

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

September 2011

Final

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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.

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] 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.

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. 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.

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.

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. 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, hence the rationale for their undertaking the writing of this report.

1 **FORMATION OF THE VACCINE SAFETY WORKING GROUP**

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

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

15
16 To address this charge, the NVAC formed the Vaccine Safety Working Group (VSWG), which
17 deliberated on the draft ISO Scientific Agenda from April 2008 through May 2009. The Working
18 Group identified gaps in the ISO Scientific Agenda and developed prioritization criteria for
19 research topics. The Working Group made 32 recommendations in three general categories:
20 general recommendations, capacity recommendations, and research needs recommendations.
21 These recommendations were approved by the NVAC on June 2, 2009.

22 **CURRENT CHARGE TO THE VACCINE SAFETY WORKING GROUP**

23 One month later, the VSWG began work on its
24 second charge of obtaining expert advice on
25 utilizing 21st century science and technology to
26 enhance the federal vaccine safety system. In July
27 2009, the HHS ASH asked the NVAC VSWG "to
28 review the current federal vaccine safety system
29 and develop a White Paper describing the
30 infrastructure needs for a federal vaccine safety
31 system to fully characterize the safety profile of
32 vaccines in a timely manner, reduce adverse events
33 whenever possible, and maintain and improve
34 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

35
36 This NVAC White Paper reports NVAC's findings and recommendations based on a review of
37 the current federal vaccine safety system by the VSWG and a draft it provided the NVAC. The
38 charge to the NVAC from the ASH recognizes the importance of vaccinations and vaccine safety
39 to the American public. With the advances in the scientific, social, and fiscal landscape since the
40 last review of the vaccine safety was undertaken in 1998, the NVAC believes this review of the
41 system is timely.

1

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

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

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

17

18 **METHODS FOR ADDRESSING ITS CHARGE**

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

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

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

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

33 In 1999, the NVAC reviewed and strongly endorsed the Vaccine Safety Action Plan, which
34 is the formal implementation plan for the 1998 Task Force report. [60] In the intervening
35 years, there has been partial implementation of these recommendations, though the lack of a
36 sufficient budget process has hampered full implementation of this Action Plan. [61]

37

38 **Reviews by the Institute of Medicine**

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

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

13 14 **Review of CDC ISO Scientific Agenda**

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

20
21 The NVAC VSWG review [62] of the CDC ISO research agenda [53] provided the
22 opportunity for a coordinated review of vaccine safety research activities, though it was
23 confined to activities occurring only through the ISO. The Working Group was challenged to
24 limit discussion of vaccine safety only to the ISO, acknowledging that "many other
25 governmental agencies and departments have important roles in vaccine safety research" and,
26 as a result, suggested that there is a "strong need for a federal vaccine safety research agenda
27 that encompasses research undertaken by non-ISO CDC offices, FDA, and the NIH and
28 requires increased collaboration and coordination between all federal agencies with a stake in
29 vaccine safety."

30
31 The VSWG's recommendations were approved by the full NVAC on June 9, 2009, and
32 transmitted to the ASH and the CDC. Following this approval, the VSWG began work on its
33 review of the federal vaccine safety system (Charge 2).

34 35 36 37 **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.

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.

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).

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

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.

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.

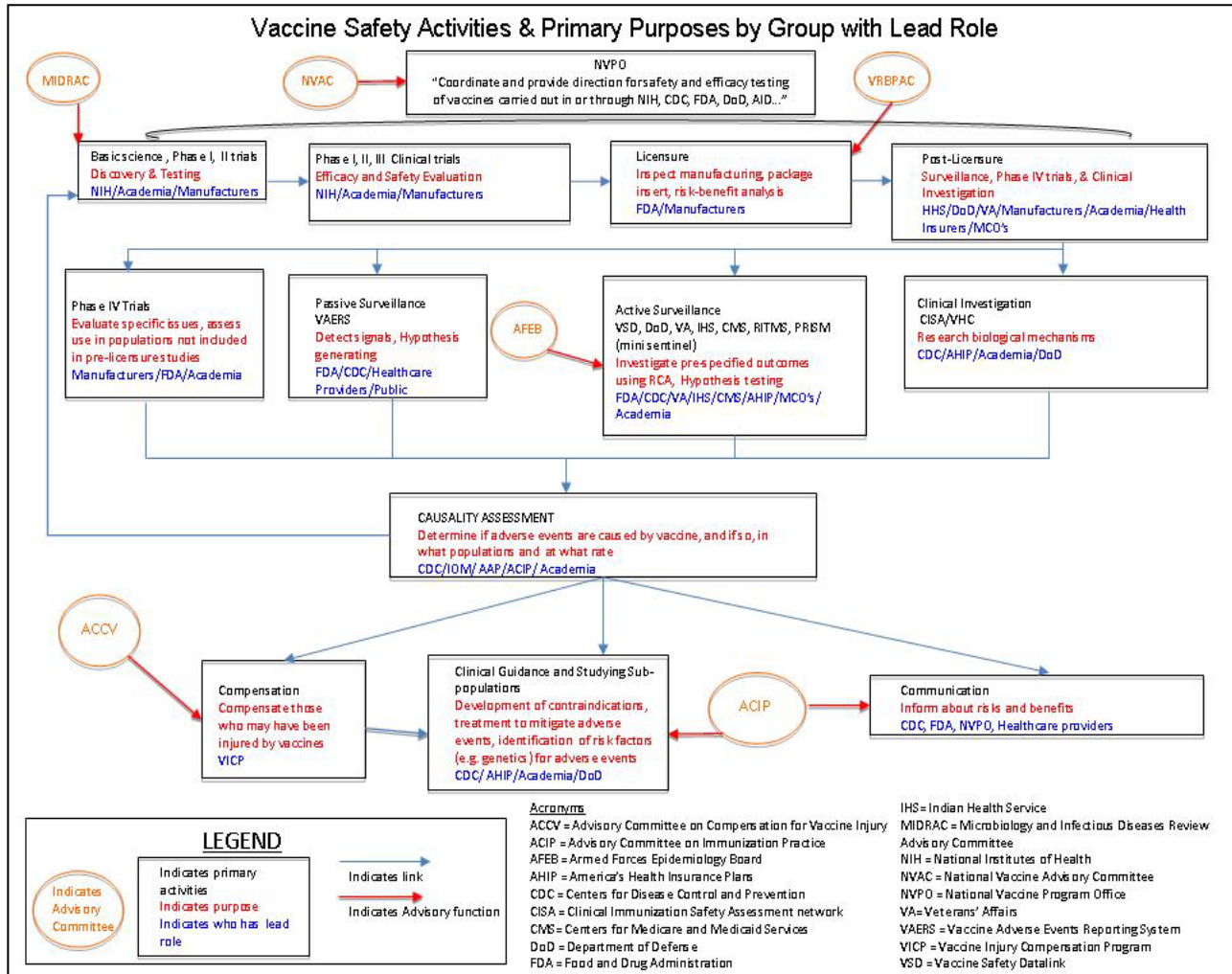
THE CURRENT VACCINE SAFETY SYSTEM

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. The components of this system provide multiple levels of focus and assurance of the safety of vaccines in the United States.

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. 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.

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.

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

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

24
25 Basic research can also be vaccine-focused/targeted. An example of this type of targeted
26 research involves the concerns raised in 1999 regarding infant exposure to ethyl mercury as a
27 result of thimerosal used as a preservative in some vaccines, with subsequent
28 epidemiological studies including outcomes associated with (methyl) mercury. [65] [66]
29 However, a lack of basic research on the comparative biological effects of and clearance of
30 ethyl mercury and methyl mercury impacted the public health response to concerns regarding
31 the safety of thimerosal in 1999. The identified need for these targeted biomedical studies led
32 to research done since 1999 on the metabolism of ethyl mercury. [67] [68] [69] CDC studies
33 examining thimerosal-containing vaccines and neurodevelopmental outcomes, including
34 autism, have not found evidence to support an association between thimerosal-containing
35 vaccines and autism. [65] [66] These types of feedback mechanisms between basic biomedical
36 research and epidemiologic research are critical to identifying priority study areas in both
37 fields.

38 **Pre-licensure Activities**

39 The NIH also plays a role in vaccine discovery and in early phase clinical evaluation through
40 the Vaccine and Treatment Evaluation Units (VTEUs), a group of National Institute of

1 Allergy and Infectious Diseases (NIAID)-funded medical research institutions. Before
2 biologics, such as vaccines, are licensed for marketing, they must undergo extensive clinical
3 trials for efficacy and safety. The FDA Center for Biologics Evaluation and Research
4 (CBER) is responsible for working with industry from preliminary application through
5 clinical trials leading to licensure. A key area of vaccine development and pre-licensure
6 activities is animal and toxicology studies conducted prior to beginning clinical trials. One
7 example of these extensive tests was the studies on Madin-Darby Canine Kidney cells
8 proposed for use in cell-culture influenza vaccine development. [70]

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

21 **Vaccine Licensure**

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

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

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

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

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

10
11 The role of the ACIP is to provide advice that will lead to a reduction in the incidence of
12 vaccine preventable diseases in the United States, and an increase in the safe use of vaccines
13 and related biological products. The Committee develops written recommendations for the
14 routine administration of vaccines to children and adults in the civilian population;
15 recommendations include age for vaccine administration, number of doses and dosing
16 interval, and precautions and contraindications. The ACIP is the only entity in the federal
17 government that makes such recommendations. ([URL](#))

18 19 **Post-licensure Activities**

20 Adverse Event Surveillance

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

33 The VAERS receives reports of possible vaccine adverse events from a wide variety of
34 sources, including parents, providers, manufacturers, pharmacists, and the military.
35 Healthcare providers and manufacturers are required to report two types of adverse
36 events to the VAERS within a seven-day period: (1) those that the vaccine manufacturer
37 has identified as contraindicating reactions to the vaccine as specified within the
38 manufacturer's package insert and (2) any adverse events present on the National Vaccine
39 Injury Compensation Program (VICP) Vaccine Injury Table. [100] Healthcare providers

1 and manufacturers also are encouraged to report any other adverse event they believe to
2 be clinically important. From 2006-2010, approximately 61% of all domestic reports
3 came from either healthcare providers or vaccine manufacturers, and approximately 10%
4 came from vaccine recipients or their parent/guardian. In addition, approximately 5%
5 came from State Health Coordinators (CDC, personal communication, 2010).

6
7 The strength of the VAERS is its ability to detect potential signals for followup; this was
8 demonstrated through the identification of an increase in cases of intussusception
9 following receipt of the first licensed rotavirus vaccine. The identification of this signal
10 led to further vaccine safety studies, ultimately resulting in the removal of the vaccine
11 from the market and the development of safer rotavirus vaccines. [76]

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

31 While information regarding the VAERS is on the Vaccine Information Statements
32 provided with every vaccination, immunizing physicians and nurses may not spend
33 adequate time discussing specific elements of vaccine safety, the vaccine safety system,
34 or the VAERS with their patients or their parents. [82] [83] Improved education of and
35 communication to physicians may decrease inaccurate perceptions of the system, such as
36 inability to perform causality studies or the perception that VAERS reports trigger public
37 health or medical responses to individual adverse events.

38
39 In addition to the VAERS, there are other surveillance systems in the United States to
40 detect AEFI:

- 1 • Adverse Drug Event Report System (ADERS) – A VA system that standardizes
2 adverse event reporting at the facility level, centralizes adverse drug event data
3 analysis, and improves the efficiency of adverse drug event report coding used to
4 categorize and classify symptoms associated with the event.

- 5 • Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) – A
6 collaboration between the American Academy of Asthma, Allergy and
7 Immunology, the Organization of Teratology Information Specialists, and the
8 Pregnancy Health Interview Study at the Slone Epidemiology Center, Boston
9 University ([URL](#)).

- 10 • FDA Sentinel Initiative – Developed after the passage of the FDA Amendments
11 Act of 2007 [54] to create an additional mechanism to acquire information on
12 vaccine safety. The Sentinel Initiative is intended to create the Sentinel System, a
13 large surveillance system that will be used for medical product safety evaluations,
14 including devices, drugs, and vaccines. Currently, development and refinement of
15 the system is being conducted through the Mini-Sentinel Pilot Project ([URL](#)). [95]
16 Mini-Sentinel provides a systematic means to interrogate a distributed network of
17 independent healthcare databases, and is intended to include access to data of at
18 least 100 million patients by July 1, 2012. The Mini-Sentinel Pilot Project
19 incorporates, and is expanding on, the vaccine safety-related systems of the
20 PRISM System (described below) to provide infrastructure that will permit
21 evaluation of the full range of adult and pediatric vaccines.

22
23 Two surveillance systems were developed to detect AEFI during the 2009 H1N1
24 influenza pandemic:

- 25 • Real Time Immunization Monitoring System (RTIMS) – Implemented through
26 the Institute for Vaccine Safety at the Johns Hopkins Bloomberg School of Public
27 Health. RTIMS used web-based queries to identify adverse events at 1 day, 1
28 week, and 6 weeks following immunization, and was used for targeted follow-up
29 for nearly 10,000 H1N1 immunizations. Most AEFI identified through RTIMS
30 were reported to VAERS.

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

37
38 Active surveillance (i.e., close and regular monitoring) is a tool used to detect AEFI when
39 new vaccine development for an emerging, widespread disease, such as the 2009 H1N1

1 influenza vaccine, is ramped up. During this event, the DoD implemented active
2 surveillance for AEFI in active duty military through examination of electronic health
3 records. Additionally, the CDC Emerging Infections Program (EIP) and CMS conducted
4 enhanced surveillance for Guillain-Barre Syndrome (GBS) during the pandemic.
5

6 Surveillance data alone usually cannot prove causation. Instead, VAERS data and data
7 from other surveillance system detect vaccine signals that need to be validated. Also, this
8 data is used to generate hypotheses for further study and testing by laboratory, clinical,
9 and epidemiologic methods.
10

11 Vaccine Signal Validation and Hypothesis Testing

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

26 RCA is an analytical technique whereby data from medical care encounters is monitored
27 and analyzed continuously to examine the potential association between selected health
28 outcomes and vaccination. By making these comparisons repeatedly—often on a weekly
29 basis—as new immunization and adverse event occurrence data are collected, researchers
30 have the ability to quickly assess potential associations between a particular vaccine and
31 adverse event. [93]
32

33 While the VSD does cover a large number of individuals, it may still be difficult to detect
34 very rare adverse events and AEFI potentially related to vaccines recommended for a
35 smaller population (e.g., meningococcal vaccine recommended for adolescents) which
36 would only constitute a subset of the total VSD population. Multi-year studies may
37 overcome this limitation. Additionally, the VSD sites typically have a very small
38 population of Medicaid patients, which may impact socio-economic diversity in the
39 population under study.
40

Biological Mechanisms Research

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

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

The CISA also manages a biospecimen repository for samples collected from patients experiencing unusual AEFI, which holds great promise for studying a variety of vaccine safety questions. Inherent challenges in specimen collection as well as lack of resources have limited the use of the repository except for specific studies that include specimen collection in the protocol. Federal efforts are underway to identify opportunities for enhancing the biospecimen repository, which are critical to maximizing its utility for biological mechanisms research.

There are other federal research programs addressing the clinical components of vaccine adverse reactions. The FDA has been active in this arena. One example is the FDA initiative to use VAERS data on cases of post-Lyme Disease vaccination arthritis to facilitate a case-control study of the underlying genetics of this adverse event. [97] More recently, the FDA CBER Office of Biostatistics and Epidemiology established the Genomics Evaluation Team for Safety to examine the genomics of vaccine adverse reactions. [98] Additionally, the Vaccine Healthcare Centers (VHC) Network is a DoD

1 organization that performs clinical consultation, conducts research into vaccine adverse
2 events research, and develops and disseminates educational materials about clinical
3 vaccine safety concerns in the military. [99] The VHC Network collaborates with other
4 research and healthcare related entities, such as the CISA and the Military Vaccine
5 Agency, which supports DoD vaccination programs protecting military service members
6 and their dependents and beneficiaries and provides educational support and training
7 resources for DoD healthcare providers and clinicians. ([URL](#))
8

9 On a final note, it is important to recognize the role that manufacturers play in biological
10 mechanisms research. The vaccine industry has a strong incentive to ensure that their
11 products are safe and effective, and, thus, has invested significant resources into
12 determining the biological mechanisms of adverse reactions, not only during the pre-
13 licensure phase, but also post-licensure.
14

15 Causality Assessment

16 On the population level, causality assessments often use set standards, and include factors
17 such as: the strength and consistency of the association; the specificity of the outcome of
18 interest; a clear temporal relationship between the vaccine and the adverse health
19 outcome; whether there is a biological mechanism to cause the adverse event; a dose
20 response relationship; experimental evidence; coherence between studies; and analogies
21 to other causal relationships. Population level causality assessments are done by many
22 individuals and groups, such as academics publishing in peer reviewed literature,
23 advisory groups such as the ACIP and the American Academy of Pediatrics (AAP) who
24 make vaccine recommendations, and most notably the IOM.
25

26 The IOM was initially charged by Congress in the National Childhood Vaccine Injury
27 Act (NCVIA) in 1986 to review the evidence for causality assessments. Since then,
28 the IOM has done 11 reviews, with the most comprehensive review being completed in
29 August, 2011. These IOM causality assessments have been hindered by an inadequate
30 understanding of potential biologic effects elicited by immunization. Because 60% of the
31 IOM causality assessments have found "inadequate evidence to make a determination,"
32 [50] further research into this area may lead to more definitive causality assessments.
33

34 Vaccine Injury Compensation

35 No vaccines or any other medications can be proven to be 100% safe; therefore, adverse
36 reactions or vaccine-related injuries could occur in some individuals. While there are
37 societal benefits from vaccination, costs following vaccine adverse reactions are borne by
38 the injured individual or their family. Recognizing that monetary compensation does not
39 fully address the hardship created by vaccine adverse events in all cases, the NCVIA
40 created the VICP, which is administered by the HRSA. The VICP uses causality

1 assessment information to establish a Vaccine Injury Table, which lists and explains
2 injuries or conditions that are presumed to be caused by vaccines. It also lists time
3 periods in which the first symptom of these injuries or conditions must occur after
4 receiving the vaccine. If the first symptom of these injuries or conditions occurs within
5 the listed time periods, it is presumed that the vaccine was the cause of the injury or
6 condition unless another cause is found. If an injury or condition is not on the Table or if
7 an injury or condition did not occur within the time period on the Table, the injured
8 person must prove that the vaccine caused the injury or condition. Such proof must be
9 based on medical records or opinion, which may include expert witness testimony. After
10 reviewing the injury claim, a "special master" (an appointed lawyer) decides if the claim
11 will be paid and, if so, how much will be paid for the claim. [100] A more current review
12 to address changes in the Table regarding more recently recommended vaccines and
13 adverse events potentially associated with them has just been published.¹
14

15 Public Health Response

16 When an acute concern arises about the safety of a vaccine, elements of the federal, state
17 and local public health systems may be mobilized to participate in the response. The
18 CDC has both proactive and reactive public health response capabilities. The agency
19 develops and disseminates clinical guidelines and recommendations for safe vaccination,
20 provides education to healthcare providers on safe vaccination practices, and participates
21 in and coordinates public health responses when vaccine safety questions arise. For
22 example, in 1999, when intussusception was suspected to be occurring following
23 vaccination with the first licensed rotavirus vaccine, identified through VAERS reports,
24 the CDC mobilized its Epidemic Intelligence Service (EIS) officers, and state and local
25 health departments participated in case finding as part of a large multistate, case-control
26 study. The findings from these activities led to the halting of the use of this vaccine
27 shortly after identification of the intussusception case cluster in the VAERS.
28

29 Communication and Information Dissemination

30 An important component of the public health response is the manner in which
31 information is communicated to the public and to healthcare providers regarding vaccine
32 safety issues. The CDC and the FDA have been responsible for rapid communication and
33 outreach following identification of potential vaccine safety issues as well as preemptive
34 efforts to inform the public about the safety of coming vaccines (e.g., 2009
35 H1N1 influenza vaccine). There is much publicly available information on vaccines and
36 vaccine safety, particularly through publicly available websites (e.g., www.cdc.gov,

¹ 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 www.fda.gov), as well as through information distributed through the CDC Health Alert
2 Network (HAN) ([URL](#)), which is a national program that provides vital health
3 information and the infrastructure to support the dissemination of information at the state
4 and local levels, and beyond. Efforts at coordinated public communication on vaccines
5 more broadly, through websites such as www.flu.gov and www.vaccines.gov, have
6 proven beneficial.

7 8 Reduction of Vaccine Administration Errors

9 Another area of safety concerns related to vaccination is vaccine administration errors.
10 Common identified administration errors are administration of the wrong vaccine, the
11 wrong dose of the vaccine, or administration at an incorrect timeframe relative to the
12 recommended vaccination schedule. [102] [103] One way to address these errors is through
13 the "five rights" framework: Right Vaccine, Right Time, Right Dose, Right Route, and
14 Right Patient. [102]

15
16 The IOM, in *To Err is Human*, referenced five questions recommended by the National
17 Patient Safety Partnership for patients to ask to reduce the possibility of medication error.
18 While these are directed more towards prescription medications, the intent is similar for
19 vaccines.

20
21 There is no central reporting mechanism for tracking vaccine administration errors. If an
22 administration error results in injury (e.g., shoulder injury related to incorrect vaccine
23 administration) [104], it should be reported to the VAERS, but errors for which no injury
24 occurs are not required to be reported to the VAERS. Other databases and reporting
25 systems that track vaccine administration errors include MEDMARX [105], the
26 Medication Error Reporting Program at the Institute for Safe Medication Practices [106],
27 and the FDA MedWatch Program [107].

28
29 One way to help ensure proper vaccine administration is the use of barcode systems for
30 identifying and tracking the immunizations provided. The FDA currently is developing
31 processes and guidance for expanded use of barcode labeling systems. [108]

32 33 Management of Vaccine Adverse Events in Clinical Practice

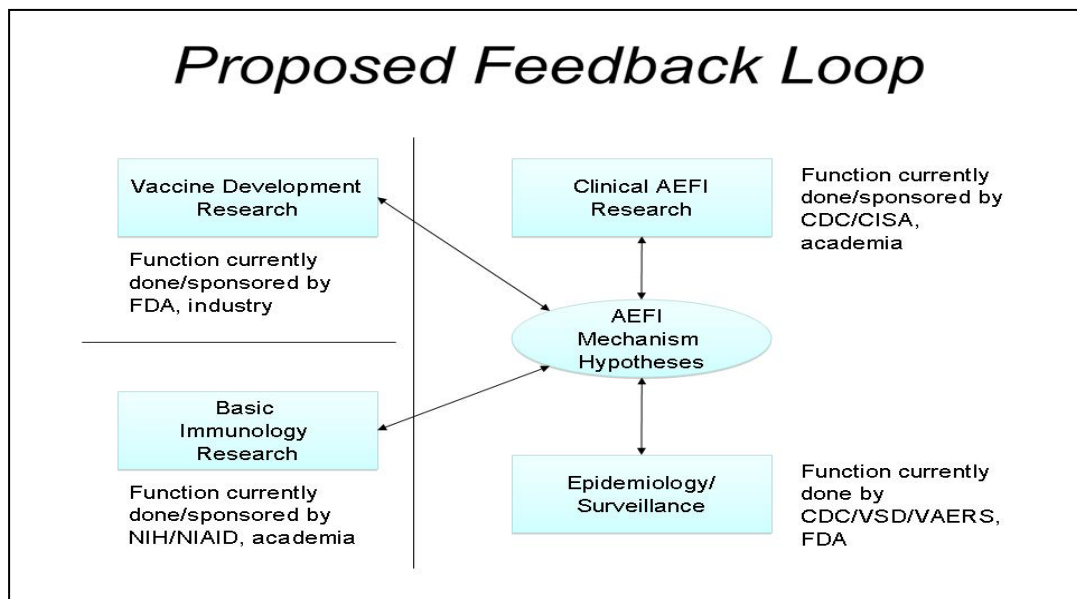
34 Once a vaccine adverse reaction is identified in a patient, the clinician must be able to
35 evaluate and manage the severity of the reaction through clinical guidance. The CDC
36 "Pink Book" contains information on identifying and managing AEFI, with a focus on the
37 more common, and typically less severe, AEFI. [109] The CDC ISO Scientific Agenda,
38 previously reviewed by the NVAC VSWG, contains a call for the development of
39 evidence-based clinical guidance protocols for managing AEFI [53], but there does not
40 currently appear to be a central repository of such clinical guidance.

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Feedback Mechanisms

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

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



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

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

7

8 **Coordination of the System**

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

- 11 • The system has the ability to coordinate prompt, cross-agency responses to specific
12 issues (e.g., the H1N1 influenza pandemic response, the ISFT as a coordinating
13 body).
- 14 • Multiagency program coordination has been demonstrated by the VAERS and the
15 Vaccine Analytics Unit (VAU), a collaboration among the CDC, the FDA, and the
16 DoD.
- 17 • The system includes agencies that serve high-risk patients in the vaccine safety
18 system (e.g., the IHS, the CMS, and the VA).
- 19 • NVPO has the ability to capitalize on opportunities for innovation (e.g., the PRISM
20 System, the Biospecimen Repository Meeting held in April 2010) through its role and
21 broad view of agency and departmental activities.
- 22 • Prior independent and external reviews of safety issues have been conducted by the
23 NVAC, such as was done in the 2009 NVAC report on the CDC ISO Scientific
24 Agenda.
- 25 • Federal Advisory committees (e.g., the NVAC, the ACIP, the VRBPAC, the
26 MDRAC, the Advisory Committee on Childhood Vaccines [ACCV], the Defense
27 Health Board [DHB]) which hold public meetings and have public representatives
28 play a role in decision making processes regarding vaccination policy and practices
29 (i.e. licensure alone is not sufficient for incorporation into the recommended vaccine
30 schedule).

31

32 **Basic Biomedical Research**

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

- 35 • Current vaccines have an excellent safety profile. Numerous studies have been
36 conducted to address outstanding safety issues. ([URL](#))

- 1 • The updated ISO scientific agenda is a key step for the direction of vaccine safety
2 research
- 3 • Multiple new research methods have been developed and utilized to evaluate the
4 safety of vaccines and their components.

5

6 **Pre-licensure Activities**

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

- 9 • Code of Federal Regulations (CFR) standards for Good Laboratory Practices, Good
10 Manufacturing Practices, and Good Clinical Practices.
- 11 • IRB standards for clinical trial approval and monitoring.
- 12 • The FDA CBER process for review of Investigative New Drug (IND) applications.
- 13 • Peer review process for underlying science and clinical results of IND applications.
- 14 • Rigor of pre-licensure assessment, including basic science evaluation, animal
15 testing, and randomized control trials of individual vaccines, and in combination to
16 evaluate safety, immunogenicity, and efficacy.

17

18

19 **Vaccine Licensure**

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

- 22 • The FDA has successfully kept up with an expanding number of licensure
23 applications for new vaccines while their budget has not expanded accordingly.
- 24 • Clinical trials for licensure include minorities, women, and other disadvantaged
25 groups.
- 26 • The FDA has developed methodologies and laboratory capacity to ensure adequate
27 evidence is available for licensure decisions.
- 28 • The FDA has been quick in addressing new technologies and urgent needs, such as
29 the H1N1 influenza vaccine.

30

31 **Post-licensure Activities**

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

- 1 • The ACIP provides advice that leads to a reduction in the incidence of vaccine
2 preventable diseases in the United States and an increase in the safe use of vaccines
3 and related biological products.
- 4 • Multimodal post marketing surveillance is in place, such as the VAERS, the VSD, the
5 Real Time Immunization Monitoring System (RTIMS), and the CDC EIP.
- 6 • Population-focused monitoring is conducted on vulnerable subgroups by departments
7 and agencies, such as the IHS, the DoD, the VA, and the CMS.
- 8 • Ongoing prospective reviews of safety are conducted on newly licensed vaccines.
- 9 • Safety signals have been picked up rapidly (i.e., intussuption in rotavirus vaccine),
10 and the VSD has conducted large number of studies examining possible associations.
- 11 • Public health investigations are responsive to potential safety concerns.
- 12 • The system has an ad hoc ability to mount larger scale studies or studies of special
13 populations (e.g., the PRISM and the Vaccines and Medications in Pregnancy
14 Surveillance System [VAMPSS]).
- 15 • VAERS and VSD budgets are modest in comparison to the costs of vaccination
16 programming.
- 17 • Numerous studies have been conducted among subpopulations, including racial and
18 ethnic minorities.
- 19 • VSD is considered a model for drug safety surveillance, and has pioneered numerous
20 new study methodologies.
- 21 • The IOM has a long history of conducting efficacious and rigorous causality
22 assessments.
- 23 • IOM reviews exclude persons with prior vaccine funding, and have strict protocols in
24 place to ensure objectivity.
- 25 • The ACIP, the AAP, and the American Academy of Family Physicians (AAFP) have
26 procedures for addressing conflicts of interest.
- 27 • CISA has used innovative methods for their individual level causality assessment
28 studies.

29

30 **Feedback Mechanisms**

31 The identified strengths with regard to feedback mechanisms in the federal vaccine safety
32 system include the following:

- 33 • Established mechanisms for feeding back information and changing decisions are in
34 place.

- 1 • A mechanism exists for establishing vaccine related adverse events and compensation
2 for injury (i.e., the VICP).
- 3 • Petitioner attorneys are reimbursed regardless of outcome, ensuring that petitioners
4 have representation.
- 5

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

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

- 11 • Accurately detect AEFI with high sensitivity and specificity.
- 12 • Accurately quantify the risk of AEFI to allow benefit/risk comparisons.
- 13 • Assess whether an AEFI is causally linked to vaccination.
- 14 • Conduct an appropriate public health response to emerging vaccine safety issues.
- 15 • Appropriately communicate results between the scientific community and the public.
- 16 • Ensure that system processes and results are transparent.
- 17 • Better understand AEFI to develop proactive research into AEFI occurrence and
18 prevention.
- 19 • Perform these tasks in a timely manner.
- 20

21 The NVAC identified nine functions (Appendix 11) of a vaccine safety system and 10 attributes
22 (Appendix 12) by which these functions could be best performed. Attributes are defined as
23 qualities or characteristics the NVAC hopes to maximize for each essential system function.
24 Each of these attributes is important for all functions of the vaccine safety system, and each was
25 considered on a continuum. The NVAC identified three attributes that should be prioritized:
26 evidence-based decision making, objectivity, and transparency.

27

28 The NVAC used these ideal vaccine system goals as a guide to develop the recommendations
29 made in the next section.

30

31

32

33

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. 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.

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. 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. The NVAC believes further that, as resources are available, the federal vaccine safety system should be enhanced in response to these recommendations.

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.

The NVAC determined that the National Vaccine Program (NVP) includes all the requisite functions for a vaccine safety system (i.e., research, regulation, post-licensure surveillance,

1 guidance for immunization programs, guidance for clinicians, injury compensation, and
2 oversight) and that the organizational placements of these functions are consistent with the
3 missions of the respective participating agencies and offices. The NVAC also determined that,
4 while fundamentally sound, the leadership, coordination, and ongoing assurance of the current
5 vaccine safety system can be improved.

6
7 For some of the recommendations below, the NVAC went beyond simply stating the objective to
8 include details regarding either how the objective should be achieved or what the completed
9 objective should include. This approach was taken for three reasons: First, the NVAC seeks to
10 avoid ambiguity regarding its thinking; absent the associated details, a reader could reasonably
11 interpret the recommendation substantially differently than does the NVAC. Second, in response
12 to a recent RAND Corporation study commissioned by the National Vaccine Program Office
13 (NVPO) that found many previous NVAC recommendations to be lacking sufficient details to
14 guide implementation and called for future NVAC recommendation to be "actionable," [144], the
15 NVAC sought to make its intended actions clear. Third, the NVAC recognizes that the U.S.
16 Department of Health and Human Services (HHS) may wish to consider alternative approaches
17 to implementing the recommendations below; therefore, the NVAC believes that the details it
18 offers will provide a valuable benchmark against which to compare any given alternative
19 approach and determine whether it is more or less superior to that recommended here.

20
21 The VSWG worked diligently for two years to put together its draft findings and
22 recommendations on behalf of the NVAC. As it reviewed the current national vaccine safety
23 system, the VSWG developed 23 draft recommendations for the NVAC to consider under the
24 following topic areas: leadership, coordination, assurance and accountability, research, post-
25 licensure surveillance, clinical practice, communications, stakeholder and public engagement,
26 and cost evaluation.

27 28 **RELATIONSHIP OF WHITE PAPER TO THE NATIONAL VACCINE PLAN**

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

33
34 One of the goals of the Strategic Plan portion of the National Vaccine Plan is to enhance the
35 nation's vaccine safety system. The vision of this goal is to "address safety-related issues,
36 strengthen the system that monitors the safety of vaccines throughout production and use, and
37 advance the safety profile of vaccines." The plan states that, "Specifically, this goal aims to
38 prevent adverse events and fully characterize the safety profile of vaccines in a timely manner."
39

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

7 **1. LEADERSHIP FINDINGS AND RECOMMENDATIONS**

8 **FINDINGS**

9
10 Acting as the operational arm of the NVP, the NVPO is charged with coordinating activities
11 across the federal government to implement the goals of the National Vaccine Plan. [116]
12 However, the HHS Assistant Secretary of Health (ASH), who is the Director of the NVP, does
13 not have organizational authority over the agencies that comprise the NVP, which may limit
14 his/her ability to directly change or coordinate activities within these agencies. Instead, this
15 authority resides with the Secretary of HHS and Secretaries of non-HHS Departments involved
16 in vaccination and vaccine safety. It would be beneficial to increase awareness of the functions
17 and activities of the vaccine safety system among these Secretaries, and to increase their role in
18 meeting their respective charges relative to vaccine safety. It also would be beneficial for the
19 coordinating entity for the vaccine safety system (the NVPO) to be given clear authorization and
20 support to perform these coordinating functions and be held accountable for executing this
21 authority. Improved coordination will provide a greater ability to be flexible with a given
22 program to adapt to an emergent need, such as those adapted to assess "real-time" risk during the
23 H1N1 influenza pandemic.

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

35 Outside of the federal government structure, public advisory committees make recommendations
36 to appropriate agencies. For example, the legislation that established the NVAC listed eight NVP
37 responsibilities in addition to vaccine safety on which the NVAC was to provide advice. Given
38 this broad scope and a limited membership size, with some membership categories prescribed by
39 the NVAC charter [117], there is a potential limit to the amount of vaccine safety expertise within
40 the full committee. This need has been addressed by subcommittees and working groups that can

1 enlist non-NVAC members, as needed. Depending on the task at hand, these groups can be task-
2 oriented with specific timelines for completion, possibly precluding long-term evaluation. The
3 advances in science and technology in the 21st century require increased vaccine safety expertise
4 on the NVAC or on an NVAC vaccine safety working group.
5

6 **OPPORTUNITIES FOR IMPROVEMENT**

7 The leadership within the HHS Office of the Secretary to exercise its inherent authorities to
8 improve coordination among United States government agencies and offices could be clarified
9 and improved. This improved leadership should be able to fully engage all of HHS and the other
10 federal agencies that should be involved in the national vaccine safety system. Enhanced
11 collaboration on vaccine-safety initiatives between agencies could improve the overall system.

12 Public advisory committees and their related subcommittees/working groups could benefit from
13 enhanced, expert representation to address vaccine safety issues by inclusion of subject matter
14 experts in areas such as understanding, preventing, and treating vaccine-associated adverse
15 events.
16

17 **RECOMMENDATIONS**

18 **Leadership Recommendation 1.1**

19 **Reaffirmation of the System Structure**

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

- 23 • The NVP is a coordinated effort among the Food and Drug Administration (FDA), the
24 Centers for Disease Control and Prevention (CDC), the National Institutes of Health
25 (NIH), the Health Resources and Services Administration (HRSA), and the Centers for
26 Medicare and Medicaid Services (CMS), and the Departments of Defense (DoD) and the
27 VA and the United States Agency for International Development (USAID).
- 28 • The ASH, having been designated as Director of the NVP, is responsible for the direction
29 of the NVP activities related to coordination of vaccine safety.
- 30 • The NVPO is charged with advising the ASH regarding implementation of the
31 responsibilities of the NVP and coordinating the vaccine safety-focused activities of the
32 NVP² (see related recommendation in Coordination Recommendation 2.1).
- 33 • The NVAC is responsible for reviewing vaccine safety policy and the vaccine safety-

² 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 focused activities, developing recommendations based on these reviews, and transmitting
2 its recommendations to the ASH and to the Secretary pending implementation of
3 Leadership Recommendation 1.3.

4 **Leadership Recommendation 1.2**

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

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

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

19 The Secretary should define performance expectations related to vaccine safety for NVP-
20 coordinated agencies.

21 **Leadership Recommendation 1.3**

22 **National Vaccine Advisory Committee Charter**

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

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

30 The NVAC should help evaluate the progress of the NVP-coordinated agencies toward
31 enhancing vaccine safety both in response to requests from the Secretary and at its own initiative.
32 This task could prove especially beneficial to evaluating NVP-wide initiatives to enhance
33 research, post-licensure surveillance, public information, and stakeholder engagement. The ASH
34 should charge the NVAC to create a Standing Working Group on Vaccine Safety. Members of
35 this Working Group should be selected using a similar approach as used for the H1N1 Vaccine

1 Safety Risk Assessment Working Group. Membership also should include representatives from
2 entities such as ACIP, the Advisory Commission on Childhood Vaccines (ACCV), the Vaccines
3 and Related Biological Products Advisory Committee (VRPAC), and others, as appropriate, and
4 should address issues of conflict of interest as they arise. This Working Group would, at a
5 minimum, be charged with reviewing the following long-term goals and activities:

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

14 **2. COORDINATION FINDINGS AND RECOMMENDATION**

16 **FINDINGS**

17 The need for improved coordination of components of the vaccine safety system parallels an
18 ongoing NVAC theme of increased coordination within the United States vaccine enterprise [44]
19 [62], as well citations in a number of earlier reports. [44] [46] [110] [111] Interviews with
20 representatives from different federal agencies within the vaccine safety system reflected room
21 for improvement with respect to coordination within the NVP and between its complex mix of
22 governmental and non-governmental partners and stakeholders. [101] There is recent evidence
23 that this type of coordination is possible and can pay dividends for public health. The rapid
24 response of the NVPO in implementing the NVAC recommendations of July [20] and August
25 [112] 2009 related to H1N1 influenza vaccine safety monitoring provides support for this concept.
26 When the Institute of Medicine (IOM) made recommendations related to coordination in
27 *Priorities for the National Vaccine Plan*, they cited these H1N1 safety monitoring
28 recommendations as an example of what could be accomplished through these coordinated
29 efforts. [46]

31 Recommendations stressing coordination in the National Vaccine Plan [46] [113] highlighted the
32 need for coordination across all components of the vaccine enterprise, including the vaccine
33 safety system. There are some examples of strong coordination, including the Vaccine Adverse
34 Event Reporting System (VAERS), co-administered by the CDC and the FDA [114], and bi-
35 weekly conference calls between the leadership of the Immunization Safety Office (ISO) and the
36 Center for Biologics Evaluation and Research (CBER) (FDA and CDC, personal
37 communication, 2011). Improved coordination among the various parts of the NIH or other

1 federal agencies directly or indirectly involved in vaccine safety was an area for improvement
2 identified by the NVAC.

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

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

22 23 **OPPORTUNITIES FOR IMPROVEMENT**

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

29
30 Enhanced collaboration on vaccine-safety initiatives between agencies is needed. A formalized,
31 visible coordinating body for vaccine safety within the federal government could enhance this
32 collaboration and provide assurance and accountability of the vaccine safety system.

33 **RECOMMENDATION**

34 **Coordination Recommendation 2.1**

35 **Expanded Role and Composition for the ISTF, ISCG, or Other Similar Coordinating Body**

36 The ISTF, the ICSG, or other similar coordinating body should make regular reports, in
37 accordance with the structure described in Assurance and Accountability Recommendation 3.2.
38 The scope of the ISTF's or ICSG's vaccine safety coordinating activities, under the leadership of

1 the ASH and the NVPO Director, should specifically include focused effort involving
2 subcommittees of the ISTF, ISCG, or a similar coordinating body in the following areas:
3 research, post-licensure surveillance, clinical practice, communications, and stakeholder and
4 public engagement. This may best be carried out by establishing a subcommittee or some other
5 body.

6
7 The NVPO should expand the membership of the ISTF or create the ISCG or other similar
8 coordinating body to ensure representation from the agencies and departments specified as
9 contributing to the NVP components outlined in the NCVIA, or subsequently redesignated or
10 renamed agencies, including the CMS, the AHRQ, and the USAID.

11 12 **3. ASSURANCE AND ACCOUNTABILITY FINDINGS AND** 13 **RECOMMENDATIONS**

14 15 **FINDINGS**

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

20
21 As part of drafting this White Paper, the VSWG engaged in a fact-finding session at its first
22 meeting in July 2009 where a panel discussion was held to present different approaches to
23 assurance in other safety arenas (see Appendix 2). Based on this session and further staff
24 research, the VSWG developed and discussed three options for external independent assurance
25 related to vaccine safety, with the second of these options having three potential configurations
26 (see Appendix 13). These included the following:

- 27 • Option 1 – Empower the NVAC to be responsible for vaccine safety assurance.
- 28 • Option 2 – Establish a fixed-tenure panel outside of the HHS to monitor the efforts of the
29 NVP and the NVAC, respectively, to improve the vaccine safety system. (Option 2a was
30 to establish a Presidential Commission, Option 2b was to establish an IOM Committee,
31 and Option 2c was to create an Independent Agency within the Executive Branch to
32 oversee the vaccine safety system.)
- 33 • Option 3 – Create an Independent Agency within the Executive Branch to focus on the
34 safety of vaccines (i.e., to operate some or all components of the system).

35
36 The VSWG worked for over a year to develop, define, and discuss the assurance options. The
37 VSWG developed a set of pros and cons for each recommendation to further its discussions. The
38 options were included in the Vaccine Safety White Paper version 2.0 that was published for

1 public comment and was the subject of the June 2011 Stakeholder's Meeting. Despite extensive
2 efforts by its members to debate and discuss the options over a period of many months, the
3 VSWG was not able to come to a consensus on the preferred assurance option prior to the June
4 2011 NVAC meeting where the White Paper recommendations were discussed in detail. At this
5 meeting, the NVAC reviewed the options developed by the VSWG and provided strong support
6 for Option 1: NVAC should continue to be the advisory entity primarily responsible for
7 evaluating the NVP programs.

8
9 A straw poll following the Stakeholder and NVAC meetings, with 11 of 14 VSWG members
10 responding, showed six in favor of Option 1, one in favor of Option 2a, three in favor of Option
11 2b, and one in favor of Option 3. A synopsis of their opinions on these options is provided
12 below.

- 13 • Those favoring Option 1 viewed it as the most efficient and effective use of existing
14 resources available for vaccine safety assurance. They saw this option as capitalizing on
15 the authority previously bestowed upon the NVAC through the U.S. Public Health
16 Services Act and as the most feasible for implementation and fully within the scope of
17 the original act and role of the NVAC. Additionally, supporters of Option 1 noted that the
18 NVAC has shown leadership and capability to perform this assurance role as
19 demonstrated through responsive actions in the development, operation, and public
20 reporting of the Vaccine Safety Risk Assessment Working Group (VSRAWG) during the
21 2009 H1N1 pandemic. This option was noted as the least disruptive mechanism to current
22 vaccine safety activities. Supporters of this option thought that the major drawbacks of
23 the other options included substantial feasibility issues regarding operational, financial,
24 and political implementation, and lack of evidence to warrant recommending an
25 additional layer of complexity to the system.
- 26 • Option 2 supporters thought the major factors in favor of this option (and its three
27 configurations) included increased objectivity, the ability to build on existing models and
28 systems, and the perception of external accountability. Supporters thought the major
29 drawbacks to this option were potential financial and political feasibility issues for
30 establishing any of the Option 2 configurations.
- 31 • Supporters of Option 3 thought the major factors in favor of this option included a
32 definitive separation of vaccine safety activities and accountability operations and
33 increased objectivity. They thought the major drawbacks were the high financial
34 resources needed for implementation and potential for ineffectiveness if the option was
35 not executed appropriately.

36
37 See Appendix 13 for more detailed information about VSWG discussion about these options.
38

39 **OPPORTUNITY FOR IMPROVEMENT**

1 As with most important governmental functions, an ongoing, publically accessible process of
2 external review of the work the United States vaccine safety system could help assure the
3 effective functioning of the system and may increase confidence in its work.
4

5 **RECOMMENDATIONS**

6 **Assurance and Accountability Recommendation 3.1**

7 **Enhanced Role of the NVAC**

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

18 **Assurance and Accountability Recommendation 3.2**

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

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

31 **Assurance and Accountability Recommendation 3.3**

32 **External Assessment of Adverse Event Causality**

33 To resolve difficult scientific questions through external scientific review of available evidence
34 and provide regular updates to the National Vaccine Injury Compensation Program (VICP)
35 Vaccine Injury Table, a mechanism should be developed to conduct causality evaluation of
36 selected vaccine adverse events. On an annual basis, the ISTF, ISCG, or other similar

1 coordinating body, in consultation with the NVAC Standing Working Group on Vaccine Safety
2 (see Leadership Recommendation 1.3), will conduct a review of potential topics for examination,
3 based on AEFI for which a review of causality is warranted and for which there is scientific
4 literature addressing the topic. If serious adverse events that meet these criteria are identified, the
5 Secretary of HHS should continue using the IOM method to assess the causal relationship
6 between the identified vaccine(s) and suspected adverse event(s). Results of assessments should
7 be reported to the NVAC, the ACCV, and other entities as determined by the NVAC.
8

9 **Assurance and Accountability Recommendation 3.4**

10 **Progress in Enhancing the Vaccine Safety System**

11 To assure progress in enhancing the vaccine safety system, as highlighted in the
12 recommendations in this White Paper, a formal mechanism for review and accountability is
13 needed. The NVAC should continue to be the advisory entity primarily responsible for
14 evaluating the NVP programs and commissioning vaccine-specific investigations. Opportunities
15 exist for the HHS to enhance the NVAC's standing and authorities, as described in Leadership
16 Recommendations 1.1 and 1.3, Assurance and Accountability Recommendations 3.1 and 3.2, and
17 Stakeholder and Public Engagement Recommendation 8.1. Additionally, NVAC should
18 periodically review and report to the ASH on its assessment of progress toward implementation
19 of the recommendations of this report. In addition, another entity, such as the IOM, should be
20 charged to undertake a review in three to five years to assess progress toward vaccine safety
21 system assurance as defined in this report. As with all recommendations made in this White
22 Paper, assurance and accountability mechanisms will need to be in place for proper oversight of
23 the NVAC as they fulfill this recommendation.
24

25 **4. RESEARCH FINDINGS AND RECOMMENDATIONS**

26 **FINDINGS**

27 The need for coordination in the vaccine safety system extends to the research realm. Basic
28 research, clinical research, and epidemiological research must all be well-coordinated and inform
29 one another. Without formal linkages between vaccine-related entities—such as the National
30 Institute of Allergy and Infectious Disease (NIAID), Vaccine and Treatment Evaluation Units
31 (VTEUs), the CDC, the Clinical Immunization Safety Assessment (CISA) Network, the FDA,
32 the DoD, and the AHRQ—complimentary expertise and infrastructure cannot be fully leveraged.
33 A mechanism is needed for collaborating with experts outside of the vaccine safety arena when
34 questions arise that would benefit from their expertise. Not only would these external linkages
35 aid in understanding the potential adverse events, but also these subspecialists could be sources
36 of cases for study or samples for a vaccine safety repository.
37

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

9
10 Improved coordination is important to ensure that appropriate data related to vaccination and
11 adverse events are collected when opportunities to do so present themselves. Long-term,
12 longitudinal studies, such as the National Children's Study, provide the opportunity for analysis
13 of large cohorts of children, and efforts need to be leveraged to ensure that accurate
14 immunization data are collected. While these studies are not designed solely to address effects,
15 both beneficial and adverse, of vaccination, they do provide an opportunity to improve data
16 retrieval methods (e.g., through medical records or through immunization information system
17 review).

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

30 Basic research into the molecular and cellular responses making up the immune response to
31 vaccination that may be related to adverse events, including studies of vaccine antigens,
32 adjuvants and other related components [123], needs to be improved and incentivized, as was
33 done with the use of American Recovery and Reinvestment Act funds to begin a study to model
34 the human immune response. [124] NIH activities could also be integrated into existing
35 FDA/CDC studies of vaccine safety to enhance the inclusion of information from basic research.
36 It may be beneficial to develop systematic methods to prioritize which vaccine adverse reactions
37 should be studied or to consider incorporation of public input into the prioritization process.

38
39 In light of the interest and investment being made in these respective scientific disciplines, there
40 is great opportunity to collaborate and inform vaccine safety science through the lenses of

1 immunology and genomics. This will require collaboration among scientists and entities
2 conducting research, funding, and access to specimens through an effective biobank able to
3 capture the necessary samples from patients who experience very rare events. Formalized data
4 sharing will inform a coordinated scientific agenda that includes biological mechanisms, which
5 is critical to ensure that the biological basis behind vaccine adverse events is properly
6 understood. Research cannot be undertaken without a strong vaccine safety science work force,
7 which is currently small and inadequately supported.

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

23
24 While proactive monitoring efforts are used to identify rarer AEFI with more widespread vaccine
25 use, the current system for research into biological mechanisms of vaccine adverse reactions is,
26 by its inherent nature, primarily reactive. While basic research projects, such as the NIH's
27 Human Phenotyping Project, provide a great opportunity to build and sustain a consortium
28 approach for profiling human immune responses, little has been done to capture potential
29 synergies between these efforts with others, such as the development of a biospecimen
30 repository. Indeed, more thought and leadership is needed on approaches to incentivize novel
31 research that will provide critical information to guide vaccine safety policy decisions across all
32 aspects of the life cycle of a vaccine

33
34 Many opportunities exist to gain new fundamental insights into the molecular and cellular
35 mechanisms that may be involved in vaccine adverse reactions that could improve prevention
36 and treatment of vaccine adverse events. Although the purpose of this report is not to prescribe
37 specific vaccine safety activities, the VSWG would like to reaffirm that the NVAC made
38 recommendations related to biological mechanisms in its June 2009 report, [62] including
39 "Consider detailed mechanistic studies of common but mild adverse events such as fever or rash.
40 These might provide insights into mechanisms of severe but rare adverse events." [62] This prior

1 NVAC recommendation was made to attempt to understand if there are common mechanisms
2 underlying adverse events that are common and mild as well as more severe adverse events.
3 Attempts to understand underlying mechanistic issues for adverse events may allow examination
4 of severe adverse events through the proxy of other, more common, adverse events.

5
6 Comprehensive education on adverse event identification and proper vaccine administration and
7 treatment of adverse events is very important, particularly for immunization providers. This
8 education will require research and development of treatment algorithms. The DoD Vaccine
9 Healthcare Centers (VHC) Network has developed related algorithms, more of which are needed
10 for vaccines given in the general population.

11 Clinical guidance for managing and coping with vaccine injuries is limited for healthcare
12 providers and individuals who believe that they have experienced a vaccine injury. Even within
13 *Epidemiology and Prevention of Vaccine Preventable Diseases* (also known as "The Pink
14 Book") [109] there is limited information on clinical guidance for managing adverse events
15 following immunization.

16 The development of a scientific agenda and coordinated research program (see Research
17 Recommendations 4.1 and 4.2) also could help the development of a National Vaccine Safety
18 Biospecimen Repository. Currently, an Institutional Review Board (IRB)-approved specimen
19 repository is maintained through the CISA. Expansion into a larger-scale repository could
20 increase the ability to perform necessary biological mechanisms research. However,
21 development of a National Vaccine Safety Biospecimen Repository has a number of logistical
22 challenges that need to be addressed, including, but not limited to, the following: (1) identifying
23 the types of samples to be banked and the associated information needed for the samples to be
24 useful and (2) identifying who would contribute samples to the repository, how the samples
25 would be distributed, who would determine which requests for samples would be approved, who
26 would maintain the samples, and who would ship the samples, and (3) determining how the
27 repository would be funded.

28
29 With regard to ascertainment of public concerns and perceptions, the CDC and others conduct
30 public polling to understand public concerns about vaccine safety. Information from such polls
31 can assist in developing educational messages and materials on vaccine safety. Such information
32 could also inform the vaccine safety research agenda.

33 **OPPORTUNITIES FOR IMPROVEMENT**

34 A federal government-wide vaccine safety research agenda for enhancing research in critical
35 subject matters, including both pre-licensure research activities and post-licensure surveillance,
36 needs to be created.

37
38 Research into the molecular and cellular mechanisms that may be involved in vaccine-associated
39 adverse events is occurring but could benefit from increase coordination, planning, and
40 resources.

1 Coordinating research efforts into the molecular and cellular mechanisms that may be involved
2 in vaccine-associated adverse events such research and more clearly identifying their possible
3 application to vaccine safety potentially could enhance prevention and treatment of vaccine
4 adverse events.

5
6 A consistent funding mechanism for vaccine safety research could support program project
7 grants and investigator-initiated research into vaccine safety under the scope of a national
8 vaccine safety scientific agenda.

9
10 The CDC could use the findings from its data collection of public opinions to assist in the
11 implementation of the vaccine safety agenda and recommendations made in this White Paper.
12 Clinical guidance and other support related to identification, evaluation, treatment, management,
13 and coping with AEFI could be improved and widely disseminated to vaccination providers,
14 patients, and caregivers.

15 Formalized data sharing could inform a coordinated scientific agenda that includes biological
16 mechanisms, which is critical to ensure that the biological basis behind vaccine adverse events is
17 properly understood.

18 Expansion into a larger-scale repository, such as a National Vaccine Safety Biospecimen
19 Repository, could increase the ability of the vaccine safety system to perform necessary
20 biological mechanisms research.

21 Increased support for training for the vaccine safety research workforce is needed.

22

23 Greater accessibility to existing vaccine safety data could enhance current vaccine safety
24 research and foster additional research.

25 **RECOMMENDATIONS**

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

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

- 35 • Needs and opportunities for eliminating unnecessary redundancy across these activities to
36 make these research activities more effective and efficient.
- 37 • Needs and opportunities for new or redirected studies toward reducing or eliminating
38 gaps in knowledge relevant to vaccine safety.

- 1 • Needs and opportunities to assess the potential risks of vaccines currently in use.
- 2 • Strengths and limitations of the processes for assessing vaccine safety before and after
3 licensure.
- 4 • Existing basic research programs and findings that may have applicability in the broader
5 scope of vaccine safety research, to create linkages between these research programs to
6 improve the broader knowledge of vaccine safety science.
- 7

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

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

- 13 • Facilitate a community of vaccine safety researchers that crosses the boundaries from
14 basic research, clinical research, and epidemiology to ensure continuity of research from
15 different arenas, entities, and disciplines.
- 16 • Share vaccine safety-related research findings with all members of the ISTF/ISCG at
17 regular monthly Task Force meetings.
- 18 • Leverage existing infrastructure and investments for vaccine safety research, such as
19 CISA and the National Children's Study.
- 20 • Engage vaccine manufacturers to capitalize on their expertise, large preclinical and
21 clinical databases, specimen repositories, and scientific resources to inform further
22 vaccine safety studies.
- 23 • Coordinate the development, implementation, and periodic update of the National
24 Vaccine Safety Scientific Agenda, as described in Research Recommendation 4.1.
- 25 • Ensure feedback between stakeholders within the vaccine safety enterprise so that
26 research findings translate into safer products and guidelines for their use when
27 appropriate.
- 28

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

- 30 • The NIH should identify and link multidisciplinary, internal and external vaccine safety
31 research programs and funding, including encouragement of researchers to highlight
32 research that may have a potential application to vaccinology and vaccine safety through
33 targeted applications of keywords and requested reviewers, and through appropriate
34 revisions of "PA-08-256: Research to Advance Vaccine Safety" to ensure a wide range of
35 applicability across multiple disciplines.

- 1 • The HHS and its related agencies, along with academic partners and professional
2 organizations, should develop training programs for scientists and medical professionals
3 in basic vaccinology and in related sciences that will contribute to informing vaccine
4 safety research.
- 5 • The HHS and its related agencies, along with academic partners and professional
6 organizations should support training in vaccine safety for scientists in non-biomedical
7 research areas (e.g. cost/benefit analyses, quality assurance, and policy analysis).

8 9 **Research Recommendation 4.4 – Ascertainment of Public Concerns and Perceptions**

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

14 15 **Research Recommendation 4.5 – Research Directed to Clinical Practice**

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

30 31 **Research Recommendation 4.6 – Data Access**

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

- 36 • Final data that were used for decisions about vaccine safety (following "reproducible

1 research" [145] strategies).

- 2 • General data that have not been used for a specific adverse event, such as VSD, CISA,
3 and associated specimen banks, to the extent possible.
- 4 • Preclinical, clinical, and post-licensure data that are part of the application process.
5

6 **Research Recommendation 4.7 – Biological Specimens**

7 The CDC and the CISA Network should complete the planning and implementation of
8 recommendations for the enhancement of a National Vaccine Safety Biospecimen Repository
9 linking biological samples to clinical data for unusual AEFI to accelerate studies of biological
10 mechanism and subpopulations at increased risk for adverse events.
11

12 **5. POST-LICENSURE SURVEILLANCE FINDINGS AND RECOMMENDATIONS**

13 **FINDINGS**

14 *Surveillance/Signal Detection*

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

21 The utility of VAERS was well demonstrated following the initial post-licensure period for the
22 first licensed rotavirus vaccine. However, the limitations of a passive reporting system, along
23 with reports containing incomplete data, can affect the strengths of the system, and new
24 technologies should be employed as possible to address these limitations. [125] Additionally,
25 some reports published using VAERS data [126] [128] included analytic interpretations beyond
26 what is recognized as feasible with these data [77] [78], which can lead to misunderstandings of
27 the value and application of this system.
28

29 Expanded technologic approaches to surveillance of early concerns and "warning signs" among
30 the public have not been widely utilized. While focus groups and town meetings are important
31 for getting more in-depth sense of public concerns and responses to messages, they do not
32 provide a sense of the distribution of the concerns in the general population or in vulnerable
33 subpopulations.
34

35 *Signal Assessment/Hypothesis Testing*

36 Post-licensure data collection for vaccine safety is required through Title 21, Code of Federal
37 Regulations (CFR), Part 600.80, "Post marketing reporting of adverse experiences" [129] and

1 existing FDA guidance to industry on vaccine safety reporting. [130] However, the extent of post-
2 licensure vaccine safety monitoring may not be readily apparent to the public, potentially leading
3 to concerns about the adequacy of this type of evaluation.

4 Post-licensure studies of vaccine safety can require extensive time and effort, and there may be
5 the perception of a trade-off between timeliness and quality of the results. However, as seen with
6 the NVAC H1N1 VSRAWG [131], high quality and rapid evaluation of vaccine safety data can
7 be performed, though the intensive effort required may not be sustainable for all, or even most,
8 vaccine safety examinations. Ad hoc development of systems such as the Meningococcal
9 Vaccine Study[18] and the Post-licensure Rapid Immunization Safety Monitoring (PRISM)
10 System [23] to supplement the VSD can be effective for defined and targeted analyses, though an
11 evaluation for more widespread application still needs to be performed. Increased sample sizes
12 and increased technological advances (e.g., Rapid Cycle Analysis [RCA]) can increase the
13 timeliness for detection of significant levels of adverse events. [93] [132]

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

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

27 *Causality Assessment*

28 The lack of coordination around vaccine safety research described above may create
29 opportunities to improve knowledge and understanding of vaccine safety. In 18 of 30 (60%)
30 assessments since 2001, the IOM concluded there was not adequate information to accept or
31 reject a causal association between vaccination and specific adverse events³. [50] Part of the
32 problem with vaccine adverse event causality assessments is the lack of statistical power
33 associated with smaller studies. The use of large linked databases has begun to reduce this
34 problem, but, even in the VSD, the population under active surveillance may still be too small
35 for examination of very rare adverse events (e.g., 1-2 cases / 100,000 for Guillain Barre
36 Syndrome [GBS]) or events among important subgroups such as pregnant women.

³ 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

2 *Injury Compensation*

3 The current Vaccine Injury Table became effective November 10, 2008. Four vaccines (hepatitis
4 A vaccine, trivalent influenza vaccine, meningococcal [polysaccharide and conjugate] vaccines
5 and HPV vaccine) have not undergone full review of adverse events that may be considered for
6 compensation under the VICP. [100] An IOM review is underway for these, and other, vaccines.⁴
7 [133] Until this review is completed and new entries are made to the Vaccine Injury Table,
8 adverse events following receipt of these vaccines must be proven to be associated with
9 vaccination in order for compensation to be provided. Often claims alleging conditions not listed
10 in the Vaccine Injury Table are compensated on the basis of negotiated settlements between both
11 parties. Since FY 2007, over half of claims adjudicated annually are compensated on the basis of
12 litigative risk settlements.

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

23

24 *Public Health Response*

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

34 By definition, public health response activities are primarily reactive. While the CDC has an
35 impressive track record of providing support through the Epi-AID system for disease

⁴On 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 investigation and control, there may be room for coordination of public health response activities
2 across departments and agencies involved in the vaccine safety system. Additionally, aside from
3 high-profile situations, such as the rotavirus vaccine/intussusception case and the H1N1
4 influenza vaccination campaign, there does not appear to be broad communication to the public
5 about the public health functions involved in vaccine safety.

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

12 **OPPORTUNITIES FOR IMPROVEMENT**

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

17
18 Even well-developed epidemiological studies of actual or potential vaccine-associated adverse
19 events could benefit from increased sample sizes to be able to more quickly detect rare adverse
20 events.

21 Expanded efforts to obtain information on background rates of potential AEFI in subpopulations
22 would assist in vaccine safety risk assessment.

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

25 Strategies are needed to enhance the quality of data reported to VAERS. Some potential
26 examples are outreach to individuals who make reports encouraging more complete data
27 reporting and utilization of technology and data abstraction methods from electronic health
28 records to enhance reporting.

29
30 For an increasingly proactive way to measure AEFI, the vaccine safety enterprise needs an
31 expanded array of surveillance approaches to ascertain early concerns through public opinion
32 polling and active monitoring the "new media," such as blogs. Causality assessment, as
33 performed by the IOM, is a useful and robust process. Institutionalizing a standing causality
34 assessment group is needed.

35
36 Acute investigations (e.g., association between first licensed rotavirus vaccine and
37 intussusception) have worked, but the broader responsibilities of federal departments and
38 agencies involved in causality assessments may benefit from improved coordination to maximize
39 available data and expertise.

1 The timeframe for updating the vaccine injury compensation table could be improved
2 commensurate to the pertinent and existing knowledge base.

3
4 Provider and public awareness of the VICP could be increased.

5
6 Recognizing the work of the CDC in vaccine safety-related public health response, best practices
7 and collaborative efforts could be promulgated among federal departments and agencies that may
8 be involved in these types of public health response activities.

9
10 Future public health response could benefit from increased data linkages between sources of
11 immunization data, both from traditional and non-traditional immunization settings, and sources
12 of health outcomes data.

13 14 **RECOMMENDATIONS**

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

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

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

25 26 **Post-licensure Surveillance Recommendation 5.2 –Data Considerations**

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

- 30 • Ensure vaccine safety data are collected on ACIP-recommended vaccine usage not
31 covered by FDA-approved labeling.
- 32 • Utilizing coordination efforts detailed in Coordination Recommendation 2.1 and research
33 coordination efforts detailed in Research Recommendation 4.2, post-licensure vaccine
34 safety surveillance activities should be informed by manufacturer's expertise and
35 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 new vaccines or vaccine formulations/combinations (see Post-licensure Surveillance Recommendation 5.1).

6. CLINICAL PRACTICE FINDINGS AND RECOMMENDATIONS

FINDINGS

Comprehensive education on adverse event identification and proper vaccine administration and treatment and reporting of adverse events is important for immunization providers. This education will require research and development of treatment algorithms. The DoD VHC Network has developed related algorithms, more of which are needed for vaccines given in the general population.

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

Clinical guidance for managing and coping with vaccine injuries is limited for healthcare providers and individuals who believe that they have experienced a vaccine injury. Even within *Epidemiology and Prevention of Vaccine Preventable Diseases* (also known as "The Pink Book") [109] there is limited information on clinical guidance for managing adverse events following immunization. One way to help ensure proper vaccine administration is the use of barcode systems for identifying and tracking the immunizations provided. Currently, the FDA is developing processes and guidance for expanded use of barcode labeling systems [108], with the most current guidance, as of August 2010, available at

1 [http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInform](http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM225099.pdf)
2 [ation/Guidances/General/UCM225099.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM225099.pdf).

4 **OPPORTUNITIES FOR IMPROVEMENT**

5 Clinical guidance and other support related to identification, evaluation, treatment, management
6 and coping with AEFI could be improved and widely disseminated to vaccination providers,
7 patients, and caregivers.

8 The use of barcode systems for identifying and tracking the immunizations provided could
9 ensure proper vaccine administration.

11 **RECOMMENDATIONS**

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

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

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

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

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

32 **7. COMMUNICATION FINDINGS AND RECOMMENDATION**

33 **FINDINGS**

34 Over the last decade how information is disseminated and used has changed dramatically and has
35 profoundly influenced how consumers make healthcare decisions. The Internet and social media

1 have helped shape attitudes and beliefs regarding immunization and have brought vaccine
2 decision making to the forefront as consumers seek credible and easily accessible information.
3 The NVAC believes it is important to recognize these societal shifts recommending
4 improvements in how the federal government communicates immunization information to
5 consumers, healthcare providers and the public health community.

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

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

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

33 The NVAC could not determine if improvements in the vaccine safety system will change public
34 attitudes in general. In particular, the NVAC found no data suggesting that, for individuals in
35 specific populations who oppose vaccination for their children, improvements in the vaccine
36 safety system will modify attitudes. The general public is likely largely unaware of the vaccine
37 safety system and its function in ensuring vaccine safety, and it is not clear that knowledge of the
38 system would change these attitudes or behavior. On the other hand, increasing awareness of and
39 improving appreciation of enhancements to the vaccine safety system by practicing physicians
40 may increase their ability to rapidly communicate vaccine safety information to parents. This is

1 of particular importance with the large amount of information to be communicated, both vaccine-
2 related and non-vaccine-related, during routine physician visits where time may be limited. [83]
3 However, regardless of whether a CQI process in the vaccine safety system will improve public
4 confidence, resulting in increased acceptance of vaccines, these improvement processes should
5 be considered if they could strengthen the system and improve scientific understanding and
6 patient safety.

7 **OPPORTUNITIES FOR IMPROVEMENT**

8 The provision of a one-stop source of comprehensive information about vaccine safety for the
9 public and providers, such as how to report adverse events, how the vaccine safety system has
10 successfully identified previous actual adverse events following immunizations, how the vaccine
11 injury compensation program works, what safety-related research is underway, could improve
12 communications to the public on these topics. Vaccines.gov is a good start to providing this type
13 of comprehensive information but could be improved upon.

14 Coordination between the different federal departments and agencies (e.g., the CDC, the FDA,
15 the DoD, the VA) with respect to their outreach about the safety of vaccines could be improved.
16

17 **RECOMMENDATION**

18 **Communication Recommendation 7.1**

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

- 27 • The Vaccine Information Statement.
- 28 • The official package insert, as prepared and issued by the FDA, and the FDA's analysis
29 provided to VRBPAC.
- 30 • Summaries of the design, scope, and results of the key clinical trials that supported
31 licensure.
- 32 • Summaries of the design, scope, and results of any post-licensure clinical trials required
33 by the FDA or being conducted under the auspices of one or more of the other NVP-
34 participating agencies.
- 35 • Abstracts of product-specific peer-reviewed research reports published after licensure.
- 36 • Abstracts of ongoing product-specific research studies funded by the HHS or other

1 departments of the federal government.

- 2 • A clearer public explanation of each agency's role in post-licensure vaccine safety.

3
4 This communications plan also should focus on utilizing existing mechanisms, and where
5 necessary, establishing mechanisms and publicizing means by which members of the public can
6 obtain information about vaccines.

7
8 The CDC should utilize and disseminate findings from research into public concerns (see
9 Research Recommendation 4.4) to develop communications tools applicable to address public
10 concerns and perceptions.

11
12 The CDC and the FDA should improve methods for communication about the extent to which
13 follow-up to individual VAERS reports may be conducted.

14 15 **8. STAKEHOLDER AND PUBLIC ENGAGEMENT FINDINGS AND** 16 **RECOMMENDATION**

17 18 **FINDINGS**

19 The NVPO and the HHS, through the Office of External Affairs, have actively sought
20 stakeholder and public engagement in the development of important health policy initiatives. The
21 NVAC believes that vaccine safety should be incorporated into ongoing efforts to obtain
22 stakeholder and public input.

23 24 **OPPORTUNITIES FOR IMPROVEMENT**

25 The national vaccine safety system could benefit from the input of stakeholders and the general
26 public and through the enhanced assurance, accountability, and transparency that engaging these
27 groups provides.

28 Vaccine safety-focused engagement activities could benefit from expert advice representing all
29 pertinent scientific and technical disciplines.

30 31 **RECOMMENDATION**

32 **Stakeholder and Public Engagement Recommendation 8.1**

- 33 • The ASH should direct the NVPO to work with the NVAC and the ISTF, ISCG, or other
34 similar coordinating body Subcommittee on Stakeholder and Public Engagement (see
35 Coordination Recommendation 2.1) to develop and maintain an ongoing and meaningful
36 program of appropriate stakeholder engagement around vaccine safety. This program
37 should focus on ensuring that appropriate stakeholders and the public have the

1 opportunity to regularly provide feedback, through routine stakeholder and public
2 engagement processes, during planning and evaluation of major NVP activities, such as
3 the development of the vaccine safety research agenda (see Research Recommendation
4 4.1) and the NVAC reviews of NVP activities.

- 5 • This program also should publicize various means by which members of the public can
6 share concerns and recommendations about vaccine safety not related to a specific
7 occurrence of a specific AEFI, as would be reported through the VAERS.
- 8 • The ASH should direct the NVPO to continue working with the NVAC and NVP-
9 coordinated agencies to ensure that all vaccine safety-focused engagement activities
10 benefit regularly from expert advice representing all pertinent scientific and technical
11 disciplines.

13 **9. COST EVALUATION OF NVAC RECOMMENDATIONS FINDINGS AND** 14 **RECOMMENDATION**

15 **FINDINGS**

16
17 Vaccine safety activities and vaccine science require financial resources and staff support.
18 Substantial investments will be needed to improve the ability to engage in causality assessment
19 and to improve scientific understanding of mechanisms and individual risk. Staffing dedicated to
20 vaccine safety activities is not commensurate with the responsibilities and workload necessary to
21 fulfill their obligations. [118] Funding within the federal infrastructure for post-licensure vaccine
22 safety has not increased significantly since 2004. In general, funding for vaccine safety system
23 partners has remained flat over many years, while the number of vaccines and the number of
24 people vaccinated has increased substantially, though there have been some targeted increases,
25 such as the funding dedicated to development of the Mini-Sentinel program. Because many
26 activities that impact vaccine safety, either directly or indirectly occur without the specific
27 moniker of "vaccine safety," it is difficult to identify what proportion of agencies' and
28 Departments' funding is allocated to vaccine safety-related functions.

29
30 The NVAC previously highlighted the need for additional funding for vaccine safety research,
31 with focus on the CDC ISO [62], as well as general recommendations addressing the need for
32 additional funding for vaccine safety activities in 1996, [119] 1997, [120] 1998, [121] and 1999.
33 [60] The IOM also recommended funding increases as part of its review of the National Vaccine
34 Plan. [46] Additionally, the increased infrastructure capacity to address the H1N1 influenza
35 pandemic was developed using temporary funding allocations, and there was no clear plan to
36 maintain these improvements. In February, 2010, NVAC resolved that important improvements
37 made in public health infrastructure (including but not limited to vaccine safety) should be

1 maintained. [122] Specifically, NVAC recognized the need to continue funding infrastructure
2 improvements that were put in place to deal with the H1N1 influenza pandemic.

3
4 Efforts to study biological mechanisms of vaccine adverse effects are under-resourced and could
5 contribute more to this effort with additional funding and research staff. The need for research to
6 understand biological mechanisms and inform clinical guidance to medical providers is clear, but
7 additional resources may be needed to adequately support these efforts. As an example, CISA
8 faces challenges in recruiting sufficient subjects for some of their protocols due to limited
9 funding and the difficulties inherent in studying very rare outcomes.

10
11 The NVAC is mindful that, per its charge, its recommendations need not be constrained by the
12 budgets for the NVP-coordinated agencies and departments—either current funding levels or
13 projected ones. Nevertheless, in formulating these recommendations, the NVAC was aware of
14 potential budget implications, recognizing that they would have a long-term impact on the
15 vaccine safety system, and not be solely constrained by the current fiscal environment. The
16 NVAC recognizes that some recommendations can be accommodated readily within current
17 operating levels; that other recommendations will require modest increments beyond current
18 spending; and that still other recommendations will require commitment of substantial additional
19 funds. In general, the budget implications of each recommendation are self-evident from the
20 description and associated discussion.

21
22 The NVAC understands that vaccine safety is but one of many worthy claimants for funding as
23 the Executive Branch and the Congress weigh difficult choices throughout the annual budget
24 process. The NVAC also understands that the flexibility inherent in this process is considerable.
25 In particular, the discretionary budget for the Department of Health and Human Services (HHS)
26 for Fiscal Year 2010 (October 01, 2009 to September 30, 2010) was almost \$79 billion; and the
27 corresponding item in the President's Budget Request for Fiscal Year 2011 is over \$81 billion.
28 Reprioritization of a small portion of the annual HHS discretionary budget toward enhancing the
29 vaccine safety infrastructure over the next few years seems realistic.

30 **OPPORTUNITY FOR IMPROVEMENT**

31 NVAC recognizes that substantial activities to promote vaccine safety are currently underway.
32 To maintain and enhance the vaccine safety system, NVAC strongly recommends that, at a
33 minimum, budgets for these activities not be reduced. As the Federal budget permits, resources,
34 including fiscal support and staffing, provided to vaccine safety activities should be increased at
35 level commensurate with the needs and opportunities that exist.

36 37 **RECOMMENDATION**

38 **Cost Evaluation of Recommendations Recommendation 9.1**

1 The NVPO should coordinate, across the relevant departments and agencies, a cost evaluation of
2 the recommendations in this report approved by the NVAC. This evaluation should be presented
3 to the NVAC at a regularly scheduled NVAC meeting.

4

5

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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

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.

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.

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]

Reviews by the Institute of Medicine

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.

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

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

25 **VSWG MEETINGS**

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

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

35
36 Following the July 2009 kickoff meeting, the entire VSWG met regularly, holding 18
37 conference call meetings and two in-person meetings. In addition to regular working

1 meetings to discuss and deliberate topics under consideration, the working group also
2 received a series of presentations that provided information on a number of broad-scale
3 vaccine safety topics. The following presentations were given to the full VSWG:

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

14 **VSWG SUBGROUPS**

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

24 **Biomechanisms Subgroup**

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

31
32 This subgroup focused on basic and laboratory science, genomics, and resources for
33 addressing these topic areas. Specific topics examined included research on biological
34 mechanisms underlying vaccine adverse events, genetic risk factors and environmental
35 triggers, biomarkers, and prevention and treatment of vaccine adverse events. The role of
36 NIH in vaccine safety research also was discussed.

37

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

4 5 **Surveillance and Epidemiology Subgroup**

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

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

22
23 This subgroup focused on the pre- and post-licensure infrastructure for vaccine safety
24 research to identify gaps in the infrastructure and suggest opportunities for improvement.
25 Topics discussed by the subgroup included passive and active surveillance infrastructure,
26 pre-licensure and post-licensure research, epidemiological needs, novel information
27 technology, new statistical methods, and resources for these activities. Consideration was
28 given to new vaccine safety research platforms and infrastructure that do not yet exist or
29 have not traditionally been utilized in the area of vaccine safety.

30
31 The Surveillance and Epidemiology Subgroup held seven working meetings and eight
32 information gathering meetings. A summary of presentations given during these
33 information gathering meetings is provided in Appendix 7.

34 35 36 **Structure and Governance Subgroup**

37 The Structure and Governance Subgroup was chaired by William Raub. This subgroup
38 focused on topics related to the structure, oversight, resources, and processes for the

1 vaccine safety system. Topics discussed included transparency, mechanisms for engaging
2 and involving the public and stakeholders, objectivity, organization, funding, authority,
3 coordination, and responsibilities. The Structure and Governance Subgroup met for 11
4 working meetings.
5

6 **DEVELOPMENT OF RECOMMENDATIONS**

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

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

21 **STAKEHOLDER AND PUBLIC INPUT**

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

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

34 Information obtained from a public comment period and an open stakeholder's meeting on
35 June 13, 2011 varied in viewpoints. Some people thought that the draft White Paper was too
36 critical of the current vaccine safety system; some thought it was not critical enough. Others
37 thought accountability and assurance checks were not in place while others thought that they
38 were. A summary of public comments is included in Appendix 9.
39

1 Thirteen of the 16 NVAC members were able to attend the June 13, 2011 stakeholder
2 meeting to hear the views presented and engage stakeholders.

4 **NVAC DISCUSSION**

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

16 Following the June 2011 NVAC discussion, revision responsibility was transferred from the
17 VSWG to the NVAC in preparation for a September 2011 vote on the report. In service to the
18 NVAC, the NVPO contracted a medical writer with content knowledge of vaccines to
19 complete the revisions recommended from the June deliberations. The medical writer worked
20 in consultation with the NVAC Chair and the VSWG co-chairs via the NVPO to complete
21 the revised report.
22

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

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	Associate Professor, Research 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
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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 Baciuc, 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/NICHHD
 Rita Helfand, CDC/ NCPDCID
 Alice Kau, NIH/NICHHD
 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

1 **APPENDIX 6. VSWG BIOMECHANISMS SUBGROUP INFORMATION**
2 **GATHERING BRIEFINGS**

- 3
- 4 • Immune providing and vaccine related activities
- 5 ○ Chuck Hackett, NIH
- 6
- 7 • Coordination of NIH vaccine activities
- 8 ○ Barbara Mulach, Sarah Landry, Chuck Hackett, NIH
- 9
- 10 • Causality evaluations performed by the Institute of Medicine
- 11 ○ Kathleen Stratton, IOM
- 12
- 13 • National biospecimen repository
- 14 ○ Phil LaRussa, Columbia University
- 15 ○ Barbara Slade, CDC Immunization Safety Office
- 16
- 17 • Vaccine manufacturers role in identifying biomechanisms of adverse events
- 18 ○ Mark Feinberg, Merck & Co., Inc.
- 19 ○ Clem Lewin, Novartis Vaccines
- 20 ○ Lance Gordon, Immunobiologics Corp.
- 21
- 22 • Clinical Immunization Safety Assessment network
- 23 ○ Colin Marchant, Boston Medical Center and New England Medical Center
- 24 ○ Neal Halsey, Johns Hopkins University
- 25 ○ Kathryn Edwards, Vanderbilt University
- 26
- 27
- 28

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, 2010,⁵ 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

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25

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27

⁵ 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**

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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
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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.

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Function 5. Causality Assessment

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

Function 6. Injury Compensation

- Compensates individuals who experience vaccine adverse events.

Function 7. Practice

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

Function 8. Communications

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

Function 9. Engagement

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

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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.

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

In completing their charge, the National Vaccine Advisory Committee (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 developed by the VSWG for external, independent assurance of the vaccine safety system, with the second of these options having three potential configurations. The NVAC reviewed the three options at the June 2011 meeting and provided strong support for Option 1: NVAC should continue to be the advisory entity primarily responsible for evaluating the NVP programs. Below is a review of the two options not selected by the NVAC.

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.

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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.⁶⁷

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).

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

⁶ 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.

⁷ 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.**⁸

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:

8

- 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