (new)

Any large complex system, such as the national vaccine safety system, should operate within a CQI framework whereby, from the research and development process to vaccine administration to adverse event monitoring and reporting, the system has processes in place to develop and administer safe, effective vaccines and to detect and prevent adverse events following immunization (AEFI). Additionally, lessons learned from these processes should be used to enhance the vaccine safety system so that the quality of the system can be improved upon on a continuous basis. However, during its review of the system, it was not clear to the NVAC that the current system fully operates within a CQI framework. (new).

1 The NVAC determined that the National Vaccine Program (NVP) includes all the requisite
2 functions for a vaccine safety system (i.e., research, regulation, post-licensure surveillance,
3 guidance for immunization programs, guidance for clinicians, injury compensation, and
4 oversight) and that the organizational placements of these functions are consistent with the
5 missions of the respective participating agencies and offices. The NVAC also determined that,
6 while fundamentally sound, the leadership, coordination, and ongoing assurance of the current
7 vaccine safety system can be improved. (page 28, lines 32-38)

8
9 For some of the recommendations below, the NVAC went beyond simply stating the objective to
10 include details regarding either how the objective should be achieved or what the completed
11 objective should include. This approach was taken for three reasons: First, the NVAC seeks to
12 avoid ambiguity regarding its thinking; absent the associated details, a reader could reasonably
13 interpret the recommendation substantially differently than does the NVAC. Second, in response
14 to a recent RAND Corporation study commissioned by the National Vaccine Program Office
15 (NVPO) that found many previous NVAC recommendations to be lacking sufficient details to
16 guide implementation and called for future NVAC recommendation to be "actionable," [144], the
17 NVAC sought to make its intended actions clear. Third, the NVAC recognizes that the U.S.
18 Department of Health and Human Services (HHS) may wish to consider alternative approaches
19 to implementing the recommendations below; therefore, the NVAC believes that the details it
20 offers will provide a valuable benchmark against which to compare any given alternative
21 approach and determine whether it is more or less superior to that recommended here. (page 40,
22 lines 16-26)

23
24 The VSWG worked diligently for two years to put together its draft findings and
25 recommendations on behalf of the NVAC. As it reviewed the current national vaccine safety
26 system, the VSWG developed 23 draft recommendations for the NVAC to consider under the
27 following topic areas: leadership, coordination, assurance and accountability, research, post-
28 licensure surveillance, clinical practice, communications, stakeholder and public engagement,
29 and cost evaluation. (new)

30 31 **RELATIONSHIP OF WHITE PAPER TO THE NATIONAL VACCINE PLAN (new)**

32 The National Vaccine Plan, released in February 2011, is the nation's roadmap for a 21st century
33 vaccine and immunization enterprise. It consists of two phases: a Strategic Plan with overall
34 goals and objectives to achieve over a 10-year period and an Implementation Plan with
35 measurable outcomes and processes to achieve the goals of the plan.

36
37 One of the goals of the Strategic Plan portion of the National Vaccine Plan is to enhance the
38 nation's vaccine safety system. The vision of this goal is to "address safety-related issues,
39 strengthen the system that monitors the safety of vaccines throughout production and use, and

1 advance the safety profile of vaccines." The plan states that, "Specifically, this goal aims to
2 prevent adverse events and fully characterize the safety profile of vaccines in a timely manner."
3

4 The National Vaccine Plan was released over a year and a half after the VSWG began work on
5 its second charge of reviewing the national vaccine safety system; therefore, the Working Group
6 did not have access to the Plan for much of the work on its second charge. However, the findings
7 and recommendations made within this White Paper do align with and will help to inform
8 implementation of this particular goal of the National Vaccine Plan.
9

10 **1. LEADERSHIP FINDINGS AND RECOMMENDATIONS**

11 **FINDINGS**

12
13 Acting as the operational arm of the NVP, the NVPO is charged with coordinating activities
14 across the federal government to implement the goals of the National Vaccine Plan. [116]
15 However, the HHS Assistant Secretary of Health (ASH), who is the Director of the NVP, does
16 not have organizational authority over the agencies that comprise the NVP, which may limit
17 his/her ability to directly change or coordinate activities within these agencies. Instead, this
18 authority resides with the Secretary of HHS and Secretaries of non-HHS Departments involved
19 in vaccination and vaccine safety. It would be beneficial to increase awareness of the functions
20 and activities of the vaccine safety system among these Secretaries, and to increase their role in
21 meeting their respective charges relative to vaccine safety. It also would be beneficial for the
22 coordinating entity for the vaccine safety system (the NVPO) to be given clear authorization and
23 support to perform these coordinating functions and be held accountable for executing this
24 authority. Improved coordination will provide a greater ability to be flexible with a given
25 program to adapt to an emergent need, such as those adapted to assess "real-time" risk during the
26 H1N1 influenza pandemic. (page 29, lines 39-50)
27

28 It is important to identify and build on the best practices of collaboration and coordination that
29 occurred in recent years, primarily in response to public health emergencies (e.g.,
30 rotavirus/intussusception and H1N1 influenza pandemic), including steps to ensure the most
31 efficient use of resources in basic, clinical, and surveillance research, as well as communications
32 to external stakeholders and the public. (page 29, lines 7-11) In particular, the NVAC H1N1
33 Vaccine Safety Risk Assessment Work Group provided a rapid and transparent approach to
34 monitoring safety studies of the 2009 H1N1 vaccine, which can serve as a model in the future.
35 Additionally, it would be beneficial to have agencies with a role in immunizations, such as the
36 Indian Health Service (IHS), the Agency for Healthcare Research and Quality (AHRQ), and the
37 U.S. Department of Veterans Affairs (VA), to have adequate representation through NVP-related
38 task forces, advisory committees, and working groups. (page 29, line 12)

39 Outside of the federal government structure, public advisory committees make recommendations
40 to appropriate agencies. For example, the legislation that established the NVAC listed eight NVP

1 responsibilities in addition to vaccine safety on which the NVAC was to provide advice. Given
2 this broad scope and a limited membership size, with some membership categories prescribed by
3 the NVAC charter [117], there is a potential limit to the amount of vaccine safety expertise within
4 the full committee. This need has been addressed by subcommittees and working groups that can
5 enlist non-NVAC members, as needed. Depending on the task at hand, these groups can be task-
6 oriented with specific timelines for completion, possibly precluding long-term evaluation. (page
7 30, lines 1-8) The advances in science and technology in the 21st century require increased
8 vaccine safety expertise on the NVAC or on an NVAC vaccine safety working group.

10 OPPORTUNITIES FOR IMPROVEMENT

11 The leadership within the HHS Office of the Secretary to exercise its inherent authorities to
12 improve coordination among United States government agencies and offices could be clarified
13 and improved. This improved leadership should be able to fully engage all of HHS and the other
14 federal agencies that should be involved in the national vaccine safety system. Enhanced
15 collaboration on vaccine-safety initiatives between agencies could improve the overall system.
16 (page 30, lines 39-40)

17 Public advisory committees and their related subcommittees/working groups could benefit from
18 enhanced, expert representation to address vaccine safety issues by inclusion of subject matter
19 experts in areas such as understanding, preventing, and treating vaccine-associated adverse
20 events. (page 30, lines 45-48)

22 RECOMMENDATIONS

23 Leadership Recommendation 1.1

24 Reaffirmation of the System Structure

25 As the federal vaccine safety system incorporates 21st century science and technology, the
26 Secretary of HHS should affirm the commitment of the Department to vaccine safety by issuing
27 a policy statement that reaffirms the following components of the system:

- 28 • The NVP is a coordinated effort among the Food and Drug Administration (FDA), the
29 Centers for Disease Control and Prevention (CDC), the National Institutes of Health
30 (NIH), the Health Resources and Services Administration (HRSA), and the Centers for
31 Medicare and Medicaid Services (CMS), and the Departments of Defense (DoD) and the
32 VA and the United States Agency for International Development (USAID).
- 33 • The ASH, having been designated as Director of the NVP, is responsible for the direction
34 of the NVP activities related to coordination of vaccine safety.
- 35 • The NVPO is charged with advising the ASH regarding implementation of the
36 responsibilities of the NVP and coordinating the vaccine safety-focused activities of the

1 NVP³ (see related recommendation in Coordination Recommendation 2.1).

- 2 • The NVAC is responsible for reviewing vaccine safety policy and the vaccine safety-
3 focused activities, developing recommendations based on these reviews, and transmitting
4 its recommendations to the ASH and to the Secretary pending implementation of
5 Leadership Recommendation 1.3.

7 **Leadership Recommendation 1.2**

8 **Structural Organizational Changes in the National Vaccine Program**

9 Include the IHS and the AHRQ as participants in the NVP. Also, direct HHS agencies
10 coordinated under the NVP—accompanied by a request to the DoD, the VA, and the USAID—to
11 do the following:

- 12 • Fully participate in NVPO vaccine-safety coordination efforts.
- 13 • Identify and pursue opportunities for collaborative projects relevant to NVP vaccine
14 safety objectives with other NVP-coordinated agencies.
- 15 • Regularly obtain the advice of appropriate subject matter experts and consumers to guide
16 initiatives related to vaccine safety.
- 17 • Provide other governmental agencies, vaccine manufacturers, appropriate stakeholder
18 organizations, and representatives of the public the opportunity to provide feedback
19 regularly during the planning and implementation of initiatives related to vaccine safety,
20 and tell them about initiatives and outcomes related to vaccine safety
- 21 • Define performance expectations related to vaccine safety for NVP-coordinated agencies.

23 **Leadership Recommendation 1.3**

24 **National Vaccine Advisory Committee Charter**

25 The charter of the NVAC should be modified to reflect the following changes:

- 26 • Specify that the NVAC advises the Secretary as well as the ASH, thereby defining a
27 relationship between the NVAC and the Secretary akin to that which already exists for
28 the Advisory Committee on Immunization Practices (ACIP) and other major HHS public
29 advisory committees.
- 30 • Specify additional federal *ex officio* representation from the IHS and the AHRQ.

31 The NVAC should help evaluate the progress of the NVP-coordinated agencies toward
32 enhancing vaccine safety both in response to requests from the Secretary and at its own initiative.

³ Note that this includes NVPO being the central coordinating office of the Immunization Safety Task Force, an entity that did not exist in 1986 at the time the NCVIA was written.

1 This task could prove especially beneficial to evaluating NVP-wide initiatives to enhance
2 research, post-licensure surveillance, public information, and stakeholder engagement. The ASH
3 should charge the NVAC to create a Standing Working Group on Vaccine Safety. Members of
4 this Working Group should be selected using a similar approach as used for the H1N1 Vaccine
5 Safety Risk Assessment Working Group. Membership also should include representatives from
6 entities such as ACIP, the Advisory Commission on Childhood Vaccines (ACCV), the Vaccines
7 and Related Biological Products Advisory Committee (VRPAC), and others, as appropriate, and
8 should address issues of conflict of interest as they arise. This Working Group would, at a
9 minimum, be charged with reviewing the following long-term goals and activities:

- 10 • Implementation of these and other related NVAC safety recommendations through
11 regular reports from the Immunization Safety Task Force (ISTF), Immunization Safety
12 Coordinating Group (ISCG) (see Coordination Findings and Recommendations below),
13 or other similar coordinating body as described in Assurance and Accountability
14 Recommendation 3.2.
- 15 • Agencies' vaccine safety plans and progress in implementing them.
- 16 • Response to emerging vaccine safety issues as they arise.

18 **2. COORDINATION FINDINGS AND RECOMMENDATION**

20 **FINDINGS**

21 The need for improved coordination of components of the vaccine safety system parallels an
22 ongoing NVAC theme of increased coordination within the United States vaccine enterprise [44]
23 [62], as well citations in a number of earlier reports. [44] [46] [110] [111] Interviews with
24 representatives from different federal agencies within the vaccine safety system reflected room
25 for improvement with respect to coordination within the NVP and between its complex mix of
26 governmental and non-governmental partners and stakeholders. [101] There is recent evidence
27 that this type of coordination is possible and can pay dividends for public health. The rapid
28 response of the NVPO in implementing the NVAC recommendations of July [20] and August
29 [112] 2009 related to H1N1 influenza vaccine safety monitoring provides support for this concept.
30 When the Institute of Medicine (IOM) made recommendations related to coordination in
31 *Priorities for the National Vaccine Plan*, they cited these H1N1 safety monitoring
32 recommendations as an example of what could be accomplished through these coordinated
33 efforts. [46] (page 28, lines 40-51)

34
35 Recommendations stressing coordination in the National Vaccine Plan [46] [113] highlighted the
36 need for coordination across all components of the vaccine enterprise, including the vaccine
37 safety system. There are some examples of strong coordination, including the Vaccine Adverse
38 Event Reporting System (VAERS), co-administered by the CDC and the FDA [114], and bi-

1 weekly conference calls between the leadership of the Immunization Safety Office (ISO) and the
2 Center for Biologics Evaluation and Research (CBER) (FDA and CDC, personal
3 communication, 2011). (page 29, lines 1-7) Improved coordination among the various parts of
4 the NIH or other federal agencies directly or indirectly involved in vaccine safety was an area for
5 improvement identified by the NVAC. (new)

6
7 The ISTF was formed at the request of the Secretary of HHS in April 2008 "to ensure that all
8 federal efforts relevant to immunization safety are coordinated and integrated and that
9 opportunities to enhance synergies across the federal government in immunization safety are
10 identified." The ISTF contains representatives from HHS—encompassing the CDC, the FDA,
11 the HRSA, the NIH, the CMS, the IHS, and the AHRQ—and the DoD and the VA. It provides
12 overall coordination of the vaccine safety system; it is not a decision making body. (new) The
13 extent of involvement of the ISTF in coordination, funding, and setting of research agenda was
14 not clear to the VSWG in its review. (page 15, lines 45-46) The ISTF does not meet regularly or
15 issue routine reports, and has never provided any direct reports to the NVAC. (page 16, lines 2-
16 3)

17
18 The NVAC determined that some agencies with roles in immunization delivery and vaccine
19 safety, particularly as became apparent during enhanced vaccine safety monitoring activities of
20 the H1N1 influenza vaccination campaign (e.g., IHS), may not be fully represented through the
21 NVP or on the ISTF. (page 15, lines 50-51; page 16, lines 1-2) While the ISTF represents a good
22 model for an interagency task force that could achieve the coordination and communication
23 needs of the NVP, it is an organizational decision by the NVPO if the ISTF is the appropriate
24 coordinating body. If the NVPO does not deem the ISTF as the appropriate coordinating body, it
25 should appoint another coordinating body, hereafter referred to as the Immunization Safety
26 Coordinating Group (ISCG), which should include at least the agencies represented on the ISTF.
27 (new)

28 29 **OPPORTUNITIES FOR IMPROVEMENT**

30 The ASH and the NVPO Director could increase the scope of the ISTF's vaccine safety
31 coordinating activities and expand its membership to include agencies with roles in
32 immunization delivery and vaccine safety or the ASH and the NVPO Director could create a new
33 ISCG or other coordinating body to fulfill the recommendations made herein (i.e., the ISTF
34 could be expanded or a new group that includes the ISTF could be formed). (new)

35
36 Enhanced collaboration on vaccine-safety initiatives between agencies is needed. (page 30, line
37 37) A formalized, visible coordinating body for vaccine safety within the federal government
38 could enhance this collaboration and provide assurance and accountability of the vaccine safety
39 system. (new)

40

1 **RECOMMENDATION**

2 **Coordination Recommendation 2.1**

3 **Expanded Role and Composition for the ISTF, ICSG, or Other Similar Coordinating Body**

4 The ISTF, the ICSG, or other similar coordinating body should make regular reports, in
5 accordance with the structure described in Assurance and Accountability Recommendation 3.2.
6 The scope of the ISTF's or ICSG's vaccine safety coordinating activities, under the leadership of
7 the ASH and the NVPO Director, should specifically include focused effort involving
8 subcommittees of the ISTF, ICSG, or a similar coordinating body in the following areas:
9 research, post-licensure surveillance, clinical practice, communications, and stakeholder and
10 public engagement. This may best be carried out by establishing a subcommittee or some other
11 body.

12
13 The NVPO should expand the membership of the ISTF or create the ICSG or other similar
14 coordinating body to ensure representation from the agencies and departments specified as
15 contributing to the NVP components outlined in the NCVIA, or subsequently redesignated or
16 renamed agencies, including the CMS, the AHRQ, and the USAID.

18 **3. ASSURANCE AND ACCOUNTABILITY FINDINGS AND** 19 **RECOMMENDATIONS**

21 **FINDINGS**

22 Assurance and accountability are important attributes of the vaccine safety system, as with any
23 governmental program. Mechanisms to affirm that the system is operating according to its design
24 (assurance) and that the responsibilities of the different components of the system are fulfilled
25 (accountability) are important for reasons of both effectiveness and transparency.

26
27 As part of drafting this White Paper, the VSWG engaged in a fact-finding session at its first
28 meeting in July 2009 where a panel discussion was held to present different approaches to
29 assurance in other safety arenas (see Appendix 2). Based on this session and further staff
30 research, the VSWG developed and discussed three options for external independent assurance
31 related to vaccine safety, with the second of these options having three potential configurations
32 (see Appendix 13). These included the following:

- 33 • Option 1 – Empower the NVAC to be responsible for vaccine safety assurance.
- 34 • Option 2 – Establish a fixed-tenure panel outside of the HHS to monitor the efforts of the
35 NVP and the NVAC, respectively, to improve the vaccine safety system. (Option 2a was
36 to establish a Presidential Commission, Option 2b was to establish an IOM Committee,

1 and Option 2c was to create an Independent Agency within the Executive Branch to
2 oversee the vaccine safety system.)

- 3 • Option 3 – Create an Independent Agency within the Executive Branch to focus on the
4 safety of vaccines (i.e., to operate some or all components of the system).

5
6 The VSWG worked for over a year to develop, define, and discuss the assurance options. The
7 VSWG developed a set of pros and cons for each recommendation to further its discussions. The
8 options were included in the Vaccine Safety White Paper version 2.0 that was published for
9 public comment and was the subject of the June 2011 Stakeholder's Meeting. Despite extensive
10 efforts by its members to debate and discuss the options over a period of many months, the
11 VSWG was not able to come to a consensus on the preferred assurance option prior to the June
12 2011 NVAC meeting where the White Paper recommendations were discussed in detail.

13
14 A straw poll following the Stakeholder and NVAC meetings, with 11 of 14 VSWG members
15 responding, showed six in favor of Option 1, one in favor of Option 2a, three in favor of Option
16 2b, and one in favor of Option 3. A synopsis of their opinions on these options is provided
17 below.

- 18 • Those favoring Option 1 viewed it as the most efficient and effective use of existing
19 resources available for vaccine safety assurance. They saw this option as capitalizing on
20 the authority previously bestowed upon the NVAC through the U.S. Public Health
21 Services Act and as the most feasible for implementation and fully within the scope of
22 the original act and role of the NVAC. Additionally, supporters of Option 1 noted that the
23 NVAC has shown leadership and capability to perform this assurance role as
24 demonstrated through responsive actions in the development, operation, and public
25 reporting of the Vaccine Safety Risk Assessment Working Group (VSRAWG) during the
26 2009 H1N1 pandemic. This option was noted as the least disruptive mechanism to current
27 vaccine safety activities. Supporters of this option thought that the major drawbacks of
28 the other options included substantial feasibility issues regarding operational, financial,
29 and political implementation, and lack of evidence to warrant recommending an
30 additional layer of complexity to the system.
- 31 • Option 2 supporters thought the major factors in favor of this option (and its three
32 configurations) included increased objectivity, the ability to build on existing models and
33 systems, and the perception of external accountability. Supporters thought the major
34 drawbacks to this option were potential financial and political feasibility issues for
35 establishing any of the Option 2 configurations.
- 36 • Supporters of Option 3 thought the major factors in favor of this option included a
37 definitive separation of vaccine safety activities and accountability operations and
38 increased objectivity. They thought the major drawbacks were the high financial

1 resources needed for implementation and potential for ineffectiveness if the option was
2 not executed appropriately.

3
4 See Appendix 13 for more detailed information about VSWG discussion about these options.
5

6 **OPPORTUNITY FOR IMPROVEMENT**

7 As with most important governmental functions, an ongoing, publically accessible process of
8 external review of the work the United States vaccine safety system could help assure the
9 effective functioning of the system and may increase confidence in its work. (new)
10

11 **RECOMMENDATIONS**

12 **Assurance and Accountability Recommendation 3.1**

13 **Enhanced Role of the NVAC**

14 The Secretary of HHS should assign the NVAC a broader and stronger role regarding
15 independent, periodic review and evaluation of the NVP. The NVAC, through the Standing
16 Working Group on Vaccine Safety (see Leadership Recommendation 1.3), should assess (1)
17 whether NVP-coordinated agencies are coordinating their efforts effectively and creating
18 appropriate NVP-wide agendas, (2) whether these agendas are being implemented and their
19 objectives met, and (3) whether NVP-coordinated agencies are complying with performance
20 expectations defined by the Secretary and other Secretarial guidance. The NVAC, consistent
21 with advisory functions, should communicate the outcomes of its assessments in a transparent
22 manner to the Secretary through the ASH.
23

24 **Assurance and Accountability Recommendation 3.2**

25 **Relationship between the ISTF, ISCG, or Other Similar Coordinating Body**

26 The ISTF, ISCG, or a similar coordinating body should meet at least annually with the NVAC
27 Standing Working Group on Vaccine Safety (see Leadership Recommendation 1.3) and file an
28 annual progress report, with an associated presentation at an NVAC meeting, on processes
29 undertaken to monitor and evaluate vaccine safety, including, but not limited to, meeting the
30 recommendations specified in the recommendations for research and post-licensure surveillance
31 of this White Paper. These regular meetings with the NVAC Standing Working Group on
32 Vaccine Safety may occur through means other than in-person meetings (e.g., teleconferences).
33
34
35
36

37 **Assurance and Accountability Recommendation 3.3**

External Assessment of Adverse Event Causality

To resolve difficult scientific questions through external scientific review of available evidence and provide regular updates to the National Vaccine Injury Compensation Program (VICP) Vaccine Injury Table, a mechanism should be developed to conduct causality evaluation of selected vaccine adverse events. On an annual basis, the ISTF, ISCG, or other similar coordinating body, in consultation with the NVAC Standing Working Group on Vaccine Safety (see Leadership Recommendation 1.3), will conduct a review of potential topics for examination, based on AEFI for which a review of causality is warranted and for which there is scientific literature addressing the topic. If serious adverse events that meet these criteria are identified, the Secretary of HHS should continue using the IOM method to assess the causal relationship between the identified vaccine(s) and suspected adverse event(s). Results of assessments should be reported to the NVAC, the ACCV, and other entities as determined by the NVAC.

Assurance and Accountability Recommendation 3.4

Progress in Enhancing the Vaccine Safety System

To assure progress in enhancing the vaccine safety system, as highlighted in the recommendations in this White Paper, a formal mechanism for review and accountability is needed. The NVAC should continue to be the advisory entity primarily responsible for evaluating the NVP programs and commissioning vaccine-specific investigations. Opportunities exist for the HHS to enhance the NVAC's standing and authorities, as described in Leadership Recommendations 1.1 and 1.3, Assurance and Accountability Recommendations 3.1 and 3.2, and Stakeholder and Public Engagement Recommendation 8.1. Additionally, NVAC should periodically review and report to the ASH on its assessment of progress toward implementation of the recommendations of this report. Consideration should be given to charging another entity, such as the IOM, to undertake a review in 3 to 5 years to assess progress toward vaccine safety system assurance as defined in this report. As with all recommendations made in this White Paper, assurance and accountability mechanisms will need to be in place for proper oversight of the NVAC as they fulfill this recommendation. (new)

4. RESEARCH FINDINGS AND RECOMMENDATIONS

FINDINGS

The need for coordination in the vaccine safety system extends to the research realm. Basic research, clinical research, and epidemiological research must all be well-coordinated and inform one another. Without formal linkages between vaccine-related entities—such as the National Institute of Allergy and Infectious Disease (NIAID), Vaccine and Treatment Evaluation Units (VTEUs), the CDC, the Clinical Immunization Safety Assessment (CISA) Network, the FDA,

1 the DoD, and the AHRQ—complimentary expertise and infrastructure cannot be fully leveraged.
2 A mechanism is needed for collaborating with experts outside of the vaccine safety arena when
3 questions arise that would benefit from their expertise. Not only would these external linkages
4 aid in understanding the potential adverse events, but also these subspecialists could be sources
5 of cases for study or samples for a vaccine safety repository. (page 29, lines 14-21)

6
7 While the CDC ISO has a 5-year research agenda [53] in place, on which the NVAC previously
8 made recommendations [62], this represents only one component of vaccine safety research.
9 While activities are currently underway in other agencies [64] [97], they do not represent a federal
10 government -wide vaccine safety research plan. Development and implementation of such a plan
11 would require a coordinated effort to ensure that the goals of the plan are being met. Such
12 reviews were envisioned by IOM in *Vaccine Safety Research, Data Access, and Public Trust*
13 where the NVAC was called on to annually review and provide advice on the research plan for
14 the Vaccine Safety Datalink (VSD). [115] (page 29, lines 23-29)

15
16 Improved coordination is important to ensure that appropriate data related to vaccination and
17 adverse events are collected when opportunities to do so present themselves. Long-term,
18 longitudinal studies, such as the National Children's Study, provide the opportunity for analysis
19 of large cohorts of children, and efforts need to be leveraged to ensure that accurate
20 immunization data are collected. While these studies are not designed solely to address effects,
21 both beneficial and adverse, of vaccination, they do provide an opportunity to improve data
22 retrieval methods (e.g., through medical records or through immunization information system
23 review). (page 29, lines 31-37)

24
25 Many investigators are working to understand the physiologic responses of the complex human
26 immune system and how they change over a person's lifetime. The knowledge base related to the
27 biological basis of vaccine adverse reactions exhibits substantial gaps and uncertainties and
28 critical opportunities to address them are receiving insufficient attention and funding. (new)
29 Several efforts to examine biological mechanisms behind the immune response to vaccination in
30 particular are ongoing. Such research may be helpful to better understand and possibly treat or
31 prevent vaccine adverse reactions. However, these efforts, for the most part, remain insular and
32 not well coordinated with each other. Discussions with scientists determined that no inventory of
33 basic research related to vaccine response and adverse reactions has been formed or maintained.
34 Additionally, no current effort is underway to perform this research. As a result, there may be
35 important opportunities to link basic research to vaccinology and the study of vaccine adverse
36 reactions. (page 31, lines 3-13)

37
38 Basic research into the molecular and cellular responses making up the immune response to
39 vaccination that may be related to adverse events, including studies of vaccine antigens,
40 adjuvants and other related components [123], needs to be improved and incentivized, as was

1 done with the use of American Recovery and Reinvestment Act funds to begin a study to model
2 the human immune response. [124] NIH activities could also be integrated into existing
3 FDA/CDC studies of vaccine safety to enhance the inclusion of information from basic research.
4 It may be beneficial to develop systematic methods to prioritize which vaccine adverse reactions
5 should be studied or to consider incorporation of public input into the prioritization process.

6 (page 31, lines 15-22)

7
8 In light of the interest and investment being made in these respective scientific disciplines, there
9 is great opportunity to collaborate and inform vaccine safety science through the lenses of
10 immunology and genomics. This will require collaboration among scientists and entities
11 conducting research, funding, and access to specimens through an effective biobank able to
12 capture the necessary samples from patients who experience very rare events. Formalized data
13 sharing will inform a coordinated scientific agenda that includes biological mechanisms, which
14 is critical to ensure that the biological basis behind vaccine adverse events is properly
15 understood. Research cannot be undertaken without a strong vaccine safety science work force,
16 which is currently small and inadequately supported. (page 31, lines 31-39)

17
18 While a substantial amount of basic research with applicability to vaccinology is occurring
19 through NIH support, linkages between these individual research activities and a broader
20 connection to vaccinology is needed. Increasing the awareness of the potential interoperability of
21 these research activities within the scope of vaccine safety science is essential to ensure that an
22 appropriately broad array of vaccine-related research is moving towards a common end point.
23 While the NVAC identified lack of a vaccine safety study section at the NIH as a gap, there may
24 be other processes that can be refined to meet the goal of improved coordination of vaccine
25 safety related activities. (new) An emphasis on a multidisciplinary approach to addressing
26 vaccine safety questions, including the development of linkages across funding opportunities, is
27 needed. Possible solutions include highlighting the use of particular keywords, such as "vaccine
28 safety," and requests for targeted review by vaccine safety experts, to ensure that the
29 interdisciplinary benefits of the study are made known. The existing program announcement for
30 vaccine safety-related research [64] is one step in attracting the desired high-quality,
31 multidisciplinary investigators to this field, but it is critical that there be a mechanism within the
32 NIH to track research with applicability to vaccine safety and to work to foster these linkages.

33 (page 31, lines 41-51; page 32, lines 1-3)

34
35 While proactive monitoring efforts are used to identify rarer AEFI with more widespread vaccine
36 use, the current system for research into biological mechanisms of vaccine adverse reactions is,
37 by its inherent nature, primarily reactive. While basic research projects, such as the NIH's
38 Human Phenotyping Project, provide a great opportunity to build and sustain a consortium
39 approach for profiling human immune responses, little has been done to capture potential
40 synergies between these efforts with others, such as the development of a biospecimen

1 repository. Indeed, more thought and leadership is needed on approaches to incentivize novel
2 research that will provide critical information to guide vaccine safety policy decisions across all
3 aspects of the life cycle of a vaccine. (page 34, lines 41-48)

4
5 Many opportunities exist to gain new fundamental insights into the molecular and cellular
6 mechanisms that may be involved in vaccine adverse reactions that could improve prevention
7 and treatment of vaccine adverse events. Although the purpose of this report is not to prescribe
8 specific vaccine safety activities, the VSWG would like to reaffirm that the NVAC made
9 recommendations related to biological mechanisms in its June 2009 report, [62] including
10 "Consider detailed mechanistic studies of common but mild adverse events such as fever or rash.
11 These might provide insights into mechanisms of severe but rare adverse events." [62] This prior
12 NVAC recommendation was made to attempt to understand if there are common mechanisms
13 underlying adverse events that are common and mild as well as more severe adverse events.
14 Attempts to understand underlying mechanistic issues for adverse events may allow examination
15 of severe adverse events through the proxy of other, more common, adverse events. (page 34,
16 lines 50-51; page 35, lines 1-8)

17
18 Comprehensive education on adverse event identification and proper vaccine administration and
19 treatment of adverse events is very important, particularly for immunization providers. This
20 education will require research and development of treatment algorithms. The DoD Vaccine
21 Healthcare Centers (VHC) Network has developed related algorithms, more of which are needed
22 for vaccines given in the general population. (page 37, lines 35-38)

23
24 Clinical guidance for managing and coping with vaccine injuries is limited for healthcare
25 providers and individuals who believe that they have experienced a vaccine injury. Even within
26 *Epidemiology and Prevention of Vaccine Preventable Diseases* (also known as "The Pink
27 Book") [109] there is limited information on clinical guidance for managing adverse events
28 following immunization. (page 37, lines 40-43)

29
30 The development of a scientific agenda and coordinated research program (see Research
31 Recommendations 4.1 and 4.2) also could help the development of a National Vaccine Safety
32 Biospecimen Repository. Currently, an Institutional Review Board (IRB)-approved specimen
33 repository is maintained through the CISA. Expansion into a larger-scale repository could
34 increase the ability to perform necessary biological mechanisms research. (page 32, lines 7-10)
35 However, development of a National Vaccine Safety Biospecimen Repository has a number of
36 logistical challenges that need to be addressed, including, but not limited to, the following: (1)
37 identifying the types of samples to be banked and the associated information needed for the
38 samples to be useful and (2) identifying who would contribute samples to the repository, how the
39 samples would be distributed, who would determine which requests for samples would be

1 approved, who would maintain the samples, and who would ship the samples, and (3)
2 determining how the repository would be funded. (page 32, lines 20-26)

3
4 With regard to ascertainment of public concerns and perceptions, the CDC and others conduct
5 public polling to understand public concerns about vaccine safety. Information from such polls
6 can assist in developing educational messages and materials on vaccine safety. Such information
7 could also inform the vaccine safety research agenda. (new)

9 **OPPORTUNITIES FOR IMPROVEMENT**

10 A federal government-wide vaccine safety research agenda for enhancing research in critical
11 subject matters, including both pre-licensure research activities and post-licensure surveillance,
12 needs to be created. (page 30, lines 42-43)

13
14 Research into the molecular and cellular mechanisms that may be involved in vaccine-associated
15 adverse events is occurring but could benefit from increase coordination, planning, and
16 resources. (page 35, lines 19-21)

17
18 Coordinating research efforts into the molecular and cellular mechanisms that may be involved
19 in vaccine-associated adverse events such research and more clearly identifying their possible
20 application to vaccine safety potentially could enhance prevention and treatment of vaccine
21 adverse events. (page 32, lines 15-18)

22
23 A consistent funding mechanism for vaccine safety research could support program project
24 grants and investigator-initiated research into vaccine safety under the scope of a national
25 vaccine safety scientific agenda. (page 32, lines 5-7 edited)

26
27 The CDC could use the findings from its data collection of public opinions to assist in the
28 implementation of the vaccine safety agenda and recommendations made in this White Paper.
29 (new)

30
31 Clinical guidance and other support related to identification, evaluation, treatment, management,
32 and coping with AEFI could be improved and widely disseminated to vaccination providers,
33 patients, and caregivers. (page 37, lines 47-49)

34
35 Formalized data sharing could inform a coordinated scientific agenda that includes biological
36 mechanisms, which is critical to ensure that the biological basis behind vaccine adverse events is
37 properly understood. (page 31, lines 35-37)

1 Expansion into a larger-scale repository, such as a National Vaccine Safety Biospecimen
2 Repository, could increase the ability of the vaccine safety system to perform necessary
3 biological mechanisms research. (page 32, lines 9-11)

4
5 Increased support for training for the vaccine safety research workforce is needed. (new)

6
7 Greater accessibility to existing vaccine safety data could enhance current vaccine safety
8 research and foster additional research. (new)

9

10 **RECOMMENDATIONS**

11 **Research Recommendation 4.1 – Development of a Vaccine Safety Research Agenda**

12 The ISTF, ISCG, or other similar coordinating body should develop and update on a regular
13 basis, approximately every 3 to 5 years, an NVP-wide vaccine safety research agenda.
14 Development and updating this agenda should use the ISTF, ISCG, or other similar coordinating
15 body Subcommittees specified in Coordination Recommendation 2,1, under the direction of the
16 ISTF, ISCG, or other similar coordinating body Subcommittee on Research. This agenda should
17 address research in both vaccine safety science (e.g., epidemiological, clinical, and laboratory
18 studies) as well as post-licensure surveillance for adverse events. Key focus areas of this agenda
19 should include, but not be limited to, identifying and addressing the following:

- 20 • Needs and opportunities for eliminating unnecessary redundancy across these activities to
21 make these research activities more effective and efficient.
- 22 • Needs and opportunities for new or redirected studies toward reducing or eliminating
23 gaps in knowledge relevant to vaccine safety.
- 24 • Needs and opportunities to assess the potential risks of vaccines currently in use.
- 25 • Strengths and limitations of the processes for assessing vaccine safety before and after
26 licensure.
- 27 • Existing basic research programs and findings that may have applicability in the broader
28 scope of vaccine safety research, to create linkages between these research programs to
29 improve the broader knowledge of vaccine safety science.

30 31 **Research Recommendation 4.2 – Building a Vaccine Safety Research Community**

32 Given that research into vaccine safety is broadly defined to contain a variety of fields and
33 disciplines, including, but not limited to, immunology, clinical practice, epidemiology, and
34 pathophysiology, the NVP, with the assistance of the ISTF/ISCG Subcommittee on Research
35 (see Coordination Recommendation 2.1), should implement the following coordination efforts:

- 1 • Facilitate a community of vaccine safety researchers that crosses the boundaries from
2 basic research, clinical research, and epidemiology to ensure continuity of research from
3 different arenas, entities, and disciplines.
- 4 • Share vaccine safety-related research findings with all members of the ISTF/ISCG at
5 regular monthly Task Force meetings.
- 6 • Leverage existing infrastructure and investments for vaccine safety research, such as
7 CISA and the National Children's Study.
- 8 • Engage vaccine manufacturers to capitalize on their expertise, large preclinical and
9 clinical databases, specimen repositories, and scientific resources to inform further
10 vaccine safety studies.
- 11 • Coordinate the development, implementation, and periodic update of the National
12 Vaccine Safety Scientific Agenda, as described in Research Recommendation 4.1.
- 13 • Ensure feedback between stakeholders within the vaccine safety enterprise so that
14 research findings translate into safer products and guidelines for their use when
15 appropriate.
- 16

17 **Research Recommendation 4.3 – Research Funding and Investigator Training**

- 18 • The NIH should identify and link multidisciplinary, internal and external vaccine safety
19 research programs and funding, including encouragement of researchers to highlight
20 research that may have a potential application to vaccinology and vaccine safety through
21 targeted applications of keywords and requested reviewers, and through appropriate
22 revisions of "PA-08-256: Research to Advance Vaccine Safety" to ensure a wide range of
23 applicability across multiple disciplines.
- 24 • The HHS and its related agencies, along with academic partners and professional
25 organizations, should develop training programs for scientists and medical professionals
26 in basic vaccinology and in related sciences that will contribute to informing vaccine
27 safety research.
- 28 • The HHS and its related agencies, along with academic partners and professional
29 organizations should support training in vaccine safety for scientists in non-biomedical
30 research areas (e.g. cost/benefit analyses, quality assurance, and policy analysis).
- 31

32 **Research Recommendation 4.4 – Ascertainment of Public Concerns and Perceptions**

33 The CDC should evaluate the usefulness of rapidly deployed and analyzed public opinion polling
34 and active monitoring of electronic media to ascertain public concerns and perceptions about

1 vaccine safety. Findings should be used to inform both the vaccine safety research agenda and
2 communications programs.

4 **Research Recommendation 4.5 – Research Directed to Clinical Practice**

- 5 • The NVP, working through the ISTF, ISCG, or other similar coordinating body
6 Subcommittees on Research and Clinical Practice (see Coordination Recommendation
7 2.1) and relevant non-governmental partners (e.g., the CISA Network) should coordinate
8 research to improve clinical guidance and methods for the identification, evaluation,
9 clinical management, and reporting of adverse events, including information on clinical
10 follow-up for individuals who experience AEFI. Best practices identified from sources
11 such as the DoD VHC Network, AHRQ, and the Brighton Collaboration should be
12 utilized to the greatest possible extent.
- 13 • The CDC and the FDA should develop a consistent and systematic approach using
14 VAERS or another related reporting mechanism to characterize the extent to which
15 vaccine administration errors occur. The CDC and the FDA also should implement
16 strategies for reducing these errors as appropriate for quality improvement and patient
17 safety. The long-term goal of this approach is to establish a standard mechanism for
18 surveillance of administration errors.

20 **Research Recommendation 4.6 – Data Access**

21 The NVPO should establish a temporary expert committee, such as the IOM, to look at the
22 feasibility of and mechanisms for providing researchers access to preclinical, clinical, and post-
23 licensure vaccine safety data. This committee should consider the strengths and weaknesses of
24 developing a data center that may include the following:

- 25 • Final data that were used for decisions about vaccine safety (following "reproducible
26 research" [145] strategies).
- 27 • General data that have not been used for a specific adverse event, such as VSD, CISA,
28 and associated specimen banks, to the extent possible.
- 29 • Preclinical, clinical, and post-licensure data that are part of the application process.

31 **Research Recommendation 4.7 – Biological Specimens**

32 The CDC and the CISA Network should complete the planning and implementation of
33 recommendations for the enhancement of a National Vaccine Safety Biospecimen Repository
34 linking biological samples to clinical data for unusual AEFI to accelerate studies of biological
35 mechanism and subpopulations at increased risk for adverse events.

5. POST-LICENSURE SURVEILLANCE FINDINGS AND RECOMMENDATIONS

FINDINGS

Surveillance/Signal Detection

Because of the lack of sufficient power to detect many rare outcomes that can be temporally associated with immunization (which are needed to evaluate data acquired during the course of immunization), the significance of small increases in risk is difficult to evaluate with confidence. Efforts to estimate background rates of AEFI that may be temporally associated with pandemic influenza vaccination during preparations for the H1N1 influenza vaccination campaign was a key step in increasing this knowledge base. [84] (page 33, lines 11-16)

The utility of VAERS was well demonstrated following the initial post-licensure period for the first licensed rotavirus vaccine. However, the limitations of a passive reporting system, along with reports containing incomplete data, can affect the strengths of the system, and new technologies should be employed as possible to address these limitations. [125] Additionally, some reports published using VAERS data [126] [128] included analytic interpretations beyond what is recognized as feasible with these data [77] [78], which can lead to misunderstandings of the value and application of this system. (page 33, lines 19-23)

Expanded technologic approaches to surveillance of early concerns and "warning signs" among the public have not been widely utilized. While focus groups and town meetings are important for getting more in-depth sense of public concerns and responses to messages, they do not provide a sense of the distribution of the concerns in the general population or in vulnerable subpopulations. (page 33, lines 25-28)

Signal Assessment/Hypothesis Testing

Post-licensure data collection for vaccine safety is required through Title 21, Code of Federal Regulations (CFR), Part 600.80, "Post marketing reporting of adverse experiences" [129] and existing FDA guidance to industry on vaccine safety reporting. [130] However, the extent of post-licensure vaccine safety monitoring may not be readily apparent to the public, potentially leading to concerns about the adequacy of this type of evaluation. (page 33, lines 50-51; page 34, lines 1-3)

Post-licensure studies of vaccine safety can require extensive time and effort, and there may be the perception of a trade-off between timeliness and quality of the results. However, as seen with the NVAC H1N1 VSRAWG [131], high quality and rapid evaluation of vaccine safety data can be performed, though the intensive effort required may not be sustainable for all, or even most, vaccine safety examinations. Ad hoc development of systems such as the Meningococcal Vaccine Study[18] and the Post-licensure Rapid Immunization Safety Monitoring (PRISM)

1 System [23] to supplement the VSD can be effective for defined and targeted analyses, though an
2 evaluation for more widespread application still needs to be performed. Increased sample sizes
3 and increased technological advances (e.g., Rapid Cycle Analysis [RCA]) can increase the
4 timeliness for detection of significant levels of adverse events. [93] [132] (page 34, lines 5-12)
5

6 A major opportunity to increase sample sizes for study of AEFI comes from the FDA
7 Amendments Act of 2007 [54], which calls for increasing the size of the population under active
8 surveillance for post-licensure examination of adverse events. At this time, the FDA is
9 developing the Sentinel Initiative, a large surveillance system for medical products (including
10 medical devices, drugs and vaccines) safety studies. It is anticipated that by July 1, 2012, the
11 population under surveillance will reach 100 million. The Sentinel Initiative relies on advanced
12 informatics capabilities to efficiently and accurately access information in billing information
13 and electronic health and medical records. (page 34, lines 14-20)
14

15 The transition from signal detection to signal evaluation is a mix of art and science. In order to
16 ensure the best data are available for signal detection, efforts should be improved to educate
17 medical professionals and parents to identify vaccine adverse events and to accurately and
18 completely report them (as discussed above) to ensure adequate data to perform hypothesis
19 testing. (page 34, lines 22-25)
20

21 *Causality Assessment*

22 The lack of coordination around vaccine safety research described above may create
23 opportunities to improve knowledge and understanding of vaccine safety. In 18 of 30 (60%)
24 assessments since 2001, the IOM concluded there was not adequate information to accept or
25 reject a causal association between vaccination and specific adverse events⁴. [50] Part of the
26 problem with vaccine adverse event causality assessments is the lack of statistical power
27 associated with smaller studies. The use of large linked databases has begun to reduce this
28 problem, but, even in the VSD, the population under active surveillance may still be too small
29 for examination of very rare adverse events (e.g., 1-2 cases / 100,000 for Guillain Barre
30 Syndrome [GBS]) or events among important subgroups such as pregnant women. (page 35,
31 lines 25-32)
32

33 *Injury Compensation*

34 The current Vaccine Injury Table became effective November 10, 2008. Four vaccines (hepatitis
35 A vaccine, trivalent influenza vaccine, meningococcal [polysaccharide and conjugate] vaccines
36 and HPV vaccine) have not undergone full review of adverse events that may be considered for

⁴ On August 25, 2011, the Institute of Medicine released *Adverse Effects of Vaccines: Evidence and Causality* which presents a comprehensive review of the scientific evidence about the potential risks of eight vaccines covered by the VICP. The report identifies some risks that are linked to vaccines as well as some effects that are not caused by immunization. This report was released after this NVAC White Paper was developed.

1 compensation under the VICP. [100] An IOM review is underway for these, and other, vaccines.⁵
2 [133] Until this review is completed and new entries are made to the Vaccine Injury Table,
3 adverse events following receipt of these vaccines must be proven to be associated with
4 vaccination in order for compensation to be provided. Often claims alleging conditions not listed
5 in the Vaccine Injury Table are compensated on the basis of negotiated settlements between both
6 parties. Since FY 2007, over half of claims adjudicated annually are compensated on the basis of
7 litigative risk settlements. (page 35, lines 46-51; page 36, lines 1-3)

8
9 While provision of information about VAERS and the VICP to patients is mandated for
10 administration of all vaccines, the extent to which this information may be underutilized by
11 individuals who experience an adverse reaction is unknown. One recent study observing
12 physician-patient interactions did not find any instances of providers specifically referencing the
13 VICP during vaccination visits, though Vaccine Information Statements (VIS) were routinely
14 provided. [83] Preliminary results of an assessment of provider and public awareness of the VICP
15 presented to the ACCV [134] indicated a lack of awareness of the existence, functions and role of
16 the VICP. As indicated in the Communications section, improvements in coordinated
17 distribution of vaccine safety information may help provide clarity regarding both VAERS and
18 the VICP. (page 36, lines 5-12)

19 20 *Public Health Response*

21 In recent years, public health officials have undertaken targeted active surveillance to understand
22 and quantify outbreaks of unexpected medical problems that occurred in the wake of vaccination.
23 The CDC is the lead agency for public health responses when vaccine safety questions arise, in
24 the same manner as for other acute public health emergencies (e.g., outbreaks). For example, in
25 1999, when cases of intussusception following rotavirus vaccine were reported to the VAERS,
26 the CDC initiated a multi-state investigation of intussusception following vaccination. Early case
27 finding results, preliminary results of the manufacturer's post-licensure studies, and reports to the
28 VAERS led to the CDC suspending the rotavirus immunization program within 2 months of
29 identifying the cluster of cases reported to the VAERS. (page 36, lines 23-30)

30
31 By definition, public health response activities are primarily reactive. While the CDC has an
32 impressive track record of providing support through the Epi-AID system for disease
33 investigation and control, there may be room for coordination of public health response activities
34 across departments and agencies involved in the vaccine safety system. Additionally, aside from
35 high-profile situations, such as the rotavirus vaccine/intussusception case and the H1N1

⁵On August 25, 2011, the Institute of Medicine released *Adverse Effects of Vaccines: Evidence and Causality* which presents a comprehensive review of the scientific evidence about the potential risks of eight vaccines covered by the VICP. The report identifies some risks that are linked to vaccines as well as some effects that are not caused by immunization. This report was released after this NVAC White Paper was developed.

1 influenza vaccination campaign, there does not appear to be broad communication to the public
2 about the public health functions involved in vaccine safety. (page 36, lines 32-38)

3
4 Proactive efforts to assure appropriate public health response were evident throughout the
5 planning that occurred in summer 2009 for the H1N1 influenza vaccine campaign. While
6 activities such as the PRISM System sought to establish links for immunization data across
7 multiple sources, including health plan data and immunization information systems, there were
8 still challenges in obtaining H1N1 immunization data for individuals vaccinated outside of
9 traditional immunization settings, to link to health outcomes data. (page 36, lines 40-44)

11 OPPORTUNITIES FOR IMPROVEMENT

12 Programs for post-licensure surveillance and hypothesis testing for AEFI could be enhanced
13 regarding the quality and timeliness of reports and scope of coverage, while balancing the
14 resources required for such efforts with the potential benefits. New data analysis technologies
15 can assist in improving the timeliness of these findings. (page 34, lines 30-33)

16
17 Even well-developed epidemiological studies of actual or potential vaccine-associated adverse
18 events could benefit from increased sample sizes to be able to more quickly detect rare adverse
19 events. (page 34, lines 35-37)

20
21 Calculation of background rates of potential AEFI in subpopulations would assist in vaccine
22 safety risk assessment. (page 33, lines 32-33)

23
24 Efforts to educate physicians and the public about the uses and limitations of VAERS may
25 increase their understanding of the system. (new)

26
27 Strategies are needed to enhance the quality of data reported to VAERS. Some potential
28 examples are outreach to individuals who make reports encouraging more complete data
29 reporting and utilization of technology and data abstraction methods from electronic health
30 records to enhance reporting. (page 33, lines 39-42)

31
32 For an increasingly proactive way to measure AEFI, the vaccine safety enterprise needs an
33 expanded array of surveillance approaches to ascertain early concerns through public opinion
34 polling and active monitoring the "new media," such as blogs. (page 33, lines 44-46)
35 Causality assessment, as performed by the IOM, is a useful and robust process. Institutionalizing
36 a standing causality assessment group is needed. (page 35, lines 36-37)

37
38 Acute investigations (e.g., association between first licensed rotavirus vaccine and
39 intussusception) have worked, but the broader responsibilities of federal departments and

1 agencies involved in causality assessments may benefit from improved coordination to maximize
2 available data and expertise. (page 35, lines 39-42)

3
4 The timeframe for updating the vaccine injury compensation table could be improved
5 commensurate to the pertinent and existing knowledge base. (page 36, lines 16-17)

6
7 Provider and public awareness of the VICP could be increased. (page 36, line 19)

8
9 Recognizing the work of the CDC in vaccine safety-related public health response, best practices
10 and collaborative efforts could be promulgated among federal departments and agencies that may
11 be involved in these types of public health response activities. (page 36, lines 48-50)

12
13 Future public health response could benefit from increased data linkages between sources of
14 immunization data, both from traditional and non-traditional immunization settings, and sources
15 of health outcomes data. (page 37, lines 1-3)

16 17 **RECOMMENDATIONS**

18 **Post-licensure Surveillance Recommendation 5.1 – Plans for New Vaccines**

19 The ISTF, ISCG, or other similar coordinating body Subcommittee on Post-licensure
20 Surveillance (see Coordination Recommendation 2.1) should convene relevant federal agencies
21 and departments at appropriate times to perform the following tasks:

- 22 • Review established proactive action plans for post-licensure vaccine safety evaluations.
- 23 • Ensure coordination of activities.
- 24 • Develop a systematic, integrated approach to post-marketing surveillance plans that
25 includes FDA requests for post-licensure monitoring, CDC commitments to VSD data
26 analysis, and participation from other federal agencies and departments that may
27 contribute to coordinated post-licensure surveillance.

28 29 **Post-licensure Surveillance Recommendation 5.2 –Data Considerations**

30 The ISTF, ISCG, or other similar coordinating body Subcommittee on Post-licensure
31 Surveillance should incorporate the following components into the plans reviewed in Post-
32 licensure Surveillance Recommendation 5.1:

- 33 • Ensure vaccine safety data are collected on ACIP-recommended vaccine usage not
34 covered by FDA-approved labeling.
- 35 • Utilizing coordination efforts detailed in Coordination Recommendation 2.1 and research
36 coordination efforts detailed in Research Recommendation 4.2, post-licensure vaccine

1 safety surveillance activities should be informed by manufacturer's expertise and
2 experience with pre-licensure clinical trials.

- 3 • Utilize and fully take advantage of the FDA Sentinel Project for expanding the
4 population under active surveillance to 100 million by 2012 to do signal detection,
5 validation and confirmation. Special attention should be given to federal initiatives on
6 electronic health, medical, and immunization records and alternative ways to link data,
7 and under-represented groups, such as minority populations.

9 **Post-licensure Surveillance Recommendation 5.3 – Implementation of Programs**

10 The ISTF, ISCG, or other similar coordinating body, representing the NVP-coordinated agencies
11 and departments, should lead efforts to implement the national agenda to enhance post-licensure
12 surveillance (see Research Recommendation 4.1) and the post-licensure surveillance plans for
13 new vaccines or vaccine formulations/combinations (see Post-licensure Surveillance
14 Recommendation 5.1).

16 **6. CLINICAL PRACTICE FINDINGS AND RECOMMENDATIONS**

18 **FINDINGS**

19 Comprehensive education on adverse event identification and proper vaccine administration and
20 treatment and reporting of adverse events is important for immunization providers. This
21 education will require research and development of treatment algorithms. The DoD VHC
22 Network has developed related algorithms, more of which are needed for vaccines given in the
23 general population. (page 37, lines 35-38)

25 A consistent theme in research about attitudes toward vaccination is that patients consider their
26 physician the most trusted source of information about vaccine safety. [8] [31] [140] [141]
27 Physicians then need to better understand both the safety of vaccines and the vaccine safety
28 system. They must have confidence in the scientific basis for that understanding and efforts need
29 to be undertaken to assess this understanding and related perceptions [141]. Moreover, they must
30 have adequate methods to communicate with their patients, whether through more face-to-face
31 time or other education tools. This is a difficult goal given the economic pressures in primary
32 care. (page 39, lines 4-10)

34 Clinical guidance for managing and coping with vaccine injuries is limited for healthcare
35 providers and individuals who believe that they have experienced a vaccine injury. Even within
36 *Epidemiology and Prevention of Vaccine Preventable Diseases* (also known as "The Pink
37 Book") [109] there is limited information on clinical guidance for managing adverse events
38 following immunization. (page 37, lines 40-43)

1 One way to help ensure proper vaccine administration is the use of barcode systems for
2 identifying and tracking the immunizations provided. Currently, the FDA is developing
3 processes and guidance for expanded use of barcode labeling systems [108], with the most
4 current guidance, as of August 2010, available at
5 [http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInform](http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM225099.pdf)
6 [ation/Guidances/General/UCM225099.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM225099.pdf). (page 27, lines 8-13)
7

8 **OPPORTUNITIES FOR IMPROVEMENT**

9 Clinical guidance and other support related to identification, evaluation, treatment, management
10 and coping with AEFI could be improved and widely disseminated to vaccination providers,
11 patients, and caregivers. (page 37, lines 47-49)
12

13 The use of barcode systems for identifying and tracking the immunizations provided could
14 ensure proper vaccine administration. (new)
15

16 **RECOMMENDATIONS**

17 **Clinical Practice Recommendation 6.1 – Utilizing Improvements**

18 The ISTF, ISCG, or other similar coordinating body Subcommittee on Clinical Practice should
19 ensure dissemination of information on the following topics:

- 20 • Improved clinical guidance to clinicians on the identification, evaluation, clinical
21 management, and reporting of adverse events, particularly when advances in clinical
22 practice, as described in Research Recommendation 4.5, are made and published. An
23 example of this type of guidance is the CISA hypersensitivity algorithm. [146]
- 24 • Clinical practice activities that can prevent adverse events associated with vaccine
25 administration errors, particularly when advances are made in examining the occurrence
26 of these errors, as described in Research Recommendation 4.5.
27

28 **Clinical Practice Recommendation 6.2 – Barcode Labeling of Vaccines**

29 Acknowledging efforts currently underway at the FDA, the NVAC is supportive of efforts to
30 create a routine system of barcode labeling of vaccine vials and pre-filled syringes that is
31 compatible, ideally, with international standards.
32
33
34
35
36

7. COMMUNICATION FINDINGS AND RECOMMENDATION

FINDINGS

Over the last decade how information is disseminated and used has changed dramatically and has profoundly influenced how consumers make healthcare decisions. The Internet and social media have helped shape attitudes and beliefs regarding immunization and have brought vaccine decision making to the forefront as consumers seek credible and easily accessible information. The NVAC believes it is important to recognize these societal shifts recommending improvements in how the federal government communicates immunization information to consumers, healthcare providers and the public health community. (new)

Information about vaccine safety is primarily disseminated by the CDC [135], through news releases, press conferences, and website postings. However, vaccine safety information is also distributed by other HHS agencies, such as the NIH and the FDA [136] and other departments (e.g., DoD [137] [138]), and is often related to more specific topics. The establishment and authorization of a central body within the federal government to coordinate and distribute vaccine safety information would improve communications on vaccine safety. (page 37, lines 7-12)

The CDC is the primary federal government point of contact for receiving and providing information related to vaccine safety through development of clinical guidelines and recommendations for safe vaccination, provider education on safe vaccination practices, fielding public requests for information, and performing studies related to public concerns about vaccine safety as well as funding similar external studies. However, there may be opportunities for other federal agencies to participate to improve the effort, particularly for focused topic areas (e.g., the VICP through HRSA). (page 37, lines 14-19)

In response to its charge, the VSWG considered whether public confidence in vaccine safety during recent years may impact vaccination coverage and whether the recommended improvements in the safety system could improve public confidence, resulting in higher vaccine coverage. Current coverage levels for many routinely recommended childhood vaccines are at historically high levels in the whole population [3], raising the question about whether vaccine safety concerns expressed by parents in some surveys [8] [139] have led to changes in parental vaccine decision-making. However, with the availability of alternative vaccination schedules, some parents may be delaying vaccination or requesting that their children have immunizations spread out more than called for in the recommended schedule. Also recent outbreaks of measles, as well as data on vaccination coverage at the school level, have highlighted pockets of under-immunization in subgroups concerned about vaccine safety. These pockets have adversely affected the health of the larger population by providing an opportunity for introduced diseases to take hold in under-immunized populations. In addition, it is possible that safety concerns may

1 impede the uptake of more recently recommended vaccines or will do so in the future. (page 38,
2 lines 40-50; page 39, lines 1-2)

3
4 The NVAC could not determine if improvements in the vaccine safety system will change public
5 attitudes in general. In particular, the NVAC found no data suggesting that, for individuals in
6 specific populations who oppose vaccination for their children, improvements in the vaccine
7 safety system will modify attitudes. The general public is likely largely unaware of the vaccine
8 safety system and its function in ensuring vaccine safety, and it is not clear that knowledge of the
9 system would change these attitudes or behavior. On the other hand, increasing awareness of and
10 improving appreciation of enhancements to the vaccine safety system by practicing physicians
11 may increase their ability to rapidly communicate vaccine safety information to parents. This is
12 of particular importance with the large amount of information to be communicated, both vaccine-
13 related and non-vaccine-related, during routine physician visits where time may be limited. [83]
14 However, regardless of whether a CQI process in the vaccine safety system will improve public
15 confidence, resulting in increased acceptance of vaccines, these improvement processes should
16 be considered if they could strengthen the system and improve scientific understanding and
17 patient safety. (page 39, lines 37-49)

18 19 **OPPORTUNITIES FOR IMPROVEMENT**

20 The provision of a one-stop source of comprehensive information about vaccine safety for the
21 public and providers, such as how to report adverse events, how the vaccine safety system has
22 successfully identified previous actual adverse events following immunizations, how the vaccine
23 injury compensation program works, what safety-related research is underway, could improve
24 communications to the public on these topics. (page 37, lines 23-27) Vaccines.gov is a good start
25 to providing this type of comprehensive information but could be improved upon. (new)

26
27 Coordination between the different federal departments and agencies (e.g., the CDC, the FDA,
28 the DoD, the VA) with respect to their outreach about the safety of vaccines could be improved.
29 (page 37, lines 29-31)

30 31 **RECOMMENDATION**

32 **Communication Recommendation 7.1**

33 The ISTF, ISCG, or other similar coordinating body Subcommittee on Communications (see
34 Coordination Recommendation 2.1) should ensure development and maintenance of a unified
35 program of public information about vaccines, vaccine safety, and the vaccine safety system that
36 can serve as a resource to the public and health professionals. This information should be
37 available, at a minimum, through a publicly accessible website, such as Vaccines.gov. This
38 program, and associated dissemination tools, should focus on establishing and maintaining links

1 to specific agencies information about the safety, efficacy and effectiveness of each licensed
2 vaccine, including:

- 3 • The Vaccine Information Statement.
- 4 • The official package insert, as prepared and issued by the FDA, and the FDA's analysis
5 provided to VRBPAC.
- 6 • Summaries of the design, scope, and results of the key clinical trials that supported
7 licensure.
- 8 • Summaries of the design, scope, and results of any post-licensure clinical trials required
9 by the FDA or being conducted under the auspices of one or more of the other NVP-
10 participating agencies.
- 11 • Abstracts of product-specific peer-reviewed research reports published after licensure.
- 12 • Abstracts of ongoing product-specific research studies funded by the HHS or other
13 departments of the federal government.
- 14 • A clearer public explanation of each agency's role in post-licensure vaccine safety.

15

16 This communications plan also should focus on utilizing existing mechanisms, and where
17 necessary, establishing mechanisms and publicizing means by which members of the public can
18 obtain information about vaccines.

19

20 The CDC should utilize and disseminate findings from research into public concerns (see
21 Research Recommendation 4.4) to develop communications tools applicable to address public
22 concerns and perceptions.

23

24 The CDC and the FDA should improve methods for communication about the extent to which
25 follow-up to individual VAERS reports may be conducted.

26

27 **8. STAKEHOLDER AND PUBLIC ENGAGEMENT FINDINGS AND** 28 **RECOMMENDATION**

29

30 **FINDINGS**

31 The NVPO and the HHS, through the Office of External Affairs, have actively sought
32 stakeholder and public engagement in the development of important health policy initiatives. The
33 NVAC believes that vaccine safety should be incorporated into ongoing efforts to obtain
34 stakeholder and public input. (new)

35

36

1 OPPORTUNITIES FOR IMPROVEMENT

2 The national vaccine safety system could benefit from the input of stakeholders and the general
3 public and through the enhanced assurance, accountability, and transparency that engaging these
4 groups provides. (new)

5
6 Vaccine safety-focused engagement activities could benefit from expert advice representing all
7 pertinent scientific and technical disciplines. (new)

8 9 RECOMMENDATION

10 Stakeholder and Public Engagement Recommendation 8.1

- 11 • The ASH should direct the NVPO to work with the NVAC and the ISTF, ISCG, or other
12 similar coordinating body Subcommittee on Stakeholder and Public Engagement (see
13 Coordination Recommendation 2.1) to develop and maintain an ongoing and meaningful
14 program of appropriate stakeholder engagement around vaccine safety. This program
15 should focus on ensuring that appropriate stakeholders and the public have the
16 opportunity to regularly provide feedback, through routine stakeholder and public
17 engagement processes, during planning and evaluation of major NVP activities, such as
18 the development of the vaccine safety research agenda (see Research Recommendation
19 4.1) and the NVAC reviews of NVP activities.
- 20 • This program also should publicize various means by which members of the public can
21 share concerns and recommendations about vaccine safety not related to a specific
22 occurrence of a specific AEFI, as would be reported through the VAERS.
- 23 • The ASH should direct the NVPO to continue working with the NVAC and NVP-
24 coordinated agencies to ensure that all vaccine safety-focused engagement activities
25 benefit regularly from expert advice representing all pertinent scientific and technical
26 disciplines.

27 28 9. COST EVALUATION OF RECOMMENDATIONS FINDINGS AND 29 RECOMMENDATION

30 31 FINDINGS

32 Vaccine safety activities and vaccine science require financial resources and staff support.
33 Substantial investments will be needed to improve the ability to engage in causality assessment
34 and to improve scientific understanding of mechanisms and individual risk. Staffing dedicated to
35 vaccine safety activities is not commensurate with the responsibilities and workload necessary to
36 fulfill their obligations. [118] (page 30, lines 10-14)

1 Funding within the federal infrastructure for post-licensure vaccine safety has not increased
2 significantly since 2004. In general, funding for vaccine safety system partners has remained flat
3 over many years, while the number of vaccines and the number of people vaccinated has
4 increased substantially, though there have been some targeted increases, such as the funding
5 dedicated to development of the Mini-Sentinel program. Because many activities that impact
6 vaccine safety, either directly or indirectly occur without the specific moniker of "vaccine
7 safety," it is difficult to identify what proportion of agencies' and Departments' funding is
8 allocated to vaccine safety-related functions. (new –page 30, lines 16-23)

9
10 The NVAC previously highlighted the need for additional funding for vaccine safety research,
11 with focus on the CDC ISO [62], as well as general recommendations addressing the need for
12 additional funding for vaccine safety activities in 1996, [119] 1997, [120] 1998, [121] and 1999.
13 [60] The IOM also recommended funding increases as part of its review of the National Vaccine
14 Plan. [46] Additionally, the increased infrastructure capacity to address the H1N1 influenza
15 pandemic was developed using temporary funding allocations, and there was no clear plan to
16 maintain these improvements. In February, 2010, NVAC resolved that important improvements
17 made in public health infrastructure (including but not limited to vaccine safety) should be
18 maintained. [122] Specifically, NVAC recognized the need to continue funding infrastructure
19 improvements that were put in place to deal with the H1N1 influenza pandemic. (new –page 30,
20 lines 25-33)

21
22 Efforts to study biological mechanisms of vaccine adverse effects are under-resourced and could
23 contribute more to this effort with additional funding and research staff. The need for research to
24 understand biological mechanisms and inform clinical guidance to medical providers is clear, but
25 additional resources may be needed to adequately support these efforts. As an example, CISA
26 faces challenges in recruiting sufficient subjects for some of their protocols due to limited
27 funding and the difficulties inherent in studying very rare outcomes. (page 35, lines 10-15)

28
29 The NVAC is mindful that, per its charge, its recommendations need not be constrained by the
30 budgets for the NVP-coordinated agencies and departments—either current funding levels or
31 projected ones. Nevertheless, in formulating these recommendations, the NVAC was aware of
32 potential budget implications, recognizing that they would have a long-term impact on the
33 vaccine safety system, and not be solely constrained by the current fiscal environment. The
34 NVAC recognizes that some recommendations can be accommodated readily within current
35 operating levels; that other recommendations will require modest increments beyond current
36 spending; and that still other recommendations will require commitment of substantial additional
37 funds. In general, the budget implications of each recommendation are self-evident from the
38 description and associated discussion. (page 40, lines 28-37)

1 The NVAC understands that vaccine safety is but one of many worthy claimants for funding as
2 the Executive Branch and the Congress weigh difficult choices throughout the annual budget
3 process. The NVAC also understands that the flexibility inherent in this process is considerable.
4 In particular, the discretionary budget for the Department of Health and Human Services (HHS)
5 for Fiscal Year 2010 (October 01, 2009 to September 30, 2010) was almost \$79 billion; and the
6 corresponding item in the President's Budget Request for Fiscal Year 2011 is over \$81 billion.
7 Reprioritization of a small portion of the annual HHS discretionary budget toward enhancing the
8 vaccine safety infrastructure over the next few years seems realistic. (page 40, lines 39-46)
9

10 **OPPORTUNITY FOR IMPROVEMENT**

11 Resources, including fiscal support and staffing, provided to vaccine safety activities could be
12 increased at levels commensurate with the needs and opportunities that exist. (page 30, lines 50-
13 51)
14

15 **RECOMMENDATION**

16 **Cost Evaluation of Recommendations Recommendation 9.1**

17 The NVPO should coordinate, across the relevant departments and agencies, a cost evaluation of
18 the recommendations in this report approved by the NVAC. This evaluation should be presented
19 to the NVAC at a regularly scheduled NVAC meeting.
20
21

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1
2**APPENDIX 1. GLOSSARY OF ABBREVIATIONS**

Abbreviation	Definition
ACCV	Advisory Commission on Childhood Vaccines
ACIP	Advisory Committee on Immunization Practices
AEFI	Adverse Event(s) Following Immunization
AHIP	America's Health Insurance Plans
ASH	Assistant Secretary for Health
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment Network
CMS	Centers for Medicare and Medicaid Services
CQI	Continuous Quality Improvement
CTSA	Clinical and Translational Science Awards
DoD	Department of Defense
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
Hib	<i>Haemophilus influenzae</i> type b
HHS	Department of Health and Human Services
HPV	Human papillomavirus
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
IIS	Immunization Information Systems
IOM	Institute of Medicine
ISO	Immunization Safety Office (of the CDC)
ISTF	Immunization Safety Task Force
MCO	Managed care organization
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NCVIA	National Childhood Vaccine Injury Act of 1986

Abbreviation	Definition
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Program
NVPO	National Vaccine Program Office
PRISM	Post-licensure Rapid Immunization Safety Monitoring System
RCA	Rapid cycle analysis
RTIMS	Real Time Immunization Monitoring system
US	United States of America
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Events Reporting System
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System
VHC	Vaccine Healthcare Center (of DOD)
VICP	National Vaccine Injury Compensation Program
VSD	Vaccine Safety Datalink
VSRAWG	Vaccine Safety Risk Assessment Working Group
VSWG	Vaccine Safety Working Group
VRBPAC	Vaccines and Related Biologic Products Advisory Committee
VTEU	Vaccine Trials Evaluation Unit

1

APPENDIX 2. VSWG METHODS FOR ADDRESSING CHARGE #2

To address its second charge of reviewing the national vaccine safety system and developing this White Paper, the National Vaccine Advisory Committee (NVAC) Vaccine Safety Working Group (VSWG) looked at prior reviews of the vaccine safety system by external agencies and by the VSWG itself, conducted meetings in person and by telephone, created subgroups to focus on specific information and processes, and developed initial recommendations for improvement to the national vaccine safety system. (new)

PRIOR REVIEWS OF THE VACCINE SAFETY SYSTEM

HHS Activities and Related Reviews by the NVAC

There have been several previous federal efforts to enhance the nation's vaccine safety system. The broadest reaching of these reviews was the *Final Report of the Task Force on Safer Childhood Vaccine* [44] released in 1998. This task force, convened by the National Institutes of Health (NIH), made four recommendations on greater assessment of concerns about vaccine safety, strengthened research into developing safer vaccines, increased surveillance related to vaccine safety and efficacy, and coordinated review and assurance related to federal vaccine safety efforts. (page 11, lines 43-48)

In 1999, the NVAC reviewed and strongly endorsed the Vaccine Safety Action Plan, which is the formal implementation plan for the 1998 Task Force report. [60] In the intervening years, there has been partial implementation of these recommendations, though the lack of a sufficient budget process has hampered full implementation of this Action Plan. [61] (page 11, lines 48-51; page 12, line 1)

Reviews by the Institute of Medicine (page 12, lines 8-14)

The Institute of Medicine's (IOM's) *Priorities for the National Vaccine Plan* released in December 2009 identified four high priority vaccine safety actions that were largely consistent with NIH's recommendations: [46]

1. Establish a process for identifying potential vaccine safety hypotheses for further study from annual reviews of data from the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the Clinical Immunization Safety Assessment (CISA) Network, the National Vaccine Injury Compensation Program (VICP), and from information from outside of the United States;
2. Develop a framework for prioritizing a national research agenda;
3. Create a permanent vaccine safety subcommittee in the NVAC for ongoing review and guidance on vaccine safety issues; and

- 1 4. Expand and enhance vaccine safety science research through the Centers for
2 Disease Control and Prevention (CDC) Immunization Safety Office (ISO), the
3 Food and Drug Administration (FDA), and the NIH.
4

5 **Review of CDC ISO Scientific Agenda**

6 The NVAC VSWG was established in April 2008 with a charge to review the CDC ISO
7 Draft Scientific Agenda (Charge 1). Specifically, the VSWG was asked to provide advice
8 on the content of the ISO draft research agenda, the prioritization of research topics, and
9 possible scientific barriers to implementing the research agenda, with suggestions for
10 addressing them. (page 12, lines 18-21)
11

12 The NVAC VSWG review [62] of the CDC ISO research agenda [53] provided the
13 opportunity for a coordinated review of vaccine safety research activities, though it was
14 confined to activities occurring only through the ISO. The Working Group was
15 challenged to limit discussion of vaccine safety only to the ISO, acknowledging that
16 "many other governmental agencies and departments have important roles in vaccine
17 safety research" and, as a result, suggested that there is a "strong need for a federal
18 vaccine safety research agenda that encompasses research undertaken by non-ISO CDC
19 offices, FDA, and the National Institutes of Health and requires increased collaboration
20 and coordination between all federal agencies with a stake in vaccine safety." (page 12,
21 lines 23-34)
22

23 The VSWG's recommendations were approved by the full NVAC on June 9, 2009, and
24 transmitted to the Assistant Secretary for Health (ASH) and the CDC. Following this
25 approval, the VSWG began work on its review of the federal vaccine safety system
26 (Charge 2). (new)
27

28 **VSWG MEETINGS** (page 12, lines 38-50; page 13, lines 1-6)

29 VSWG held a kickoff meeting for its current charge on July 15–16, 2009, at which 26 invited
30 participants with a broad range of expertise (Appendix 5) shared their views on the following
31 topic areas:

- 32 • Principles and policy alternatives for a robust vaccine safety system;
- 33 • Innovative ways to overcome gaps in vaccine safety science infrastructure;
- 34 • The ideal system to meet the needs of the public, public health, and healthcare
35 professionals for confidence in vaccine safety;
- 36 • Lessons learned from other safety arenas; and
- 37 • How to enhance the adoption and implementation of the forthcoming White Paper.

1
2 Following the July 2009 kickoff meeting, the entire VSWG met regularly, holding 18
3 conference call meetings and two in-person meetings. In addition to regular working
4 meetings to discuss and deliberate topics under consideration, the working group also
5 received a series of presentations that provided information on a number of broad-scale
6 vaccine safety topics. The following presentations were given to the full VSWG:

- 7 • International Vaccine Safety Systems (Gary Freed, University of Michigan; Hector
8 Izurieta, FDA; and Steve Black, Cincinnati Children's Hospital);
- 9 • Vaccine Safety Efforts at the World Health Organization (Patrick Zuber, World
10 Health Organization [WHO]), PRISM (Richard Platt, Harvard Pilgrim Health Care
11 and Harvard Medical School);
- 12 • Public Attitudes Toward Vaccines (Kathy Talkington, Association of State and
13 Territorial Health Officials [ASTHO]); and
- 14 • The State of the Science for Assessing Public Perceptions of Vaccine Safety (Allison
15 Kennedy, CDC).

16 17 **VSWG SUBGROUPS** (page 13, lines 10-51; page 14, lines 2-12)

18 To accomplish its task of reviewing the current vaccine safety system and providing advice
19 on utilizing 21st century science and technology to enhance the system, the VSWG created
20 three content-oriented subgroups for targeted information gathering and process
21 development. These subgroups focused on biological mechanisms of adverse events,
22 epidemiology and surveillance of adverse events, and structure and governance of the
23 vaccine safety system. Each subgroup elected a Chair, and subgroup membership was based
24 on VSWG member expertise and preference. Summaries of subgroup meetings and
25 information gathering are provided below.

26 27 **Biomechanisms Subgroup**

28 The Biomechanisms Subgroup focused on biological mechanisms of vaccine adverse
29 events. This subgroup was chaired by L.J. Tan, and concentrated on the four main topic
30 areas to address when examining biological mechanisms of adverse events, which are
31 hypothesis generation, causality assessment, identification of persons who may be at
32 increased risk for adverse reactions, and appropriate management of specific adverse
33 events.

34
35 This subgroup focused on basic and laboratory science, genomics, and resources for
36 addressing these topic areas. Specific topics examined included research on biological
37 mechanisms underlying vaccine adverse events, genetic risk factors and environmental

1 triggers, biomarkers, and prevention and treatment of vaccine adverse events. The role of
2 NIH in vaccine safety research also was discussed.

3
4 The Biomechanisms Subgroup held four working meetings and six information gathering
5 meetings. A summary of the presentations given during these information gathering
6 meetings is provided in Appendix 6.

7 8 **Surveillance and Epidemiology Subgroup**

9 The Surveillance and Epidemiology Subgroup focused on the epidemiology to detect,
10 quantify, and examine the cause of vaccine adverse events. This subgroup was chaired by
11 Lance Gordon, and concentrated on the five main topic areas to address when examining
12 surveillance data and epidemiologic studies on adverse events, which are as follows:

- 13 1. Identifying adverse events that occur with a temporal relationship to
14 immunization (i.e., signal detection, hypothesis generation) for additional
15 followup;
- 16 2. Examining the detailed epidemiology of adverse events following immunization
17 (AEFI) to determine the strength of association, if any, with immunization (i.e.,
18 hypothesis testing);
- 19 3. Monitoring the occurrence of specific known or hypothesized vaccine adverse
20 reactions to identify changes in patterns across time or populations;
- 21 4. Providing feedback and guidance to other components of the vaccine safety
22 research system, such as laboratory or clinical investigators; and
- 23 5. Properly and adequately reporting results of epidemiologic and surveillance data
24 to policy makers, scientific communities, and the public.

25
26 This subgroup focused on the pre- and post-licensure infrastructure for vaccine safety
27 research to identify gaps in the infrastructure and suggest opportunities for improvement.
28 Topics discussed by the subgroup included passive and active surveillance infrastructure,
29 pre-licensure and post-licensure research, epidemiological needs, novel information
30 technology, new statistical methods, and resources for these activities. Consideration was
31 given to new vaccine safety research platforms and infrastructure that do not yet exist or
32 have not traditionally been utilized in the area of vaccine safety.

33
34 The Surveillance and Epidemiology Subgroup held seven working meetings and eight
35 information gathering meetings. A summary of presentations given during these
36 information gathering meetings is provided in Appendix 7.

1 **Structure and Governance Subgroup**

2 The Structure and Governance Subgroup was chaired by William Raub. This subgroup
3 focused on topics related to the structure, oversight, resources, and processes for the
4 vaccine safety system. Topics discussed included transparency, mechanisms for engaging
5 and involving the public and stakeholders, objectivity, organization, funding, authority,
6 coordination, and responsibilities. The Structure and Governance Subgroup met for 11
7 working meetings.
8

9 **DEVELOPMENT OF RECOMMENDATIONS** (page 14, lines 16-26)

10 A list of major themes developed from the July 15–16, 2009 kickoff meeting served as a
11 starting point for the VSWG's deliberations (see Appendix 5 for the agenda for this meeting).
12 The list of potential items to be addressed ranged from very specific to very general, with
13 some examples repeated across general topic areas. Further discussion and refinement of the
14 initial list by the VSWG Structure and Governance Subgroup led to a more condensed list
15 that served as the basis for crafting directed and actionable recommendations for making
16 improvements to the vaccine safety system.
17

18 Additionally, recommendations were initially developed by each of the content-oriented
19 subgroups. Once each subgroup's recommendations were initially refined, they were collated
20 with those of the other subgroups and presented to the full VSWG for consideration. Further
21 discussion among the working group was used to clarify the scope and intent of the
22 recommendations.
23

24 **STAKEHOLDER AND PUBLIC INPUT**

25 Concurrent with information gathering, the VSWG (with the help of the Keystone Center)
26 participated in a stakeholder engagement process. Following a robust public and stakeholder
27 engagement process during Charge 1, the VSWG again desired to hear from a variety of
28 stakeholders. The Stakeholder Engagement Subgroup of the VSWG assisted in the planning
29 and execution of the Keystone-led engagement activities. (page 14, lines 30-34)
30

31 In addition to the kickoff meeting, the VSWG participated in a Writing Group meeting that
32 included 29 federal and non-federal stakeholders, including nine VSWG members. This group
33 provided input on opportunities for improvement in the vaccine safety system, and strengths
34 and weaknesses of various enhancements or alterations to the structure and governance of the
35 vaccine safety system. A memorandum listing the Writing Group meeting attendees and
36 summarizing the outcomes of the meeting is presented in Appendix 8.(new)
37

38 Information obtained from a public comment period and an open stakeholder's meeting on
39 June 13, 2011 varied in viewpoints. Some people thought that the draft White Paper was too

1 critical of the current vaccine safety system; some thought it was not critical enough. Others
2 thought accountability and assurance checks were not in place while others thought that they
3 were. A summary of public comments is included in Appendix 9. (new)
4

5 Thirteen of the 16 NVAC members were able to attend the June 13, 2011 stakeholder
6 meeting to hear the views presented and engage stakeholders. (new)
7

8 **NVAC DISCUSSION**

9 At the June 2011 NVAC meeting, the Committee discussed the draft report and draft
10 recommendations presented by the VSWG. Major thematic takeaways focused on
11 modifications to tone, readability, and organization of the report. Committee members
12 engaged extended discussion on the rationale and implementation feasibility of several
13 specific recommendations (focusing on Leadership, Coordination, and Accountability). The
14 Committee provided fairly concrete direction on the options presented for Assurance and
15 Accountability; citing the option to empower the NVAC (Option 1 in the previous draft
16 report) as the most favored by the Committee. Additionally the VSWG members completed a
17 straw poll indicating that the majority of the VSWG favored Option 1 as well. A review of
18 the Options for Accountability and Assurance deliberated on by the VSWG and presented to
19 the Committee is provided in Appendix 12. (new)
20

21 Following the June 2011 NVAC discussion, revision responsibility was transferred from the
22 VSWG to the NVAC in preparation for a September 2011 vote on the report. In service to the
23 NVAC, the NVPO contracted a medical writer with content knowledge of vaccines to
24 complete the revisions recommended from the June deliberations. The medical writer worked
25 in consultation with the NVAC Chair and the VSWG co-chairs via the NVPO to complete
26 the revised report. (new)
27
28

1 APPENDIX 3. NATIONAL VACCINE ADVISORY COMMITTEE VACCINE
2 SAFETY WORKING GROUP MEMBERSHIP, NON-FEDERAL
3 GOVERNMENT MEMBERS
4
5
6

DRAFT

Name	Affiliation	Group representation / Discipline
Tawny Buck* †	Director of Government Relations, National Vaccine Information Center Member, ACCV	Public Representative / Parent of a child injured by a vaccine
Marie McCormick, MD, ScD* †	Summer and Esther Feldberg Professor of Maternal and Child Health, Harvard School of Public Health	Academia / Maternal and Child Health
Andrew Pavia, MD* †	George and Esther Gross Presidential Professor, Department of Pediatrics, University of Utah School of Medicine	Academia / Pediatric and Adult Infectious Disease
Robert L. Beck, JD	Former ACIP Member	Public Representative / International business/law
Guthrie S. Birkhead, MD, MPH* §	Deputy Commissioner, Office of Public Health, New York State Department of Health	State Health Department / Epidemiology
Christopher Carlson, PhD	Fred Hutchinson Cancer Research Center	Academia / Genomics
Vicky Debold, PhD, RN	Affiliate Faculty, Health Administration and Policy Department, George Mason University, VRBPAC Member	Public Representative / Public Health and Nursing
Cornelia Dekker, MD	Professor of Pediatrics and Medical Director, Stanford-LPCH Vaccine Program, Division of Pediatric Infectious Diseases, Stanford University School of Medicine	Academia / Pediatrics
Lance Gordon, PhD	ImmunoBiologics Corp.	Industry / Immunology
Sean Hennessy, PharmD, PhD	Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine	Academia / Pharmacoepidemiology
Clement Lewin, PhD, MBA*	Head, Strategic Immunization Planning, Novartis Vaccines and Diagnostics	Industry / Immunization Policy
James O. Mason, MD, DrPH*	Former Director of the Centers for Disease Control and Prevention and Assistant Secretary for Health	Public Health
William Raub, PhD	Former Deputy Director of the National Institutes of Health and Science Advisory to the Secretary, Department of Health and Human Services	Public Health
Litjen (L.J.) Tan, PhD, MS*	Director, Medicine and Public Health, American Medical Association	Professional Organization / Immunology and Policy
Consultants:		
Mark Feinberg, MD, PhD *	Vice President for Policy, Public Health and Medical Affairs, Merck Vaccine Division, Merck & Co., Inc.	Industry / Immunology
Steven Goodman, MD, PhD	Professor and Co-Director, Epidemiology Doctoral Program, Johns Hopkins Bloomberg School of Public Health	Academia / Biostatistics and Epidemiology
Lawrence Gostin, JD, LL.D. (Hon)	Associate Dean, Professor of Global Health, Georgetown University Law Center	Academia / Ethics and Law
Gerald Medoff, MD	Division of Infectious Diseases, Washington University School of Medicine	Academia / Immunology

* NVAC Member

† Working Group co-chair

§ NVAC Chair

1 APPENDIX 4. NATIONAL VACCINE ADVISORY COMMITTEE VACCINE
2 SAFETY WORKING GROUP MEMBERSHIP, FEDERAL
3 EX OFFICIO MEMBERS
4
5

DRAFT

1

Name	Affiliation
Robert Ball, MD, MPH, ScM	Centers for Biologics Evaluation and Research, Food and Drug Administration
Norman Baylor, PhD	Center for Biologics Evaluation and Research, Food and Drug Administration
Jessica Bernstein, MPH	National Institute of Allergy and Infectious Diseases, National Institutes of Health
Vito Caserta, MD	Countermeasures Injury Compensation Program, Health Resources and Services Administration
Geoff Evans, MD	National Vaccine Injury Compensation Program, Health Resources and Services Administration
Rita Helfand, MD	Centers for Disease Control and Prevention
Karen Midthun, MD	Center for Biologics Evaluation and Research, Food and Drug Administration
Barbara Mulach, PhD	National Institute of Allergy and Infectious Diseases, National Institutes of Health
Daniel Salmon, PhD	National Vaccine Program Office
Melinda Wharton, MD, MPH	National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention

2

APPENDIX 5. NVAC VSWG Kickoff Meeting Agenda

Charge to the Working Group:

Review the current federal vaccine safety system and develop a White Paper describing the infrastructure needs for a federal vaccine safety system to fully characterize the safety profile of vaccines in a timely manner, reduce adverse events whenever possible, and maintain and improve public confidence in vaccine safety.

July 15, 2009

8:30 am Joint NVAC Vaccine Safety Working Group meeting with the Interagency Autism Coordinating Committee
Location: The Polaris Room at the Ronald Reagan Building, 1300 Pennsylvania Avenue NW

10:00 am Transport (on own) to Humphrey Building, 200 Independence Ave SW
Location for all panels: Room 800

10:30 am Panel 1: Principles and policy alternatives for a robust vaccine safety system

Topics of discussion may include:

- What are the basic principles that should guide the vaccine safety system?
- What aspects of the current vaccine safety system are important and/or insufficient to meet these principles?
- What policy approaches could be considered, and what are the strengths and weaknesses of these approaches?
- How can we bring together stakeholders to improve the vaccine safety system?
- How can coordination, integration, and/or organizational structure be enhanced?

Participants:

Mark Blaxill, SafeMinds
Louis Cooper, Columbia University
Robert Davis, Kaiser Permanente of Georgia
Neal Halsey, Johns Hopkins University
Gregory Poland, Mayo Clinic and Foundation

12:00 pm Welcoming remarks by Dr. Howard Koh, Assistant Secretary for Health and Director of the National Vaccine Program

12:30 pm Lunch - Discussion of H1N1 Vaccine Safety Monitoring
Food for purchase at HHS Cafeteria

2:00 pm Panel 2: Identifying innovative ways of overcoming gaps in vaccine safety science infrastructure

Topics of discussion may include:

- What are important strengths and/or deficiencies in the current vaccine safety science infrastructure?
- What new ways, technologies, or data sources are available to address some of these deficiencies?
- How can coordination, integration, and/or organizational structure be enhanced?

Participants:

Steve Black, Cincinnati Children's Hospital
Geraldine Dawson, Autism Speaks
Kathryn Edwards, Vanderbilt University
Neal Halsey, Johns Hopkins University

Samuel Katz, Duke University
Stanley Plotkin, Consultant
Gregory Poland, Mayo Clinic and Foundation

5:00 pm Working Group closed discussion

5:30 pm Meeting adjourned

July 16, 2009

8:30 am Panel 3: The ideal system to meet the needs of the public, public health, and healthcare professionals for confidence in vaccine safety

Topics of discussion may include:

- What are the basic principles that should guide the vaccine safety system?
- What aspects of the current vaccine safety system are important and/or insufficient to meet these principles?
- What mechanisms could meet public expectations for funding and conducting vaccine safety research?
- What information do providers and the public need to make informed decisions, and how can that information be best communicated?

Participants:

Sallie Bernard, SafeMinds
Thomas May, Medical College of Wisconsin
Lisa Randall, Immunization Action Coalition
David Sundwall, Utah Department of Health
David Tayloe, American Academy of Pediatrics
Collette Young, Oregon Department of Health

10:30 am Break

11:00 am Panel 4: Lessons from other safety arenas

Topics of discussion may include:

- What principles are important in your safety arena that may be important to vaccine safety?
- How does your safety arena effectively address uncertainty, gaps in knowledge, competing interests, and maintaining public confidence?
- How does your arena garner resources and support to prevent (rather than respond) to crises?
- What elements of infrastructure and organizational structure are important for achieving your principles and objectives?
- How are coordination and integration achieved in your safety arena?
- In your arena, how do you work effectively with stakeholders and the public?

Participants:

Michael Cohen, Institute for Safe Medical Practices
Robert Dodd, National Transportation Safety Board
Diane Osgood, Business for Social Responsibility
Richard Platt, Harvard University
Gerald Poje, Former Board Member of the U.S. Chemical Safety and Hazard Investigation Board

1:00 pm Lunch - Food for purchase at HHS Cafeteria

1:45 pm Panel 5: Enhancing the adoption and implementation of the NVAC white paper

Topics of discussion may include:

- What stakeholders are important to the success or failure of the NVAC white paper?
- How can the process of developing the white paper enhance its implementation?
- How does one balance the pros and cons of incrementalism with broader vision?
- How does one garner political/financial support and political will?

Participants:

Peter Bell, Autism Speaks
 Paul Kim, Foley Hoag
 Anthony Robbins, Tufts University
 David Tayloe, American Academy of Pediatrics
 Thomas Vernon, Sanofi Pasteur
 Marguerite Evans Willner

3:45 pm Working Group closed discussion

5:00 pm Meeting adjourned

Invited Meeting Participants

NVAC Vaccine Safety Working Group

Robert L. Beck
 Guthrie S. Birkhead (*Chair of NVAC*)
 Tawny Buck (*Co-Chair of Working Group*)
 Chris Carlson
 Vicky Debold
 Cornelia Dekker
 Mark Feinberg
 Lynn R. Goldman
 Steve Goodman
 Lance Gordon
 Lawrence Gostin
 Sean Hennessy
 Paul-Henri Lambert
 James O. Mason
 Marie McCormick (*Co-Chair of Working Group*)
 Gerald Medoff
 Trish Parnell
 Andrew Pavia (*Co-Chair of Working Group*)
 William Raub
 Bennett Shaywitz

Staff

Bob Bednarczyk
 Anna DeBlois Buchanan, ASTHO
 Kirsten Vannice, HHS/NVPO

Observers

Richard Clover, NVAC
 Alina Baciu, IOM

Federal Officials

Frank DeStefano, CDC/ISO
 Renata Engler, DoD
 Geoff Evans, HRSA/VICP
 Bruce Gellin, HHS/NVPO
 Charles Hackett, NIH/NIAID
 James Hanson, NIH/NICHD
 Rita Helfand, CDC/ NCPDCID
 Alice Kau, NIH/NICHD
 Phil Krause, FDA/CBER
 Nancy Levine, CDC/ISO
 Stephanie Marshall, HHS/ASPA
 Barbara Mulach, NIH/NIAID
 Melinda Neuhauser, VA
 Daniel Salmon, HHS/NVPO
 Julie Schafer, HHS/ASPR
 Rick Wilson, FDA/CBER

The Keystone Center

Janesse Brewer

APPENDIX 6. VSWG BIOMECHANISMS SUBGROUP INFORMATION GATHERING BRIEFINGS

- Immune providing and vaccine related activities
 - Chuck Hackett, NIH
- Coordination of NIH vaccine activities
 - Barbara Mulach, Sarah Landry, Chuck Hackett, NIH
- Causality evaluations performed by the Institute of Medicine
 - Kathleen Stratton, IOM
- National biospecimen repository
 - Phil LaRussa, Columbia University
 - Barbara Slade, CDC Immunization Safety Office
- Vaccine manufacturers role in identifying biomechanisms of adverse events
 - Mark Feinberg, Merck & Co., Inc.
 - Clem Lewin, Novartis Vaccines
 - Lance Gordon, Immunobiologics Corp.
- Clinical Immunization Safety Assessment network
 - Colin Marchant, Boston Medical Center and New England Medical Center
 - Neal Halsey, Johns Hopkins University
 - Kathryn Edwards, Vanderbilt University

APPENDIX 7. VSWG SURVEILLANCE AND EPIDEMIOLOGY SUBGROUP INFORMATION GATHERING BRIEFINGS

- Immunization surveillance and epidemiology for active duty military
 - Renata Engler, Department of Defense Vaccine Healthcare Centers Network
 - Hayley Hughes, Department of Defense Military Vaccine Agency
- Immunization surveillance and epidemiology for veterans
 - Fran Cunningham, Veterans Health Administration
- Post-licensure Rapid Immunization Safety Monitoring system
 - Tracy Lieu, Harvard Pilgrim Health Care
- Vaccine Safety Datalink
 - Tracy Lieu, Harvard Pilgrim Health Care;
 - Nicola Klein, Kaiser Permanente Northern California
- Public health informatics
 - Bill Brand, Public Health Informatics Institute
- Federal vaccine safety efforts
 - Frank DeStefano, CDC Immunization Safety Office
 - Bob Ball, FDA/Center for Biologics Evaluation and Research
- Barcode technology
 - Bruce Weniger, CDC
- Clinical Immunization Safety Assessment network
 - Colin Marchant, Boston Medical Center and New England Medical Center
 - Neal Halsey, Johns Hopkins University
 - Kathryn Edwards, Vanderbilt University
- Sentinel Initiative/Mini-Sentinel Program
 - Melissa Robb, FDA

APPENDIX 8. VSWG WRITING GROUP MEETING DISCUSSION

Vaccine Safety Writing Group
April 11th, 12th, & 13th, 2010
Salt Lake City, UT

To: Vaccine Safety Working Group and Interested Stakeholders

From: Salt Lake City Writing Group Meeting Participants: Rob Beck, Peter Bell, Sallie Bernard, Guthrie Birkhead, Anna Buchanan, Tawny Buck, Tracy Cron, Vicky Debold, Corry Dekker, Margaret Dunkle, Lance Gordon, Mark Grabowsky, Richard Greenaway, Alan Greene, Barbara Loe Fisher, James Mason, Thomas May, Debbie McCune Davis, Barbara Mulach, Andrew Pavia, Lisa Randall, Bill Raub, Daniel Salmon, Jim Shames, Andrea Sutherland, Zachary Taylor, Jerry Tokars, Collette Young, and Heather Zwickey (see attached list for additional detail)

Re: Salt Lake City Writing Group Meeting on April 11-13, 2010

Date: April 13, 2010

The Salt Lake City Writing Group met for three days of groundbreaking discussions regarding the vaccine safety system. All participants worked respectfully and in good faith. The group identified objectivity, transparency, and evidence-based decision making as highly prioritized attributes of a robust vaccine safety system.

We agreed that an improved safety system would result in the following outcomes:

1. Characterize the safety profile of vaccines and vaccination practice;
2. Detect, prevent, and reduce adverse events in a timely manner;
3. Develop guidance to detect and mitigate the effects of adverse events in individuals;
4. Earn public confidence in the effectiveness of the vaccine safety system and in the safe use of vaccines; and
5. Inform vaccine policy.

Participants agreed that an improved internal assessment system is important and that an external assessment of the vaccine safety system is either essential or acceptable in meeting these outcomes.

1 While there were different views as to the focus and organizational locus of any external
2 assessment and what it would take for it to be adequately independent, it was agreed by
3 participants that it should have the following features:

- 4 • Includes diverse expertise relevant to vaccine safety
- 5 • Regularly and meaningfully engages the public and stakeholders
- 6 • The ability to gain cooperation and response among relevant entities (i.e., has some
7 "teeth")
- 8 • A charge focused on safety, independent of other vaccination program purposes
- 9 • Use of rigorous scientific and programmatic evidence

10

11 A variety of options for fulfilling this need were discussed throughout the meeting.

12

13 The nine Vaccine Safety Working Group (VSWG) members who were present specifically
14 shared that they had learned a great deal in this session and that in some cases, their thinking has
15 shifted over the course of the three days. The VSWG members shared that these conversations
16 would continue to inform their internal deliberations on the Working Group.

17

18 On June 1, 2010,⁶ the VSWG will host an open stakeholder meeting in Washington, D.C., to
19 gain further feedback from interested stakeholders on the vaccine safety system. The Salt Lake
20 City Writing Group has provided valuable feedback that will help the VSWG further refine
21 materials for the June 1 meeting.

22

23

24

25

26

27

⁶ This date later changed to July 7, 2010 (planned)

APPENDIX 9. STAKEHOLDER'S MEETING AGENDA

**Hubert H. Humphrey Building
200 Independence Avenue, S.W. Room 800
Washington, DC 20201**

June 13, 2011

- 9:00 a.m.** **Welcome, introductions, meeting purpose, agenda review, and ground rules**
NVAC Chair - Guthrie Birkhead
- 9:30 a.m.** **Overview VSWG Charge 2 work to date**
VSWG Co-Chairs - Tawny Buck, Marie McCormick and Andy Pavia
- 10:00 a.m.** **Break**
- 10:15 a.m.** **Medical Association panel and discussion**
Moderated by: VSWG Co-Chair Tawny Buck

Dr. Kathryn Edwards
American Academy of Pediatrics

TBD

Dr. Bernard Gonik
American Congress of Obstetricians and Gynecologists

Dr. Bonnie Ward
Infectious Disease Society of America
- 11:15 a.m.** **Advocacy panel and discussion**
Moderated by: VSWG Co-Chair Dr. Marie McCormick

Richard Greenaway
Every Child By Two

Barbara Loe Fisher
National Vaccine Information Center

Dr. Deborah Wexler
Immunization Action Coalition

Sallie Bernard
Safeminds
- 12:15 p.m.** **Lunch**
- 1:15 p.m.** **Public Health panel and discussion**
Moderated by: VSWG Co-Chair Dr. Andy Pavia

Jacob Mbafor
National Association of City and County Health Officials

Claire Hannan
Association of Immunization Managers

1:15 p.m.
(cont'd)

Dr. Evone Nwankwo
American Public Health Association

Kathy Talkington
Association of State and Territorial Health Officials

2:15 p.m.

Break

2:30 p.m.

Other Perspectives panel and discussion
Moderated by: VSWG Co-Chairs

Sara Radcliffe
Biotechnology Industry Organization

Kevin Conway
Esquire, Conway, Homer and Chin-Caplan, P.C.
Firm represents Vaccine Injury Compensation cases

Sarah Despres
Current: Senior Officer, Pew Charitable Trusts
Former staffer for Congressman Henry Waxman

Alan Greene
Pediatrician, www.drgreene.com

Paul Kim
Current: Partner, Foley Hoag, LLP
Former counsel to Congressman Henry Waxman and deputy staff for
Senator Edward Kennedy

4:00 p.m.

Vaccine Safety Working Group Discussion

4:45 p.m.

Closing Comments

5:00 p.m.

Adjourn

1
2
3

APPENDIX 10. SUMMARY OF PUBLIC COMMENTS

Solicitation of Public Comment on the Draft Report and Draft Recommendations to Enhance the Federal Vaccine Safety System

Executive Summary of Comments received as of June 9, 2011

Public Comment

Fifteen individuals provided the Vaccine Safety Working Group (VSWG) with public comments. Individuals included parents, public health professionals, attorneys and physicians. Individual comments included personal narratives, specific areas for improvement to the vaccine safety system, concerns with the current system and additional references for consideration by the VSWG. The themes below emerged in the individual public comment.

Few commenters provided direct suggestions to the report, but several provided suggestions for the vaccine safety system as a whole.

- More research into adverse events associated with vaccines, outcomes in vaccinated versus unvaccinated populations, vaccine interactions, timing of vaccinations, and additional safety evaluation of vaccine components.
- Suggestions for a reminder/response system for caregivers to report AEFI to VAERS and development for a screening program prior to vaccination to test for high risk factors
- Increase in public representation and engagement in the vaccine safety policy process
- Reference to an independent safety system, and oversight entity for accountability
- Increased accessibility and user friendliness for VSD, VAERS and FDA databases
- Extensions for vaccine court filings deadlines and modifications to the current standards for proof of injury

Additionally several commenters raised concerns with the current vaccine safety system with regard to the following:

- Transparency and accountability of the vaccine manufacturing process, licensure standards, safety monitoring systems, and advisory committee process
- Concern regarding the risks associated with vaccination and the necessity certain of vaccines were voiced.

1 Commenters also provided additions to the reports as follows:

- 2 • Inclusion of reference to the CDC's Vaccine Analytic Unit and its place in the vaccine
3 safety infrastructure

4
5 **Stakeholder Comment**

6 Organizations provided the VSWG with comments on their draft report for enhancements to the
7 federal vaccine safety system. Organizations included professional medical associations, public
8 health associations, academic societies, and non- profits.

9
10 Overall comments from stakeholders included specific suggestions to:

- 11 • More clearly delineate report objectives
12 • Increase readability of the report
13 • Define limitations of the current system
14 • Reflect the significant successes of the system

15
16 **Content Additions**

17 Content additions suggested by stakeholder commenters included:

- 18 • Additional detail of the Vaccine Injury Compensation Program (VICP) processes and
19 case outcomes
20 • Greater focus on the role of pediatricians as communicators of vaccine safety information
21 • Vaccine safety considerations for usage under the Emergency Use Authorization
22 • Role of Immunization Information Systems and Immunization Registries within vaccine
23 safety
24 • Data on public confidence in vaccines and public trust in the system

25
26 **Recommendations**

27 Of the stakeholder organizations who indicated support for specific recommendations, they were
28 most supportive of recommendations on:

- 29 • Leadership (1)
30 • Research(3)
31 • Clinical Practice (5)
32 • Stakeholder and Public Engagement(7)
33

1 Stakeholders who responded to the guiding question on most critically needed recommendations
2 cited the following recommendations as most important for system enhancement:

- 3 • Research (3)
- 4 • Clinical Practice (5) – specifically barcoding
- 5 • Communications (6)
- 6 • Independent oversight (8, Option 3)

7
8 Of the options presented for assurance and accountability, the most support was for Option 1
9 (strengthened NVAC). Several organizations supported Option 3 (independent agency oversight)
10 and several noted the feasibility of Option 2b (IOM committee).

11
12 Stakeholders raised concerns on the recommendations with regard to:

- 13 • Feasibility and cost of creating and maintaining an independent oversight entity
- 14 • Immunization Safety Task Force (ISTF) role and responsibility expansion
- 15 • Necessity of secretarial reaffirmation
- 16 • Ability for implementation in current system configuration and with current funding
17 levels.

18
19 Stakeholders proposed additional recommendations focused on:

- 20 • Vaccine storage, handling and immunization technique
- 21 • Evaluation of the VICP
- 22 • Vaccination ethics and choice

23
24 Stakeholders made a number of specific system suggestions including:

- 25 • Increased of vaccine safety research
 - 26 ○ Health outcomes in vaccinated and unvaccinated populations
 - 27 ○ Biological mechanisms of AEFI
 - 28 ○ International collaborations and data sharing
 - 29 ○ Non animal testing methods
- 30 • Modifications to current vaccine safety surveillance and compensation programs
 - 31 ○ Increased statute of limitations for VICP
 - 32 ○ Mandating VAERS reporting
- 33 • Improvements to communication strategies

- 1 ○ Research into effective risk communication
- 2 ○ Publicizing of research results
- 3 • Broader involvement in vaccine policy process
- 4 ○ Inclusion of public and primary care physicians on vaccine safety committees.
- 5 • Improvements in clinical practice methodologies
- 6 ○ Adoption of Tempadot
- 7 ○ Addressing sounds-alike looks-alike administration errors
- 8
- 9
- 10

DRAFT

APPENDIX 11. VACCINE SAFETY SYSTEM FUNCTIONS AS IDENTIFIED BY THE VSWG

Function 1. Authority, Oversight, and Leadership

- Identifies agent responsible for ensuring system works, as defined by functions and optimizing key attributes, and held accountable for successes and failures.
- Oversees and coordinates vaccine safety activities within and among federal agencies and non-federal partners.
- Shares vaccine safety information with manufacturers, policy makers, and others to aid in future research and vaccine development and immunization practice.
- Develops, prioritizes, coordinates, and monitors a national scientific agenda for vaccine safety.
- Evaluates and enhances the vaccine safety system to address the scientific agenda and emerging technologies and vaccine safety issues.
- Ensures vaccine safety assets are coordinated and used to address the scientific agenda and respond to vaccine safety issues.

Function 2. Licensing

- Licenses vaccines with acceptable safety profiles.
- Ensures optimal manufacturing processes.

Function 3. Monitoring

- Detects potential signals of vaccine adverse events.
- Investigates associations between vaccination and outcomes for potential signals.

Function 4. Research

- Conducts research to enhance capacity to develop and license safer vaccines.
- Researches the immunologic and physiologic effects of vaccines and vaccine ingredients (related to vaccine safety).
- Researches the biological mechanisms of vaccine adverse events.
- Identifies methods for prevention and treatment of vaccine adverse events.
- Assesses individuals who may have experienced vaccine adverse events for additional investigation and analysis.

1

2 Function 5. Causality Assessment

- 3 • Conducts assessments to determine whether an adverse event is caused by vaccines or
4 vaccination.

5

6 Function 6. Injury Compensation

- 7 • Compensates individuals who experience vaccine adverse events.

8

9 Function 7. Practice

- 10 • Conducts individual-level causality assessment.
- 11 • Provides guidance and enhance proper administration of vaccines, including evidence-based
12 contraindications to vaccination.
- 13 • Provides clinical guidance to practitioners on reporting vaccine adverse events and managing
14 adverse events.

15

16 Function 8. Communications

- 17 • Provides information (what is known and what is not known) to the government, health
18 practitioners, advocacy organizations, and the public about vaccine safety to facilitate
19 informed decisions.
- 20 • Communicates new vaccine safety findings as they emerge.

21

22 Function 9. Engagement

- 23 • Involves the public and stakeholders in dialogue about issues of concern and priorities for the
24 vaccine safety system.

25

26

**APPENDIX 12. ATTRIBUTES OF A VACCINE SAFETY SYSTEM
IDENTIFIED BY THE VSWG**

Attribute	Definition
Accountability	Includes mechanisms to ensure that promises are kept, duties are performed, and compliance is forthcoming.
Effectiveness	Complies consistently with all prescribed performance attributes, has a well-defined strategy for implementing missions, defines clear prioritization among candidate strategic initiatives, and reassesses/revisions strategy and priorities with experience.
Efficiency	Applies adequate resources to highest priority strategic initiatives, disinvestments from unproductive or low priorities initiatives, and makes prudent use of resources.
Equity	Distributes burdens and benefits of vaccine safety functions fairly.
Evidence-Based Decision Making	Applies the best available data from the scientific method to formulate research questions, policies, and practices.
Initiative	Is self-starting in pursuit of opportunities to fulfill mission requirements.
Innovativeness	Pursues mission requirements with innovative thinking.
Objectivity	Acts without undue influence from those who have a stake in outcomes of safety assessment (e.g., programs promoting vaccines, advocacy organizations, litigants).
Responsiveness	Responds to emerging issues in a timely manner.
Transparency	Provides access to information about science, process, and rationale for decisions regarding vaccine safety.

APPENDIX 13. ASSURANCE AND ACCOUNTABILITY OPTIONS PRESENTED TO THE NVAC BY THE VSWG

In completing their charge, the National Vaccine Safety (NVAC) Vaccine Safety Working Group (VSWG) found that, in order to assure progress in enhancing the vaccine safety system, as highlighted in the recommendations made in this White Paper, a formal mechanism for review and accountability is needed. Several options were presented to or identified by the VSWG through a variety of activities including prior stakeholder and public engagement during the VSWG Task 1, the Task 2 Kickoff Meeting, the April 2010 Writing Group meeting, and deliberations by the VSWG and its Structure and Governance subgroup.

Three options were discussed for external, independent assurance related to vaccine safety, with the second of these options having three potential configurations. Below is a review of the options not selected for recommendation by the Committee.

Option 2: Establish a fixed-tenure panel outside the HHS to monitor the efforts of the NVP and the NVAC, respectively, to improve the vaccine safety system.

During its defined tenure (e.g., 5 years), the panel would be responsible for evaluating the progress of the National Vaccine Program (NVP) in implementing enhancements to the vaccine safety system and the effectiveness of the NVAC in performing independent evaluations of NVP activities. The panel would have an organizational locus outside the U.S. Department of Health and Human Services (HHS). The host administrative entity would have a role in establishing the panel, arranging for funding and other resources as necessary, receiving the panel's reports containing its findings and recommendations regarding the vaccine safety system, and sharing those reports with officials within the Executive Branch, members of the Congress, and the general public.

Among the questions that the panel might address are (a) Are the NVP-participating entities being appropriately responsive to the Secretary and the Assistant Secretary for Health (ASH) in enhancing the vaccine safety system? (b) Are NVP-wide initiatives properly focused, achieving high quality, and proceeding with appropriate speed? (c) Is the NVAC receiving the operational flexibility and resources necessary to be effective and credible in evaluating NVP activities? (d) Are NVP activities and NVAC evaluations, taken together, sufficient to foster public confidence in the vaccine safety system? Or should an Independent Agency be created to oversee the system? and (e) If such an Independent Agency is needed, what are its characteristics?

The panel could exist in a variety of forms. Three potential options are presented below.

1 Option 2a: Establish the panel as a Presidential Commission.

2 Under this option, the President would establish the Commission by some appropriate means
3 (e.g., Executive Order) to carry out monitoring and reporting activities. Most likely, the
4 President also would designate a senior official with the Executive Office of the President to
5 ensure that the Commission receives requisite support, to receive and disseminate its reports,
6 and to advise the President regarding necessary follow-up actions, if any.

7
8 The President would appoint or arrange for appointment of the members of the Commission
9 in accord with a process he or his designee deems appropriate, including possible
10 participation the Congress. For example, the Commission could have eight members—four
11 appointed by the President and four appointed by the key Congressional committees—whose
12 purviews include vaccine safety (respectively, the Senate Committee on Health, Education,
13 Labor, and Pensions; the House Committee on Energy and Commerce; the Senate Committee
14 on Appropriations; and the House Committee on Appropriations).

15
16 Option 2b. Establish the panel as an IOM Committee.

17 The host administrative entity (e.g., a component of the Executive Office of the President)
18 would contract with the Institute of Medicine (IOM) to carry out monitoring and reporting
19 activities. The IOM would appoint the members of the Committee in accord with a process it
20 deems appropriate. The host administrative entity would be responsible for ensuring that the
21 Committee has the requisite support for receiving and disseminating its reports and for
22 advising the President regarding necessary follow-up actions, if any.

23
24 Option 2c: Create an Independent Agency within the Executive Branch to oversee the
25 vaccine safety system, primarily the NVP and the NVAC.⁷⁸

26 A new Independent Agency within the Executive Branch would be responsible for oversight
27 of the vaccine safety system. In particular, the Agency would evaluate NVP programs and
28 commission vaccine-specific investigations by NVP-coordinated agencies (e.g., the Food and
29 Drug Administration [FDA]) or by non-government entities (e.g., IOM).

30
31
32 **Pros and Cons cited by the VSWG Straw Poll for Option 2 (all configurations)**

⁷ The term "Independent Agency" refers to an entity of the Executive Branch (e.g., the National Transportation Safety Board or the Consumer Products Commission) that is not part of a Cabinet Department. As a general rule, the Executive Office of the President and the Congress, respectively, relate to Independent Agencies through the same management and budget processes that apply to Cabinet Departments.

⁸ A new unit within the Executive Office of the President (EOP) would be an alternative to a new Independent Agency. Pertinent precedents are the Office of National Drug Control Policy and the Council on Environmental Quality. Because proximity to the President is the exception rather than the rule insofar as operating programs are concerned, creation of a new EOP unit almost certainly would be more difficult to justify than creation of a new Independent Agency.

1 Pros:

- 2 • IOM and Presidential Commission could provide fresh insight and increased
- 3 transparency.
- 4 • IOM has a historical track record of objectivity and independent review.
- 5 • Potential objectivity of all configurations of Option 2.
- 6 • Time limited.
- 7 • Ability to build on existing infrastructure in the vaccine safety system.
- 8 • Potentially addresses conflict of interest concerns.

9
10 Cons:

- 11 • Financial burden of implementing any of Option 2 configurations.
- 12 • Political feasibility for implementation- dependent on executive office action, IOM
- 13 contract.
- 14 • Potential lack of support by those that would fall under Option 2 created entity's purview.
- 15 • Additional layer of complexity to the vaccine safety system.

16
17 **Option 3: Create an Independent Agency within the Executive Branch to focus on the**

18 **safety of vaccines.**⁹

19 A new Independent Agency within the Executive Branch would assume responsibility for

20 operating the Vaccine Adverse Event Reporting System (VAERS) and possibly other vaccine-

21 safety related programs (e.g., the Vaccine Safety Datalink [VSD]). In addition, the Agency

22 would have authority to commission vaccine-specific investigations by NVP-coordinated

23 agencies (e.g., the FDA) or by non-government entities (e.g., the IOM). The Agency would

24 develop findings and recommendations regarding vaccine safety and share them with the NVP

25 and the general public.

26
27 **Pros and Cons cited by the VSWG Straw Poll for Option 3**

28 Pros:

- 29 • Definitive separation of vaccine safety activities and accountability assurance.
- 30 • Potential increase confidence in the safety system from vaccine hesitant community.

31
32
33
34 Cons:

⁹ Footnotes 3 and 4 above apply to Option 4 as well as to Option 3. Option 4?

- 1 • Political feasibility concerns.
- 2 • Operational feasibility concerns.
- 3 • Financial resource constraints.
- 4 • Not warranted by historical evidence of NVAC functioning.
- 5 • Additional layer of complexity to the vaccine safety system.
- 6

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