

NATIONAL VACCINE ADVISORY COMMITTEE
VACCINE SAFETY WORKING GROUP
DRAFT WHITE PAPER

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May 10, 2011

Executive Summary

Charge to the Vaccine Safety Working Group

Summary of Recommendations

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1 The draft recommendations presented here were developed by the National Vaccine Advisory Committee
2 (NVAC) Vaccine Safety Working Group (VSWG). The draft being circulated is a synthesis of the
3 information that the VSWG has obtained since July 2009 for purposes of discussion and comment. No
4 decisions have been made by the VSWG regarding the final outcome of these recommendations or their
5 components. The VSWG will consider all comments made on this draft as they prepare the penultimate
6 draft of the report for discussion and deliberation by the NVAC.
7

8 These recommendations, when finalized by the VSWG, will be deliberated on by the NVAC. The NVAC
9 serves in an advisory role to the Assistant Secretary for Health (ASH), within the United States
10 Department of Health and Human Services (HHS). If approved by the NVAC, they will be formally
11 transmitted to the ASH for his consideration and possible implementation, which may include
12 communication with various components of the Department and other interested parties.
13

14 **1. Introduction**

15 **1.1. Relative benefits and risks of vaccines**

16 Vaccines are one of the most effective public health interventions¹. Vaccines have greatly reduced
17 morbidity and mortality from diseases that were formerly major killers in this country (Table 1). In recent
18 years, new vaccines against infectious agents such as rotavirus have been successful at reducing
19 circulating disease², and high rates of vaccine coverage³ continue to protect the vast majority of
20 individuals and communities from vaccine-preventable diseases in the United States (US). In addition to
21 reducing morbidity and mortality, routinely recommended pediatric vaccines have been estimated to save
22 9.9 billion dollars in direct costs and 43.3 billion dollars in societal costs over the lifetime of a single-year
23 birth cohort⁴, for the seven-vaccine series routinely recommended as of 2001. An updated evaluation of
24 the current vaccination schedule is currently underway.
25
26

27 However, no medical product can be proven to be 100% safe and vaccines can carry some risks. Possible
28 adverse reactions vary by vaccine and population vaccinated, and can include both minor but common
29 side effects such as fever to very rare but life-threatening illnesses such as anaphylaxis (approximately
30 0.5-1.5 cases / 1,000,000 vaccinations)⁵. To fully assess the risks and benefits of vaccines, the risk of
31 adverse events following immunization (AEFI) must be carefully monitored and understood. A robust,
32 responsive and scientifically innovative vaccine safety system must be in place to detect, evaluate and
33 respond to AEFI. This system should also foster opportunities to develop tools to prevent and treat
34 vaccine adverse reactions.
35

36 **1.2. Current vaccine coverage levels**

37 Vaccination coverage estimates for children aged 19-35 months were at or near record highs in 2009, with
38 the exception of *Haemophilus influenzae* type b (Hib) vaccine, which was in shortage during this period.
39 Overall, excluding vaccines recommended recently for universal use (i.e. hepatitis A, rotavirus and
40 influenza), coverage for the remaining vaccines was 70% (excluding Hib), increasing to 78% when
41 pneumococcal conjugate vaccination was excluded from the assessment. For individual pediatric
42 vaccines, up-to-date coverage levels range as low as 44% for rotavirus vaccine to a high of 93% for
43 poliovirus vaccine (Table 2)³. In general, vaccines more recently recommended for universal use in
44 children (hepatitis A, rotavirus) have lower coverage levels than vaccines for which universal use
45 recommendations have been in place for a longer period.
46
47

48 Similarly, for more recently recommended adolescent vaccines (e.g., human papillomavirus [HPV]
49 vaccine, meningococcal conjugate vaccine)⁶ and adult vaccines (e.g., herpes zoster vaccine)⁷, coverage
50 levels are lower (Table 3), though they have been steadily increasing in recent years. Some reports have
51

1 indicated that concerns over the safety of these newer vaccines may impact uptake^{8,9}, but it is not clearly
2 known what impact these concerns have on uptake of these more recently recommended vaccines.
3 Recent NVAC recommendations targeted to adolescent¹⁰ and adult immunization¹⁰ have called for
4 increasing awareness of vaccine safety issues in these populations.
5

6 **1.3. Successes of the current vaccine safety system in the US**

7

8 The vaccine safety system is a large, complex system comprised of many components spanning the entire
9 life-cycle from basic vaccine research, development, testing, licensure and widespread use (Figure 1). A
10 detailed analysis of the composition and functions of the US vaccine safety system is presented in Section
11 4.2. Through this complex framework, the vaccine safety system has proven to be a sound system for
12 identifying, evaluating and responding to vaccine safety issues that have emerged.
13

14 ***1.3.1. Vaccine safety system activities leading to changes in vaccine recommendations***

15

16 As stated above, there may be risks associated with any medical product, and there are several prominent
17 examples where information from the vaccine safety monitoring system in the U.S. has been used to
18 change vaccines and vaccination recommendations. A few examples of these are presented below.
19

20 Polio Vaccine

21 The oral polio vaccine (OPV) offered two main advantages over the inactivated polio vaccine (IPV): 1) a
22 more robust immune response including induction of better intestinal immunity and 2) the possibility of
23 secondary immunity in household contacts and unvaccinated child contacts exposed to attenuated polio
24 virus shed by children who received OPV. However, the use of OPV is also associated with
25 approximately one case of vaccine-associated paralytic polio (VAPP) per 750,000 first doses of OPV,
26 with an overall incidence of once case of VAPP per 2.4 million doses of OPV. As polio disease was
27 eradicated in the Western Hemisphere, the benefit/risk equation of polio vaccination changed, as more
28 cases of polio were caused by OPV than by circulating virus. Therefore, in 2000 the Centers for Disease
29 Control and Prevention (CDC) recommended replacing all use of OPV in the US with IPV¹¹.
30

31 Pertussis vaccine

32 Because rare but serious adverse events occurred following receipt of the diphtheria/tetanus/whole-cell
33 pertussis (DTP) vaccine, an acellular pertussis vaccine combined with diphtheria and tetanus toxoids was
34 developed and approved for use. This acellular pertussis-containing vaccine was found to be associated
35 with a lower level of both minor and major adverse events, compared to whole cell-pertussis-containing
36 vaccines¹². Acellular pertussis containing vaccines replaced whole cell pertussis vaccines for use in
37 young infants in the US in 1997¹³.
38

39 Rotavirus vaccine

40 The association of the first licensed rotavirus vaccine (tetraivalent rhesus-based rotavirus vaccine,
41 Rotashield®) and intussusception events was recognized and investigated using a combination of pre-
42 licensure trial data, Vaccine Adverse Event Reporting System (VAERS) reports, Vaccine Safety Datalink
43 (VSD) analysis and focused epidemiologic studies. This vaccine was withdrawn from use within 12
44 months of licensure. The experience demonstrated the difficulty of detecting low frequency events
45 (estimated excess risk of 1 intussusception event per 10,000 rotavirus vaccinations¹⁴) during pre-licensure
46 clinical trials, and led to changes in the subsequent phase III and IV vaccine trials to increase sample size
47 to better detect intussusception¹⁵. In Mexico and Australia, there has been some evidence of an increased
48 risk of intussusception following use of the more recently licensed rotavirus vaccines; while no increased
49 risk has been seen in the US, the pediatric population under surveillance is too small to rule out an
50 increased risk as small as that seen outside of the US¹⁴.
51

1 MMR-V vaccine

2 A modest increased risk of febrile seizures following a first dose of combined measles-mumps-rubella-
3 varicella (MMR-V) vaccine compared to individual measles-mumps-rubella (MMR) and varicella
4 vaccines administered separately was recognized in 2008 through post licensing surveillance¹⁶, with these
5 post-licensure studies determining the risk to be an additional 4.3 febrile seizures per 10,000 MMR-V
6 doses, compared to MMR and varicella vaccines administered separately¹⁶. For the first dose of vaccine
7 given at 12-47 months, CDC now recommends that although either can be used, “unless the parent or
8 caregiver expresses a preference for MMRV vaccine...MMR vaccine and varicella vaccine should be
9 administered as separate injections”¹⁷.

10 ***1.3.2. Vaccine safety system activities providing reassurances of safety***

11 In addition to identifying risks of vaccines, the current US vaccine safety system has been able to provide
12 reassurance in instances when the safety of new vaccines was questioned. There have been many signals
13 that, following investigation, were found not to be causally related to vaccination. Two examples are
14 presented below.

15 Meningococcal vaccine

16 Initial VAERS reports of Guillain-Barre Syndrome (GBS) following receipt of the quadrivalent
17 meningococcal conjugate vaccine (MCV4) shortly after its introduction in 2005 led to the development of
18 the ad hoc Meningococcal Vaccine Study, a distributed research network utilizing medical records from
19 multiple health insurance providers¹⁸. Analysis of health care utilization by over 12 million adolescents
20 and young adults identified 99 GBS cases, none of which occurred within 6 weeks of MCV4 vaccination,
21 indicating no evidence for a causal link between MCV4 receipt and GBS¹⁹.

22 2009 H1N1 influenza vaccine

23 Illustrating the flexibility of the current vaccine safety system to respond to the need for accurate and
24 timely safety data during the rapid deployment of monovalent vaccines against the pandemic 2009 H1N1
25 influenza virus, additional coordination of the various safety information collection systems was
26 enhanced with innovative approaches to monitoring of vaccine safety in this unusual context. The NVAC
27 reviewed preliminary federal plans for monitoring H1N1 vaccine safety and made a series of
28 recommendations to the HHS²⁰, all of which were carried out. These included development of a formal
29 written plan for safety monitoring, additional active surveillance activities and an independent risk
30 assessment committee, under the auspices of the NVAC, reporting to the ASH.

31 In preparation for the 2009 H1N1 influenza vaccination program, existing vaccine safety monitoring
32 infrastructure was enhanced and new capacity was created to increase the sensitivity of the system to
33 detect rare AEFI. Included in these enhancements were active surveillance for GBS through the CDC
34 Emerging Infections Program (EIP) and creation of the Post-Licensure Rapid Immunization Safety
35 Monitoring (PRISM) system. GBS surveillance through EIP was designed to address the potential for an
36 H1N1 influenza vaccine-GBS association, as hypothesized after the 1976-7 national influenza
37 immunization program^{21,22}. PRISM linked immunization registries in a number of states with the
38 databases of large health maintenance organizations to increase the size of the population under active
39 surveillance, creating an increased ability to monitor those in vulnerable groups²³.

40 Following the NVAC recommendation to establish a mechanism for independent assessment of the
41 vaccine safety data as it became available²⁰, the NVAC Vaccine Safety Risk Assessment Working Group
42 (VSRAWG) was created by the National Vaccine Program Office (NVPO). The VSRAWG reviewed the
43 analysis done by Federal agencies of all of the vaccine safety data (it did not do any analysis itself) and
44 provided HHS and the public regular and independent reports on the safety profile of the H1N1 vaccines.
45 Reports of the VSRAWG were presented to the NVAC in a public forum and posted on the NVAC

1 website²⁴. For analyses that have been completed, initial findings of possible weak signals since April
2 2010 were examined in more detail, and it was determined that there were not vaccine safety signals.
3 Some evaluations (e.g., the EIP GBS study) are still underway, and the VSRAWG has not yet issued its
4 final report.

6 **1.4. Challenges and opportunities to the current vaccine safety system**

8 Despite its success, the current US vaccine safety system faces a number of challenges and opportunities.
9 It is important to note that the terms “challenges” and “opportunities”, as used here, should not be viewed
10 with a negative connotation. Rather, they reflect the evolving nature of science and medicine, including
11 recent biomedical and technological advances that may present new opportunities to better understand the
12 epidemiology or underlying mechanisms of vaccine adverse reactions. Integrating these advances into the
13 existing vaccine safety system, as a type of continuous quality improvement (CQI), is a necessary
14 function of evolving technology and knowledge. CQI is a key component of many healthcare and public
15 health areas, and should be considered as a model for vaccine safety as well.

17 ***1.4.1. Changes in the perception of benefit and risk of vaccines***

18
19 Unlike most medical products, vaccines are given to healthy individuals to prevent disease. As a
20 consequence of the success of vaccines in decreasing or eliminating infectious diseases, the relative
21 weight given to the perceived risk of infectious diseases compared to the risk of vaccine adverse effects
22 has changed over time²⁵. With fewer cases of vaccine-preventable diseases occurring following
23 successful immunization programs, health care providers and the public have less familiarity with these
24 diseases. A case in point is measles, a once familiar and sometimes severe disease. Most parents of
25 young children and most health-care providers who completed medical training after the last severe
26 measles outbreaks in the United States in 1989-91 have little familiarity with measles, which may
27 decrease the urgency of parents to seek vaccination for their children. This change in the perception of the
28 vaccine benefit/risk equation leads to the need for clear education about the magnitude of the risks of
29 vaccines and diseases and better understanding of this balance on the part of parents and providers.

30
31 With many vaccines recommended for children, who are considered a vulnerable population, and the
32 existence of state-level vaccination mandates for school entry, parents may weigh this balance as a
33 comparison between errors of commission (vaccine adverse reaction that may occur during the process of
34 protecting the child from a vaccine-preventable disease) and errors of omission (vaccine preventable
35 disease occurring in the absence of vaccination). In recent years, public concerns about vaccine safety
36 appear to have increased. Vaccine safety concerns that have resulted in postponed vaccination or
37 vaccination refusal include too many vaccines given at one time and the presence of ingredients perceived
38 to be unsafe^{8,26}. Similarly, concerns over possible side effects from the 2009 H1N1 influenza vaccine
39 were a commonly cited reason for adults not getting themselves or their children vaccinated²⁷. In one
40 study in 2000, approximately one fifth of parents surveyed did not think that immunizations had been
41 proven safe before they were approved for use and that children received more immunizations than are
42 good for them²⁸.

43
44 The reasons for concern about vaccines are not completely understood but may be related to a wide
45 variety of factors, such as the changing perceptions of the benefit/risk balance of vaccination, general
46 distrust in government, decreased time for primary health care providers to educate patients, lack of a
47 clear understanding of background rates of adverse event outcomes and the potential for temporal
48 associations that may not be causal, and the ready availability of both accurate and inaccurate information
49 on the internet. While physicians are most commonly cited as the most trusted source of medical
50 information, information seeking on the internet is increasingly common^{29,30}, and can be associated with
51 decisions to delay vaccination due to vaccine safety or efficacy concerns³¹.

1
2 Anything that leads to vaccination delays or refusal to vaccinate can pose a significant risk not just to the
3 unvaccinated individual but also to public's health because of the potential to decrease coverage levels
4 below levels needed for community, or "herd", immunity. Community immunity resulting from high
5 levels of vaccine coverage is necessary to interrupt disease transmission and protect those in the
6 population who cannot be vaccinated or for whom vaccination did not induce protection. It is a key public
7 health strategy to reduce and control vaccine preventable diseases. This concept may be hard to explain,
8 as one cannot usually predict who will be exposed to these diseases or develop serious complications.
9 When disease levels in the population are low, it may be difficult to communicate why we need to
10 continuously maintain high immunization rates. Vaccine hesitancy, either through vaccination delays or
11 refusals, resulting in lowered community immunity may have played a role in recent outbreaks of measles
12 in California and Hib in Minnesota^{32,33}.

13
14 Vaccine safety concerns are not new; concerns about vaccine safety were expressed as far back as the
15 1700s, relating to the first vaccine against smallpox³⁴. Concern regarding the whole-cell pertussis vaccine
16 in the 1970's and 1980's led to reductions in immunization coverage and resurgence of the disease in
17 England and other countries³⁵. Following concerns about the hypothesized association between the MMR
18 vaccine and autism in the United Kingdom (UK), which were judged to be based on ultimately
19 unsubstantiated results³⁶⁻³⁹, MMR vaccination rates in the UK dropped steadily, from 92% in 1995-6 to a
20 low of approximately 80% in 2003-4, with related increases in measles cases⁴⁰.

21
22 Studies of children whose vaccinations are either delayed or not received at all consistently find vaccine
23 safety cited as a common reason^{31,41,42}. As stated above, coverage levels for individual immunizations in
24 the US are at or near all-time highs, with only approximately 0.6% of children 19-35 months receiving
25 none of the recommended vaccines³. However, the numbers of personal belief or philosophical
26 exemptions for vaccines are increasing in states that allow philosophical exemptions or other broad
27 exemptions to school immunization requirements⁴³.

28 29 ***1.4.2. Complexity of the vaccine safety enterprise***

30
31 Considering the large number of Federal and non-Federal entities involved in vaccine safety, described in
32 detail in Section 4.1.1 of this report, one of the key challenges is the coordination of activities across these
33 groups, as well as transparent reporting of activities related to vaccine safety. With a lack of
34 coordination, there may be both redundant efforts as well as missed opportunities to take advantage of
35 new information or lines of research. This was clearly described in the 1998 Final Report and
36 Recommendations of the Task Force on Safer Childhood Vaccines⁴⁴, which called for the Inter-Agency
37 Vaccine Group (IAVG) to have the ongoing responsibility of coordinating vaccine safety activities, with
38 guidance from an external independent advisory committee. More than a decade later, coordination of
39 vaccine-related activities was again highlighted during the revision of the National Vaccine Plan, in the
40 initial letter report from the Institute of Medicine (IOM) to NVPO⁴⁵ as well as the final IOM
41 recommendations on priorities in the National Vaccine Plan⁴⁶.

42 43 ***1.4.3. Advances in biomedical science***

44
45 The benefit/risk comparisons and system complexity described in this report speak to the need for
46 excellent vaccine safety science and a strong vaccine safety system that can take advantage of modern
47 biomedical and epidemiologic science. Such improvements may also increase public and provider
48 confidence in the safety of vaccines and the safety system.

49
50 Advances in biomedical science, both vaccine science and basic research, and epidemiologic methods
51 present great opportunities and challenges for vaccine safety science. Vaccine safety research often

1 involves studying rare outcomes, many of which also occur without vaccine exposure. This is best
2 illustrated with the use of pediatric vaccines. Early childhood is a time when children are at greatest risk
3 of several infectious diseases and consequently benefit most from vaccination. However, early childhood
4 is also a period of rapid development, and many health problems or other conditions may first become
5 manifest during this time of intensive vaccination, making it difficult to determine if an apparent
6 association with vaccination is real or coincidental. Thus, a fundamental scientific challenge is “causality
7 assessment”, which seeks to determine whether the vaccine is contributing to the disease burden, and if
8 so, to identify how much, among whom, and importantly, why. To ensure rigorous science, negative
9 studies also often have to be replicated using different methods or among different populations.

10
11 New technologies, such as high-throughput sequencing, provide an opportunity to improve vaccine
12 manufacturing and quality. Paradoxically, they can also raise concerns about vaccines. In early 2010,
13 sequencing for genetic material from adventitious viruses identified the presence of porcine circovirus
14 type 1 (PCV-1) DNA fragments in two live, attenuated rotavirus vaccines⁴⁷. While PCV-1 is not a human
15 pathogen, this finding triggered a rapid response to assess if there was any impact of this viral
16 contamination⁴⁸. Findings presented to the Vaccines and Related Biological Products Advisory
17 Committee (VRBPAC)⁴⁸ were reviewed and the Food and Drug Administration (FDA) determined that it
18 was appropriate for clinicians and health care professionals to resume the use of Rotarix and to continue
19 the use of RotaTeq⁴⁹.

20 21 ***1.4.4. Technological advances in epidemiologic methods and medical records***

22
23 The need for improved science was illustrated by the work of the Immunization Safety Review
24 Committee of the IOM (2001-2004). For 18 of the 30 (60%) recent vaccine safety questions (does vaccine
25 X cause adverse event Y), the committee found that “the evidence is inadequate to accept or reject a
26 causal relationship.”⁵⁰ The committee found that incomplete understanding of biological mechanisms for
27 AEFIs was a particular weakness^{51,52}. The recently approved Scientific Agenda developed by the CDC
28 Immunization Safety Office (ISO)⁵³ proposes to address many of the unanswered epidemiologic
29 questions, yet the scope is limited to activities within the ISO. It does not lay out a national agenda or
30 engage additional scientific resources. Through the FDA Sentinel Surveillance program⁵⁴, a larger
31 proportion of the US population will be under active surveillance for drug and vaccine-related adverse
32 events, though the implementation details for this program are still under development.

33
34 Increasing use of immunization information systems (IIS) and the development of new barcoding
35 technology (e.g., 2-D barcodes) to track administered vaccinations, coupled with a wider use of electronic
36 medical records offers a technological advance for epidemiologic research on AEFI. Because vaccine
37 studies can be subject to reporting and recall biases⁵⁵⁻⁵⁷, it is important to obtain accurate and complete
38 data on the timing of vaccinations and diagnoses of potential adverse events. Additionally, with a highly
39 mobile society and the lack of a consistent medical home for some individuals, these electronic data
40 systems present a reliable way to track immunizations, which can aid in both monitoring temporal
41 associations with adverse events, correct identification of vaccines and lots administered and helping to
42 prevent duplicate vaccinations due to a lack of vaccination records.

43 44 ***1.4.5. Era of personalized medicine and more empowered patients***

45
46 New advances in immunology, genetics, molecular biology, and bioinformatics hold great potential for
47 better understanding human responses to vaccines broadly, within subpopulations, and in individuals.
48 Advances in personalized medicine for medical products and patient safety are underway: there are tests
49 available to detect particular genetic polymorphisms known to be related to drug metabolism, adverse
50 responses, or interactions between drugs. These have already resulted in regulatory changes for labeling

1 and prescribing⁵⁸. Increased understanding of individual risk factors for adverse reactions may lead to
2 more individualized vaccination strategies.

3
4 Additionally, with increased access to health and medical information from a variety of sources, including
5 the Internet, patients may come to physicians with more questions about their medical care and may be
6 more willing to question their provider's decisions. This concept of the "empowered patient" can lead to
7 a successful partnership with physicians⁵⁹, provided that the information given to the patient is accurate
8 and meets the needs of patients.

9 10 **2. Organization of the Vaccine Safety Working Group**

11 12 **2.1. Current charge to the Vaccine Safety Working Group**

13
14 To obtain expert advice on bringing the vaccine safety system into the 21st century, the ASH asked the
15 NVAC "to review the current federal vaccine safety system and develop a White Paper describing the
16 infrastructure needs for a federal vaccine safety system to fully characterize the safety profile of vaccines
17 in a timely manner, reduce adverse events whenever possible, and maintain and improve public
18 confidence in vaccine safety". The NVAC VSWG was tasked to address this charge in July 2009.

19 20 **2.2. Vaccine Safety Working Group membership**

21
22 The VSWG was comprised of 18 members, 9 of whom were current or past NVAC members. The
23 VSWG has a broad range of expertise including pediatric and adult infectious diseases, genomics,
24 immunology, epidemiology, public health, maternal and child health, pharmacoepidemiology, and
25 biostatistics. Additionally, current or past consumer representatives from each of four federal advisory
26 committees with a role in vaccine safety (NVAC, Advisory Committee on Immunization Practices
27 [ACIP], VRBPAC, and Advisory Commission on Childhood Vaccines [ACCV]) are members.

28
29 Additionally, 10 Federal ex officio members provided information about aspects of the existing safety
30 system. The Federal ex officio members did not participate in development of the Working Group's
31 conclusions and recommendations, and the conclusions and recommendations in this report do not reflect
32 their or their agencies' points of view.

33
34 The VSWG roster is presented in Appendix 2 and the Federal ex officio members are listed in Appendix
35 3.

36 37 **3. VSWG Methods for Addressing its Charge in Light of Prior Reviews**

38 39 **3.1. Prior reviews of the vaccine safety system**

40 41 **3.1.1. HHS Activities and Related Reviews by NVAC**

42
43 Previously, there have been several federal efforts to enhance the nation's vaccine safety system. The
44 broadest reaching of these reviews was the 1998 Final Report of the Task Force on Safer Childhood
45 Vaccines⁴⁴. This Task Force, convened by the National Institutes of Health (NIH), made four
46 recommendations, calling for (1) greater assessment of concerns about vaccine safety, (2) strengthening
47 research into developing safer vaccines, (3) increasing surveillance related to vaccine safety and efficacy,
48 and (4) coordinated review and assurance related to Federal vaccine safety efforts. In 1999, the NVAC
49 reviewed and strongly endorsed the Vaccine Safety Action Plan, the formal implementation plan for the
50 1998 Task Force report⁶⁰. In the intervening years, there has been at least partial implementation of these
51 recommendations, though the lack of a sufficient budget process hampered full implementation of this

1 Action Plan⁶¹. Additionally, the extent to which vaccine safety assurance functions coordinated and/or
2 conducted through the IAVG have been carried out is not transparent or readily communicated to the
3 public. In 2008, the Immunization Safety Task Force (ISTF) highlighted a series of opportunities for
4 enhancements in the vaccine safety system⁶¹.

5 6 **3.1.2. Reviews by IOM**

7
8 The recently released IOM report “Priorities for the National Vaccine Plan” identified four high priority
9 vaccine safety actions that were largely consistent with earlier recommendations⁴⁶. These included (1)
10 establishment of a process for identification of potential vaccine safety hypotheses for further study from
11 annual reviews of data from VAERS, VSD, CISA, the VICP and from information from outside the US;
12 (2) developing a framework for prioritizing a national research agenda; (3) creation of a permanent
13 vaccine safety subcommittee in NVAC for ongoing review and guidance on vaccine safety issues; and (4)
14 expansion and enhancements of vaccine safety science research through CDC ISO, FDA and NIH.

15 16 **3.1.3. Vaccine Safety Working Group Review of CDC ISO Scientific Agenda**

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

22
23 The NVAC VSWG review⁶² of the CDC ISO research agenda⁵³ provided the opportunity for a
24 coordinated review of vaccine safety research activities, though it was limited to activities occurring
25 through the ISO. Areas of broader applicability than just the ISO research agenda were identified and
26 retained as key elements of the present review. The VSWG, with the assistance of NVPO and the
27 Keystone Center, conducted several sessions to engage the public and stakeholders as part of this charge.
28 The VSWG’s recommendations were approved by the full NVAC on June 9, 2009 and transmitted to the
29 ASH and the CDC. Of note, in that report, the VSWG stated that there was a need for a similar safety
30 agenda to be developed and coordinated across the entire vaccine safety enterprise. The report noted that
31 “there is a strong need for a federal vaccine safety research agenda that encompasses research undertaken
32 by non-ISO CDC offices, FDA [Food and Drug Administration], and National Institutes of Health (NIH)
33 and requires increased collaboration and coordination between all federal agencies with a stake in vaccine
34 safety”

35 36 **3.2. VSWG Meetings**

37
38 The VSWG held a kick-off meeting for its current charge (Charge 2) on July 15-16, 2009, at which 26
39 invited participants with a broad range of expertise (Appendix 4) shared their views on:

- 40 1. Principles and policy alternatives for a robust vaccine safety system
- 41 2. Identifying innovative ways of overcoming gaps in vaccine safety science infrastructure
- 42 3. The ideal system to meet the needs of the public, public health, and healthcare professionals for
43 confidence in vaccine safety
- 44 4. Lessons from other safety arenas
- 45 5. Enhancing the adoption and implementation of the forthcoming white paper

46
47 Following the July 2009 kick-off meeting, the entire VSWG met regularly, with 18 conference call
48 meetings and two in-person meetings. In addition to regular working meetings to discuss and deliberate
49 topics under consideration, the working group also received a series of presentations that provided
50 information on a number of broad-scale vaccine safety topics.

51

1 These presentations to the full VSWG included: international vaccine safety systems (Gary Freed,
2 University of Michigan; Hector Izurieta, FDA; and Steve Black, Cincinnati Children’s Hospital), vaccine
3 safety efforts at the World Health Organization (Patrick Zuber, World Health Organization [WHO]),
4 PRISM (Richard Platt, Harvard Pilgrim Health Care and Harvard Medical School), public attitudes
5 toward vaccines (Kathy Talkington, Association of State and Territorial Health Officials [ASTHO]), and
6 the state of the science for assessing public perceptions of vaccine safety (Allison Kennedy, CDC).
7

8 **3.3. VSWG Subgroups**

9

10 To accomplish its task of reviewing the current system and identifying an improved system for the 21st
11 century, the VSWG created three content-oriented subgroups for targeted information gathering and
12 process development. The subgroups focused on 1) biological mechanisms of adverse events, 2)
13 epidemiology and surveillance of adverse events, and 3) structure and governance of the vaccine safety
14 system. Each subgroup elected a Chair, and subgroup membership was based on VSWG member
15 expertise and preference. Summaries of subgroup meetings and information gathering are presented
16 below.
17

18 **3.3.1. *Biologic basis of vaccine adverse events (Biomechanisms) subgroup***

19

20 The Biomechanisms subgroup was chaired by L.J. Tan. The four main topic areas addressed when
21 examining biological mechanisms of adverse events are: (1) hypothesis generation, (2) causality
22 assessment, and (3) identification of persons who may be at increased risk for adverse reactions and (4)
23 appropriate management of specific adverse events. This group focused on basic and laboratory science,
24 genomics, and resources for addressing these topic areas. Specific topics examined included research on
25 biological mechanisms underlying vaccine adverse events, genetic risk factors and environmental
26 triggers, biomarkers, and prevention and treatment of vaccine adverse events. The role of NIH in vaccine
27 safety research was also discussed.
28

29 The biomechanisms subgroup held four working meetings and six information gathering meetings. A
30 summary of the presentations received during the information gathering meetings is in Appendix 5.
31

32 **3.3.2. *Epidemiology to detect, quantify, and examine causality of vaccine adverse events*** 33 ***(Surveillance and epidemiology) subgroup***

34

35 The Surveillance and Epidemiology subgroup was chaired by Lance Gordon. The five main topic areas
36 addressed when examining surveillance data and epidemiologic studies on adverse events are (1)
37 identifying adverse events that occur with a temporal relationship to immunization for additional follow-
38 up (“signal detection”, “hypothesis generation”), (2) examining the detailed epidemiology of these AEFI
39 to determine the strength of association, if any, with immunization (“hypothesis testing”), (3) monitoring
40 the occurrence of specific known or hypothesized vaccine adverse reactions to identify changes in
41 patterns across time or populations, (4) providing feedback and guidance to other components of the
42 vaccine safety research system, such as laboratory or clinical investigators, and (5) properly and
43 adequately reporting results of epidemiologic and surveillance data to policy makers, scientific
44 communities and the public.
45

46 This group focused on the pre- and post-licensure infrastructure for vaccine safety research, identifying
47 gaps, and suggesting enhancements. Topics discussed included passive and active surveillance
48 infrastructure, pre-licensure and post-licensure research, epidemiologic needs, novel information
49 technology, new statistical methods, and resources for these activities. Consideration was given to new
50 platforms and infrastructure to conduct vaccine safety research that do not yet exist or have not
51 traditionally been utilized in the area of vaccine safety.

1
2 The surveillance and epidemiology subgroup held seven working meetings and eight information
3 gathering meetings. A summary of the presentations received during the information gathering meetings
4 is in Appendix 6.
5

6 **3.3.3. Structure and governance subgroup.** 7

8 The Structure and Governance subgroup was chaired by William Raub. This group focused on topics
9 related to the structure, oversight, resources, and processes for the vaccine safety enterprise. Topics
10 discussed included transparency, mechanisms for engaging and involving the public and stakeholders,
11 objectivity, organization, funding, authority, coordination, and responsibilities. The structure and
12 governance subgroup met for 11 working meetings.
13

14 **3.4. Development of recommendations** 15

16 A list of major themes developed from the July 15-16, 2009 meeting served as a starting place for the
17 VSWG’s deliberations. The list of potential items to be addressed ranged from very specific to very
18 general, with some examples repeated across general topic areas. Further discussion and refinement of
19 the initial list by the VSWG Structure and Governance subgroup led to a more condensed list that served
20 as the basis for crafting directed and actionable recommendations for making improvements to the
21 vaccine safety system.
22

23 Additionally, recommendations were initially developed by each of the content-oriented subgroups. Once
24 each subgroup’s recommendations were initially refined, they were collated with those of the other
25 subgroups and presented to the full VSWG for consideration. Further discussion among the working
26 group was used to clarify the scope and intent of the recommendations.
27

28 **3.5. Stakeholder and public input** 29

30 Concurrent with information gathering, the VSWG (with the help of the Keystone Center, an external
31 consultant) participated in a stakeholder engagement process. Following a robust public and stakeholder
32 engagement process during Charge 1, the VSWG again desired to hear from a variety of stakeholders.
33 The Stakeholder Engagement Subgroup of the VSWG assisted in the planning and execution of the
34 Keystone-led engagement activities. In addition to the Kick off meeting, the VSWG participated in a
35 “Writing Group” meeting that included a broad range of representation from a number of pertinent
36 sectors. This group worked with the VSWG to refine a set of “Evaluation Criteria” (Appendix 7) that
37 would be used to assess how well different safety system configurations would fit the proposed functions
38 and attributes of an ideal vaccine safety system. The Writing Group also provided input on opportunities
39 for improvement in the vaccine safety system, and strengths and weaknesses of various enhancements or
40 alterations to the structure and governance of the vaccine safety system. The group agreed on a set of
41 functions (Appendix 8) and essential attributes (Appendix 9) for the ideal vaccine safety system. A
42 memorandum listing the meeting attendees and summarizing the outcomes of the meeting is presented in
43 Appendix 10.
44

45 Information obtained from the public comment period and a stakeholder’s meeting on June 13, 2011 will
46 be included in the final report.

1 **4. Findings and Results**

2
3 **4.1. General background**

4
5 **4.1.1. *The National Childhood Vaccine Injury Act***

6
7 The foundation of the modern US vaccine safety system infrastructure is the National Childhood Vaccine
8 Injury Act of 1986 (NCVIA)⁶³. The NCVIA authorized the creation of the National Vaccine Injury
9 Compensation Program (VICP) and VAERS and authorized the establishment of the National Vaccine
10 Program and the NVAC. Additionally, the NCVIA mandated IOM-led studies of the relationship
11 between vaccination and adverse events as well as requiring the development of “vaccine information
12 materials” by CDC, leading to the development and distribution of Vaccine Information Statements.

13
14 The ASH was appointed Director of the National Vaccine Program, and the NVPO was created to
15 coordinate and integrate the efforts of the National Vaccine Program as the agent of the ASH. The
16 current vaccine safety system, as it has evolved since the passage of the NCVIA, encompasses a complex
17 mix involving multiple Federal departments and agencies as well as non-federal partners such as
18 academia, industry, immunization providers and their professional organizations, state and local health
19 departments, and health care payers.

20
21 **4.1.2. *General system framework***

22
23 The key Federal departments and agencies with a role in vaccine safety activities include HHS,
24 encompassing the CDC, the FDA, the Health Resources and Services Administration (HRSA), the NIH,
25 the Centers for Medicare and Medicaid Services (CMS), the Indian Health Service (IHS) and the NVPO;
26 the Department of Defense (DOD) and Department of Veterans Affairs (DVA). The relationships
27 between these Federal components of the vaccine safety system are illustrated in Figure 1.

28
29 Vaccine safety activities occur both pre-licensure and post-licensure. Pre-licensure functions include
30 vaccine discovery, laboratory, and animal research and human clinical trials to determine whether or not
31 the vaccine has sufficient safety and efficacy to merit licensure. Because it is not feasible to adequately
32 power pre-licensure clinical trials for the identification of rare adverse events (for example, GBS
33 incidence of 1-2/100,000), additional evaluation is required after vaccine licensure and widespread use.
34 Post-licensure functions include evaluation of post-licensure vaccine efficacy and safety studies in the
35 larger population when a vaccine is in wide-spread use, determining if there is a causal relationship
36 between vaccination and adverse events, investigating the biologic basis of vaccine adverse reactions, and
37 providing compensation for vaccine-related injuries.

38
39 **4.2. Review of the vaccine safety system**

40
41 **4.2.1. *Coordination of the system***

42
43 To facilitate addressing concerns about vaccine safety, the Federal ISTF was formed at the request of the
44 Secretary of HHS in April 2008. The ISTF contains representatives from the aforementioned agencies
45 and departments. The extent of involvement of this high level group in coordination, funding, and setting
46 of research agendas was not clear to the VSWG in its review. However, experience with vaccine safety
47 surveillance for the monovalent H1N1 influenza suggests that the ISTF’s potential for effective
48 collaboration, planning and investigation is promising. A detailed review by the ISTF of the components
49 of the current federal vaccine safety system may be found at
50 <http://www.hhs.gov/nvpo/nvac/subgroups/vaccine-safety-review.pdf>. However, some agencies with roles
51 in immunization delivery and vaccine safety, particularly as became apparent during enhanced vaccine

1 safety monitoring activities of the H1N1 influenza vaccination campaign (e.g., IHS) may not be fully
2 represented through the National Vaccine Program or on the Immunization Safety Task Force. The ISTF
3 does not meet regularly or issue routine reports, and has never provided any direct reports to the NVAC.
4

5 The ASH, in his role as Director of the National Vaccine Program, is charged under the NCVIA to
6 “coordinate and provide direction for activities carried out in or through the National Institutes of Health,
7 the Office of Biologics Research and Review [now Center for Biologics Evaluation and Review (CBER)]
8 of the Food and Drug Administration, the Department of Defense, and the Agency for International
9 Development to develop the techniques needed to produce safe and effective vaccines”; and “coordinate
10 and provide direction for safety and efficacy testing of vaccines carried out in or through the National
11 Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the
12 Food and Drug Administration, the Department of Defense, and the Agency for International
13 Development.”⁶³ The operational arm of the National Vaccine Program, responsible for carrying out
14 these activities, is the NVPO, which is in the Office of the ASH, HHS.
15

16 **4.2.2. Basic biomedical research**

17
18 While knowledge of immune system function has increased dramatically in recent years, much more
19 basic research needs to be done on the actual biological mechanisms that drive a successful immune
20 response to vaccine as well as the mechanisms underlying vaccine adverse reactions, how quality of the
21 antigen affects the response, how adjuvants enhance the response to vaccines and how their use may
22 affect the vaccine safety profile. The IOM Immunization Safety Review Committee has cited a lack of
23 information on the biology underlying vaccine adverse reactions^{51,52}. One potential pathway for basic
24 biomedical research related to vaccine adverse reactions is to study triggers of more common, less severe
25 reactions (e.g., fever, allergy) to identify common mechanisms that may help focus research into rarer
26 reactions while also helping to identify means to ameliorate these reactions. In addition, with the
27 increasing availability of new research technologies, an achievable goal may be to define mechanisms
28 that tip the balance toward a detrimental adverse response to immunization; in particular, why certain
29 individuals may react adversely while others respond positively to a given vaccine.
30

31 Basic research on the immunologic and physiologic effects of vaccines and vaccine ingredients is
32 typically funded by NIH and vaccine manufacturers, and conducted by academia and industry. Much of
33 the work of the NIH is organized on a disease-specific basis; applicable funding has been dedicated to the
34 Novel Adjuvant Discovery and Development program, through targeted contracts, such as the Human
35 Immune Phenotyping program, and a recent vaccine safety program announcement⁶⁴.
36

37 Basic research, including immunology research, which may not be vaccine-focused, is critical to advance
38 knowledge. By considering the biologic role of the antigenic and the non-antigenic components of a
39 vaccine, one can generate useful hypotheses about the cause of an adverse reaction to the vaccine that can
40 be tested in well-designed non-clinical, clinical and epidemiological studies. The NVAC has previously
41 recommended that “ISO should evaluate cumulative levels of non-antigen component exposure possible
42 through the schedule of recommended vaccinations.... a carefully designed screening process that places
43 ingredients into groups that are of: (1) minimal concern; (2) potential for concern and deserving of
44 research; (3) in need of further risk analysis and consideration for risk management”⁶². While the NVAC
45 has no specific concerns regarding non-antigen components of vaccines, this approach to screening is
46 more transparent and allows targeting of research efforts to specific components based on scientific
47 assessment.
48

49 Basic research can also be vaccine-focused/targeted. An example of this type of targeted research
50 involves the concerns raised in 1999 regarding infant exposure to ethyl mercury as a result of thimerosal
51 used as a preservative in some vaccines, with subsequent epidemiological studies including outcomes

1 associated with (methyl) mercury^{65,66}. However, a lack of basic research on the comparative biological
2 effects of and clearance of ethyl mercury and methyl mercury impacted the public health response to
3 concerns regarding the safety of thimerosal in 1999. The identified need for these targeted biomedical
4 studies led to research done since 1999 on the metabolism of ethyl mercury⁶⁷⁻⁶⁹. CDC studies examining
5 thimerosal-containing vaccines and neurodevelopmental outcomes, including autism, have not found
6 evidence to support an association between thimerosal-containing vaccines and autism.^{65,66} These types
7 of feedback mechanisms between basic biomedical research and epidemiologic research are critical to
8 identifying priority study areas in both fields.

9 10 **4.2.3. Vaccine development/pre-licensure activities/clinical trials**

11
12 The NIH plays a role in vaccine discovery and in early phase clinical evaluation through the Vaccine and
13 Treatment Evaluation Units (VTEUs). Before biologics such as vaccines are licensed for marketing, they
14 must undergo extensive clinical trials for efficacy and safety. The FDA's CBER is responsible for
15 working with industry from preliminary application through clinical trials leading to licensure. A key
16 area of vaccine development and pre-licensure activities is animal and toxicology studies conducted prior
17 to beginning clinical trials. One example of these extensive tests were the studies on Madin-Darby
18 Canine Kidney (MDCK) cells proposed for use in cell-culture influenza vaccine development⁷⁰.

19
20 Randomized, double-blind, placebo-controlled trials are the gold standard for research, as they attempt to
21 control for differences in characteristics across populations and reduce biases. Pre-licensure trials are
22 designed to estimate the efficacy of the vaccine itself and in combination with other vaccines and are
23 often powered to identify common AEFI; however the samples sizes of the trials are relatively small
24 when compared to the larger population for which the use of the vaccine is intended. This may preclude
25 identification of very rare AEFI⁷¹. Even with tens of thousands of clinical trial participants, the power to
26 see rare AEFI is low. The combined clinical trials for the quadrivalent HPV vaccine contained
27 approximately 20,000 total participants (approximately 11,000 in the vaccine group and 9,000 in the
28 placebo group, though the target population for this vaccine, 9-12 year olds, made up only a subset of this
29 larger sample). With this sample size, the power to observe an increased risk of vaccine adverse reactions
30 from 1/1000 to 2/1000 vaccinees is only 43%. These limitations can be overcome with enhanced
31 monitoring after the vaccine is licensed, where a larger population will be provided the vaccine; however,
32 this does eliminate the possibility to control through randomization. Even with a reduced capacity to
33 identify all vaccine-associated adverse reactions, clinical trial data are useful to indicate more common
34 AEFI as well as potential vaccine adverse event signals to monitor post-licensure.

35
36 Additionally, follow-up monitoring for safety related events during pre-licensure clinical trials is time
37 limited. Delayed onset adverse events are unlikely to be detected in initial clinical trials. One
38 immunogenicity and safety study of the bivalent HPV vaccine reported the results of active monitoring of
39 participants up to 12 months from the start of the study⁷², with additional clinical trial follow-up to
40 observe long-term safety, with long-term safety assessed after multiple years⁷³. Furthermore, clinical
41 trials are generally conducted in healthy individuals and are not representative of the full populations that
42 will ultimately be vaccinated (which may include groups such as pregnant women and individuals with
43 chronic diseases). However, those excluded from clinical trials may have unique immunological
44 responses that increase or decrease risk for vaccine adverse reactions. Some of these clinical trial
45 exclusions are related to instances when the vaccine will not be used in specific populations (e.g.,
46 contraindication for use of live viral vaccines in pregnant women).

47 48 **4.2.4. Vaccine licensure**

49
50 The vaccine licensing process includes an extensive evaluation of vaccine safety data; however, licensing
51 activities were outside of the scope of this working group, and no targeted information gathering on this

1 process was performed. The VSWG will not be making any recommendations specifically addressing the
2 licensing process, focusing rather on the vaccine safety activities occurring before and after licensure.

3 4 **4.2.5. Post-licensure activities**

5
6 Studying the epidemiology of AEFI is a difficult and complex task that involves addressing a number of
7 issues including: 1) clearly defining and characterizing AEFI, 2) determining the expected background
8 rates of health events under study to compare with observed rates following vaccination, 3) developing
9 methods to study very rare outcomes and the associated need for very large study sample sizes, 4)
10 distinguishing between AEFI that are caused by the vaccination and those that occur coincidentally or are
11 the result of multiple cofactors or predispositions, and 5) determining whether subgroups of people may
12 exist who are at increased risk for AEFI due, for example, to underlying disease or genetic predisposition.

13 14 4.2.5.1. Surveillance/signal detection/hypothesis generation

15
16 While the terms are sometimes used interchangeably, surveillance and epidemiologic studies are not
17 identical. Surveillance is defined by the CDC as “the ongoing systematic collection, analysis and
18 interpretation of health data, essential to the planning, implementation, and evaluation of public health
19 practice, closely integrated with the dissemination of these data to those who need to know. The final link
20 in the surveillance chain is the application of these data to prevention and control. A surveillance system
21 includes a functional capacity for data collection, analysis, and dissemination linked to public health
22 programs.”⁷⁴. Included in the discussion of surveillance is the notation that “surveillance is the essential
23 feature of epidemiologic practice.”⁷⁴. Surveillance systems are the primary source for the outcome data
24 used in the post-licensure vaccine safety research system. However, their usefulness is defined by the
25 quality of the data collected and the ability to use these data to perform appropriate analyses.
26 Surveillance data alone cannot usually prove causation, but suggests hypotheses for further study by
27 laboratory, clinical, and/or epidemiologic methods.

28
29 Epidemiology is defined as “the study of the distribution and determinants of health-related states or
30 events in specified populations, and the application of this study to control of health problems”⁷⁴.
31 Epidemiologic studies start with hypotheses suggested by surveillance data as well as other data streams
32 such as 1) underlying biological mechanisms of disease and health, 2) the distribution of potential
33 exposures, not limited just to the vaccines received, but exposure to other infectious diseases and
34 environmental and genetic factors, and 3) the population-level background occurrence of outcomes that
35 can also be AEFI, including the examination of determinants of these outcomes absent vaccination.

36
37 This section focuses on the surveillance systems that suggest hypotheses that can be tested by
38 epidemiologic analyses.

39 40 Vaccine Adverse Events Reporting System (VAERS)

41
42 VAERS is a voluntary, post-licensure, national passive reporting surveillance system jointly managed by
43 the CDC and FDA, and serves as an early-warning system to detect adverse events that may be related to
44 vaccines. As a passive system, all reports are made voluntarily and without active, targeted outreach by
45 surveillance system operators, and VAERS reporting can be subject to limitations and biases (described
46 below). The main utility of VAERS is the identification of rare and severe adverse events following
47 immunization, as evidenced by the rapid identification of increased intussusception following
48 administration of the first generation rotavirus vaccine⁷⁵. VAERS receives reports of possible vaccine
49 adverse events from a wide variety of sources including parents, providers, manufacturers, pharmacists
50 and the military. Health care providers and manufacturers are required to report two types of adverse
51 events within a seven-day period – those that the vaccine manufacturer has identified as contraindicating

1 reactions to the vaccine that are specified within the manufacturer's package insert and any adverse
2 events present on the Vaccine Injury Table and they are encouraged to report any other adverse event they
3 believe to be clinically important. From 2006-2010, approximately 61% of all domestic reports came
4 from either health care providers or vaccine manufacturers, and approximately 10% came from vaccine
5 recipients or their parent/guardian. In addition, approximately 5% came from State Health Coordinators
6 (CDC, personal communication, 2010).

7
8 The strength of VAERS is its ability to detect potential signals for follow-up; this was demonstrated
9 through the identification of an increase in cases of intussusception following receipt of the first licensed
10 rotavirus vaccine. The identification of this signal led to further vaccine safety studies, ultimately
11 resulting in the removal of the vaccine from the market and the development of safer rotavirus vaccines⁷⁶.

12
13 While VAERS serves as a national spontaneous reporting system that enables the early detection of
14 signals (potential vaccine safety concerns) and is particularly suited to detect potential rare adverse events
15 that can be more rigorously investigated, there are several key limitations of this system^{77,78}. First, there
16 are not precise denominator data (number of vaccine doses administered/persons vaccinated) to put the
17 number of 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 individuals, vaccine-
19 associated rates and background rates for comparison cannot be calculated. Second, reporting to VAERS
20 is not always consistent or complete, and underreporting is often cited as a significant problem for some
21 AEFI^{79,80}. Reports that are made to VAERS may not always be complete, and even a fully completed
22 VAERS report form may lack the full range of information needed for epidemiologic analysis.
23 Additionally, increased reporting related to one particular vaccine or adverse event can be stimulated by
24 increased awareness or media reporting of that event⁸¹. Newer vaccines often have higher VAERS
25 reporting rates than older vaccines due to heightened awareness of these vaccines and concern over their
26 novelty⁷⁸. Because of these limitations, VAERS reports alone cannot be used to make population-level
27 causality assessments. If it appears as though a vaccine might be causing a health problem, CDC and
28 FDA will do additional studies or investigations.

29
30 Little is known about awareness of VAERS, including the primary function and limitations of the system,
31 by the public or health care providers. While information regarding VAERS is on the Vaccine
32 Information Statements provided with every vaccination, immunizing physicians and nurses may spend
33 little time discussing specific elements of vaccine safety, the vaccine safety system, or VAERS with their
34 patients or their parents^{82,83}. This lack of communication about the uses and limitations of VAERS may
35 influence knowledge of VAERS, leading to inaccurate perceptions, particularly around the inability to
36 perform causality studies within the system, the inclusion of every adverse event that occurs or the
37 perception that VAERS reports trigger public health or medical response to individual adverse events.

38 39 4.2.5.2. Signal validation and hypothesis testing

40
41 Once a signal is identified and validated, it is tested using methods and systems described below.

42 43 Background rates of adverse health events

44
45 A specific adverse health event may occur in the absence of vaccination; the rate of such events is called
46 the background or expected rate. To establish whether an adverse event is associated with a vaccine on a
47 population level, it is critical to be able to compare the rates of events with and without vaccines.
48 Background rates may vary by age group, population, geographic location, seasonality, and a number of
49 other important factors that would affect the level of increased risk among vaccinated individuals. To
50 optimize the value of background rates, they should be calculated in populations that are primarily
51 monitored for AEFI, insofar as comparable populations exist.

1
2 While some AEFI are more common than others, more severe outcomes of interest often occur very
3 rarely. The annual incidence of GBS is estimated to be approximately 1-2/100,000^{84,85}. Following the
4 1976-1977 A/Influenza swine influenza vaccination campaign, an increased risk of GBS was identified,
5 leading to hypothesized associations with other influenza vaccines and GBS^{21,22}.

6
7 An outcome such as GBS offers another level of complexity, as this condition has been found to develop
8 following infection with microorganisms such as *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr
9 Virus, *Mycoplasma pneumoniae* and Hib. Cases of GBS arising from different antecedent infections that
10 are temporally related to receipt of a vaccine (e.g., influenza infection that occurs during the influenza
11 season when a vaccination campaign is occurring) may be difficult to distinguish from cases of GBS
12 arising from receipt of the vaccine. Issues of recall bias may affect the ability to make this distinction, as
13 a mild respiratory or gastrointestinal illness may be less memorable than vaccination.

14 Brighton Collaboration

15
16
17 A limitation of examining AEFI is the potential for inconsistent definitions of cases or outcomes of
18 interest which can affect the ability to look at results across studies. There is a need for standardized case
19 definitions of AEFI for epidemiologic research. Recognizing this need, the Brighton Collaboration, an
20 international group of volunteers co-sponsored by CDC and WHO, has multiple working groups focusing
21 on case definitions for a variety of AEFI. Case definitions take a few years to be developed and agreed
22 upon, with some evaluation and validity testing following. With widespread development and use of
23 these case definitions, there can be improved comparability across studies.

24
25 The Brighton Collaboration has developed and published 24 AEFI case definitions⁸⁶. While these case
26 definitions can be complex, initial reviews of their applicability have been favorable^{87,88}, and development
27 of checklists and forms that can be validated for use in identifying and reporting AEFI has begun⁸⁷.

28 Linking Hypothesis Generation with Hypothesis Testing

29
30
31 When performing hypothesis testing, it is important to clearly define the issue under consideration, using
32 the best available evidence and experience. This includes, but is not limited to, refining research
33 questions to include identification of specific confounders, specification of how data are to be obtained
34 and definition of appropriate populations.

35
36 For example, because fever was known to occur as part of a common response to the attenuated, live virus
37 MMR and MMRV vaccines, epidemiological studies were developed to describe the rates of post-
38 vaccination febrile seizures⁸⁹. Compared with use of separate MMR and varicella vaccines at the same
39 visit, use of MMRV vaccine is associated with a higher risk for fever and febrile seizures 5 through 12
40 days after the first dose among children aged 12 through 23 months (about one *extra* febrile seizure for
41 every 2,300–2,600 MMRV vaccine doses administered)¹⁶.

42
43 Another example of the *a priori* definition of hypotheses based on potential biological mechanisms for
44 testing involves adjuvanted vaccines. An adjuvant is a non-antigenic component of many vaccines (most
45 commonly alum) that is used to enhance the immune response to the vaccine antigen. However, adjuvants
46 may have the potential to stimulate a broader immunological response that could theoretically lead to an
47 increased risk for autoimmune diseases in some individuals. Because of this potential risk, studies of
48 vaccines that contain novel adjuvants have included epidemiological endpoints that include development
49 of autoimmune diseases^{90,91}.

50 Epidemiologic Studies Involving Large Linked Databases

1
2 Because severe vaccine adverse reactions tend to be rare, epidemiologic analysis and hypothesis testing
3 often relies on the extraction of data from large linked databases (LLDB), such as managed care
4 organization (MCO) or health maintenance organization (HMO) data (e.g., claims and administrative
5 data, electronic medical and immunization records). Medical diagnoses used to identify possible AEFI in
6 these LLDB are often coded using the International Classification of Diseases, 9th Revision (ICD-9)
7 system, and for some AEFI, there may be multiple possible ICD-9 codes that could be applied. Because
8 of this, there may be both a need to identify multiple outcomes, depending on the number of hypotheses
9 being tested, as well as many possible reporting codes that could be used for the same outcome. In
10 addition, reliance on ICD-9 codes depends on the diagnostic skills and practices of clinicians and the
11 accuracy of coders, and may be influenced by the availability of specific tests, testing procedures, and
12 billing practices, among other things, making it critical to have access to the medical records for review.
13 As an example, the positive predictive value for GBS, using ICD-9 codes, is approximately 50%⁹².
14 However, one limitation that needs to be considered with the use of LLDB is that the systems from which
15 data are extracted were designed for medical claims and billing, and not for research.

16
17 The use of LLDB, which is described through the use of examples below, has distinct strengths and
18 weaknesses. Some LLDB contain data on millions of people (“covered lives”), allowing assessment of a
19 large number of individuals relatively quickly. However, the data available may be limited with regard to
20 other factors (environmental, genetic, other health indicators) that may also play a role in the development
21 of the specified condition. To gather these additional data requires medical record review or even direct
22 specific testing, which can be time- and labor-intensive. Complete vaccine exposure data may not be
23 available for all vaccines in the records due to billing practices or lost records or receipt of vaccine
24 outside of the medical home (e.g., in a public clinic). While computerized immunization information
25 systems hold promise for supplementing immunization data, many suffer from incomplete reporting. It
26 may be possible to move beyond traditional LLDB from MCO or HMO to other large-scale data sources,
27 such as studies like the National Children’s Study.

28 29 Vaccine Safety Datalink (VSD)

30
31 One of the most commonly used LLDB for vaccine safety studies is the VSD. The VSD is the primary
32 system for testing of hypotheses in vaccine safety and is used to determine adverse event rates, assess
33 associations, complete population-based epidemiological studies to address a hypothesis, and contribute
34 to causality assessment. The VSD is a collaborative effort between CDC, 10 MCOs (facilitated by
35 America’s Health Insurance Plans (AHIP)), and academic researchers. The VSD links databases including
36 vaccination and medical records from about 9 million children and adults (about 3% of the US
37 population) and allows for testing of hypotheses and rapid cycle analysis (RCA) for “near real time”
38 surveillance. Data are actively gathered; since the whole population is known, the denominator is known.
39 Because VSD data are obtained based on MCO medical records databases, it is possible to define the
40 population under study, including direct calculations of denominator data.

41
42 RCA is an analytical technique whereby data from medical care encounters is monitored and analyzed
43 continuously, to examine the potential association between selected health outcomes and vaccination. .
44 By making these comparisons repeatedly, often on a weekly basis, as new immunization and adverse
45 event occurrence data are collected, researchers have the ability to quickly assess potential associations
46 between a particular vaccine and adverse event⁹³.

47
48 As data are already available from the routine databases of the MCOs, VSD can conduct studies more
49 rapidly than other traditional epidemiologic studies that require the establishment of specific data
50 collection activities. VSD data are suited to comparing rates of AEFI with those occurring without a
51 temporally associated vaccination. The large size of VSD allows for analysis of rare adverse events that

1 would require a long period of time to detect in sufficient quantity for analysis using traditional
2 surveillance methods.

3
4 While VSD does cover a large number of individuals, it may still be difficult to detect very rare adverse
5 events and AEFI potentially related to vaccines recommended for a smaller population (e.g.,
6 meningococcal vaccine recommended for adolescents) which would only constitute a subset of the total
7 VSD population. Additionally, VSD sites typically have a very small population of Medicaid patients,
8 which may impact socio-economic diversity in the population under study.

9 10 Meningococcal Vaccine Study

11
12 Utilizing the methodologies developed for the VSD, other LLDB have been used to address questions that
13 cannot readily be studied using the VSD. An example of this is the analysis of data from five large health
14 plans to study GBS following receipt of meningococcal vaccine by adolescents¹⁸. This study involved
15 pooling data from approximately 9.5 million adolescents aged 11-18 (approximately 25% of the US
16 adolescent population)¹⁹.

17 18 Systems Developed/Adapted to Monitor the H1N1 Influenza Vaccine

19
20 Federal plans to monitor the safety of the H1N1 influenza vaccine were described in detail in a report by
21 the Federal ISTF²³.

22
23 Throughout the H1N1 influenza pandemic and vaccination campaign, existing systems were enhanced
24 and additional systems were developed, increasing the ability to detect and examine AEFI²³. While these
25 systems were designed to address the H1N1 influenza vaccination campaign and are not currently in use
26 for routine immunizations, many of their methodologies can be applied to administration of other
27 vaccines. One example is PRISM, which used health plans data in conjunction with state IIS to capture a
28 greater percentage of vaccine receipt than through health plan records alone. The conditions monitored
29 and the sequential analysis methods used in PRISM were based on those developed through VSD.
30 PRISM monitored an estimated 30 million individuals under surveillance for adverse events following
31 H1N1 vaccination, 17 million of whom had enhanced IIS data, resulting in nearly 3 million H1N1
32 immunizations captured under surveillance.

33
34 H1N1 influenza safety studies were implemented for active duty military and veterans, through the DOD
35 and DVA respectively. DOD implemented active surveillance for AEFI among active duty military,
36 through examination of electronic health records, and DVA coordinated data transfer between their
37 Adverse Drug Event Report System (ADERS) and VAERS. RCA was performed utilizing medical
38 records from DOD and DVA electronic data systems. Additional enhanced VAERS reporting and RCA
39 were performed using data obtained through health records maintained by the IHS.

40
41 Because of concern about the possibility of an association between H1N1 vaccination and development of
42 GBS, following the experience of the 1976 National Influenza Immunization Program, enhanced
43 surveillance and RCA targeted towards GBS outcomes was undertaken by the CMS. Additionally, the
44 EIP at CDC undertook active GBS case finding with assessment of recent H1N1 influenza vaccination,
45 covering a population of approximately 45 million⁹⁴.

46
47 The development of the Real Time Immunization Monitoring System (RTIMS) has presented a unique
48 opportunity for AEFI active surveillance. RTIMS was implemented through the Institute for Vaccine
49 Safety at the Johns Hopkins Bloomberg School of Public Health. RTIMS used web-based queries to
50 identify adverse events at 1 day, 1 week and 6 weeks following immunization, and was used for targeted
51 follow-up for nearly 10,000 H1N1 immunizations, though the information collected was primarily self-

1 reported, which may impact data quality. Most AEFI identified through RTIMS were reported to
2 VAERS.

3
4 An additional, existing surveillance system used to address safety concerns for the H1N1 influenza
5 vaccination program was the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS).
6 VAMPSS is collaboration between the American Academy of Asthma, Allergy and Immunology, the
7 Organization of Teratology Information Specialists and the Pregnancy Health Interview Study at the
8 Slone Epidemiology Center, Boston University
9 (<http://www.bu.edu/slone/Research/Studies/VAMPSS/VAMPSS.htm>). While VAMPSS was in place
10 prior to the H1N1 influenza pandemic to monitor the safety of medications used by pregnant women, data
11 collection and analyses were targeted to H1N1 vaccine during the vaccination campaign. The VAMPSS
12 sample size was small (approximately 3,000 women), potentially precluding the ability to study very rare
13 outcomes, but the focus on pregnant women allowed some directed examination of maternal and fetal
14 outcomes. Still, there are limitations to the utility of a system such as VAMPSS where the safety data
15 cannot truly be “real-time”, given the need to wait for a full gestation term.

16
17 These systems, both those existing prior to the H1N1 influenza pandemic and those developed/modified
18 in response to the pandemic, share one common thread – the need for large amounts of rapidly available,
19 good quality data. While the data from health insurance plans, MCOs, and federal health care data
20 systems can be obtained quickly and in large quantities, all data necessary for epidemiologic studies may
21 not be present. More specific active surveillance programs (e.g., EIP GBS study, VAMPSS) can collect
22 data of high quality, as protocols are rapidly developed, with clearly identified needs, and in some cases,
23 can collect data quickly. Other systems that can be quickly implemented and rapidly monitored may have
24 limitations, such as the use of self-report data (e.g., RTIMS). However, because of the effort to collect
25 these data, and the potential for targeting specific subgroups, sample sizes may be limited either by
26 available participants or by financial constraints given the technical requirements for the data collection
27 and analysis.

28
29 The rapid adaptation of existing systems and development of new systems, on an ad hoc basis, is a
30 demonstration of the flexibility of the vaccine safety system to respond to emerging threats.

31 FDA Sentinel Initiative

32
33
34 Following the passage of the FDA Amendments Act of 2007⁵⁴, the FDA launched its Sentinel Initiative to
35 create an additional mechanism to acquire information on vaccine safety. The Sentinel Initiative is
36 intended to create the Sentinel System, a large surveillance system that will be used for medical product
37 safety evaluations, including devices, drugs and vaccines. Currently, development and refinement of the
38 system is being conducted through the Mini-Sentinel pilot project (http://mini-sentinel.org/about_us)⁹⁵.
39 Mini-Sentinel provides a systematic means to interrogate a distributed network of independent health care
40 databases and is intended to include access to data of at least 100 million patients by July 1, 2012. The
41 Mini-Sentinel Project incorporates, and is expanding on, the vaccine safety-related systems of the PRISM
42 System, described above, to provide infrastructure that will permit evaluation of the full range of adult
43 and pediatric vaccines. The Sentinel Initiative adheres to Federal privacy and security standards,
44 including those endorsed by the Office of the National Coordinator for Health Information Technology
45 (ONC). In addition, representatives of the Sentinel Initiative participate in technology development
46 forums led by the ONC (FDA, personal communication, 2011).

47 4.2.5.3. Biological mechanisms

48
49
50 Understanding the biological mechanisms behind the human immune response to a vaccine or a
51 confirmed adverse event may lead to (1) improved safety monitoring and assessment by defining which

1 populations or sub-populations should be monitored; (2) identification of individuals at increased risk for
2 experiencing adverse events (genetic risk factors, previous or concurrent illness); (3) better clinical
3 approaches to treating/ameliorating adverse events that occur; (4) development of improved vaccines that
4 avoid the biological mechanism in question (as appropriate); and (5) improved risk communication about
5 the safety of vaccines, particularly with regard to groups identified as higher risk for vaccine adverse
6 reactions.

7
8 Identification of subgroups at increased risk for AEFI is important for three main reasons: 1) the
9 occurrence of a particular AEFI concentrated in a specific, small subgroup may not be identified when
10 examining the epidemiology in the general population, 2) identification of these subgroups can help feed
11 relevant information to other research, such as clinical investigations and the study of biological
12 mechanisms, and 3) targeting intervention activities (e.g., screening) to these identified high-risk groups.

13
14 Now that vaccines are given to individuals across their lifespan, appropriate study populations are needed
15 in all age groups, as the risk in a 1 year old may be different than the risk in a 25 year old or 65 year old.
16 Subgroup analysis is difficult because many conditions for which hypotheses have been generated are rare
17 or poorly characterized themselves. Factoring in the relatively small number of individuals in the
18 subgroup of interest, and the rarity of serious AEFI, these studies can be challenging to perform.

19
20 For example, the 1976-1977 A/Influenza swine influenza vaccine was associated with a 4.0- to 7.6-fold
21 increased risk of GBS for the six to eight-week period after vaccination⁹⁶. While the IOM concluded that
22 the evidence favors a causal relationship between this vaccine and GBS, the biological mechanisms for
23 this adverse reaction have not been elucidated. Because previously identified vaccine adverse reactions
24 routinely serve as triggers for future vaccine safety monitoring efforts, safety surveillance for the novel
25 H1N1 vaccine program included a major focus to assess GBS²³. However, there is the potential that the
26 efforts for this enhanced monitoring could have been more targeted had there been a better understanding
27 of the biological mechanisms responsible for the association of the 1976-1977 swine flu vaccine and
28 GBS.

29 30 Clinical Immunization Safety Assessment Network (CISA)

31
32 Besides the basic biomedical research described above, targeted clinical research into biological
33 mechanisms of AEFI is essential. One locus of this work is the Clinical Immunization Safety Assessment
34 Network (CISA). CISA is comprised of six academic centers funded by CDC and its mission is to
35 conduct clinical research about adverse events and the role of individual variation, to counsel clinicians
36 on vaccine safety issues, and to assist policy makers in recommendations for exclusion criteria. CISA
37 investigates the pathophysiological basis of adverse events, identifies risk factors, and develops evidence-
38 based guidelines. CISA has made significant contributions in a number of vaccine safety areas, such as
39 smallpox vaccine effort that followed 9/11, conduct of genomics studies, and evaluation of
40 hypersensitivity reactions. CISA has the potential to rapidly develop protocols and implement studies
41 using multi-disciplinary research teams by capitalizing on the diverse expertise available in the academic
42 centers. These academic centers also have a diverse range of specialty clinics that can be used for
43 recruitment of patients. CISA and VSD have sponsored a Vaccine Safety Fellowship Program to train
44 new investigators in this important area of vaccinology, which will encourage further interest and
45 expertise in evaluating vaccine safety.

46
47 CISA also manages a biospecimen repository for samples collected from patients experiencing unusual
48 AEFI, which holds great promise for studying a variety of vaccine safety questions. Inherent challenges
49 in specimen collection as well as lack of resources have made the repository of limited utility except for
50 specific studies that include specimen collection in the protocol. Federal efforts are underway to identify

1 opportunities for enhancing the biospecimen repository, which are critical to maximize its utility for
2 biological mechanisms research.

3 4 Federal Entities Examining Biological Mechanisms

5
6 In addition to the basic biomedical research conducted through NIH that has applicability to vaccinology
7 and vaccine safety, there are other Federal research programs addressing the clinical components of
8 vaccine adverse reactions.

9
10 The FDA has been active in this arena. One example is the FDA initiative to use VAERS data on cases of
11 post-Lyme Disease vaccination arthritis to facilitate a case-control study of the underlying genetics of this
12 adverse event⁹⁷. More recently, the CBER Office of Biostatistics and Epidemiology established the
13 Genomics Evaluation Team for Safety, to examine the genomics of vaccine adverse reactions⁹⁸.

14
15 The Vaccine Healthcare (VHC) Network is a DOD organization that performs clinical consultation,
16 conducts research into vaccine adverse research and develops and disseminates educational materials
17 about clinical vaccine safety concerns⁹⁹. The VHC Network collaborates with other research and
18 healthcare related entities, such as CISA and the Military Vaccine Agency.

19 20 4.2.5.4. Causality assessment

21
22 Understanding biological mechanisms behind AEFI, sometimes referred to as biologic plausibility, is
23 important in assessing the possible causality between a vaccine and a particular type of adverse event.
24 Previous IOM causality assessments have been hindered by an inadequate understanding of potential
25 biologic effects elicited by immunization. Because 60% of the IOM causality assessments have found
26 “inadequate evidence to make a determination”⁵⁰, further research into this area may lead to more
27 definitive causality assessments.

28
29 Causality assessment between vaccination and AEFI is further complicated because there is not always a
30 clear association between a specific vaccine and a specific adverse event. While there are adverse
31 reactions more commonly associated with a particular vaccine (e.g., syncope associated with receipt of
32 HPV vaccine), other, usually non-specific AEFI (e.g., redness/pain at the injection site) may be common
33 across many different vaccines.

34
35 Another potential issue is that some adverse events with different clinical presentations may be linked by
36 similar physiologic, pathologic or genetic pathways. Identifying potential biological mechanisms
37 underlying these AEFI involves distinguishing patterns within vaccine-AEFI reports, which requires not
38 only good surveillance for appropriate epidemiologic data but also clear collaborations across disciplines.

39 40 4.2.5.5. Injury compensation

41
42 Since no vaccines or any other medications can be proven to be 100% safe and some are known to be
43 associated with adverse reactions, serious adverse reactions or vaccine-related injuries could occur in
44 some individuals. While there are societal benefits from vaccination, costs following vaccine adverse
45 reactions are borne by the injured individual or their family. Recognizing that monetary compensation
46 does not fully address the hardship created by vaccine adverse events in all cases, the NCVIA created the
47 National Vaccine Injury Compensation Program (VICP), housed in HRSA. The VICP uses causality
48 assessment information to establish an injury table¹⁰⁰ that allows compensation for persons who develop a
49 condition on the table within a specified time window after vaccination, as documented on the Table,
50 without the requirement of further evidence to establish a causal link between their condition and the
51 vaccine exposure. For injuries that are not listed on the vaccine injury table, which are the majority of

1 claims currently submitted to the program, either the government and the petitioner come to an agreement
2 or evidence for and against an association between the vaccine and injury must be presented to a special
3 master who makes a decision as to whether to make an award¹⁰⁰. There is currently a review underway to
4 address more recently recommended vaccines and their potential associated adverse events. Frustration
5 has been expressed over the speed with which data are available to update the VICP injury table.

6 7 4.2.5.6. Public health response 8

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

19 20 4.2.5.7. Communication 21

22 A major component of the public health response is the manner in which information is communicated to
23 the public and to the health care provider community regarding vaccine safety issues. CDC and FDA
24 have been responsible for rapid communication and outreach following identification of potential vaccine
25 safety issues (e.g., rotavirus and intussusception) as well as preemptive efforts to inform the public about
26 the safety of coming vaccines (e.g., 2009 H1N1 vaccine). However, there has not always been
27 coordinated messaging between federal agencies. One example of this is the difference of opinion
28 publicly presented by HHS agencies during the investigation of intussusception following the first
29 licensed rotavirus vaccine¹⁰¹. Differing conclusions were made by scientists from different Federal
30 agencies regarding the course of action to take with regard to the use of the first rotavirus vaccine, and the
31 lack of a coordinated message may have led to confusion on the part of the public¹⁰¹.

32
33 There is much publicly available information on vaccines and vaccine safety, particularly through
34 publicly available websites (e.g., www.cdc.gov, www.fda.gov), as well as through information distributed
35 through the Health Alert Network (<http://www2a.cdc.gov/han/index.asp>). However, there is not one
36 central location where information on all aspects of vaccine can be accessed, and if individuals are not
37 aware of the differences in scope and role of the various Federal agencies and Departments, it may be
38 difficult to locate the exact information desired. Efforts at coordinated public communication on vaccines
39 more broadly, through websites such as www.flu.gov and www.vaccines.gov, have proven beneficial.

40 41 4.2.5.8. Clinical practice to reduce and manage vaccine adverse events and vaccine 42 administration errors 43

44 Another area of safety concerns related to vaccination is vaccine administration errors. Common
45 identified administration errors are administration of the wrong vaccine, the wrong dose of the vaccine or
46 administration at an incorrect timeframe relative to the recommended vaccination schedule^{102,103}. One
47 way to address these errors is through the “five rights” framework: Right Vaccine, Right Time, Right
48 Dose, Right Route, and Right Patient¹⁰². As discussed in Section 1.4.5, patients have started to request
49 more information from physicians than they previously had. The IOM, in their report “To Err is Human”,
50 referenced five questions recommended by the National Patient Safety Partnership for patients to ask to
51 reduce the possibility of medication error. While these are directed more towards prescription

1 medications, the intent is similar for vaccines. Additionally, there is no central reporting mechanism for
2 tracking vaccine administration errors. If an administration error results in injury (e.g., shoulder injury
3 related to incorrect vaccine administration)¹⁰⁴, it should be reported to VAERS but errors for which no
4 injury occurs are not required to be reported to VAERS. Other databases and reporting systems that track
5 vaccine administration errors include MEDMARX¹⁰⁵, the Medication Error Reporting Program at the
6 Institute for Safe Medication Practices¹⁰⁶, and the FDA MedWatch Program¹⁰⁷.

7
8 One way to help ensure proper vaccine administration is the use of barcode systems for identifying and
9 tracking the immunizations provided. Currently, the FDA is developing processes and guidance for
10 expanded use of barcode labeling systems¹⁰⁸, with the most current guidance, as of August 2010,
11 available at
12 [http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Gu](http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM225099.pdf)
13 [idances/General/UCM225099.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM225099.pdf).

14
15 Once a vaccine adverse reaction is identified in a patient, the clinician must be able to evaluate the
16 severity and have the clinical guidance for managing the vaccine adverse reaction. The CDC's "Pink
17 Book" contains information on identifying and managing AEFI, with a focus on the more common, and
18 typically less severe, AEFI¹⁰⁹. The CDC ISO Scientific Agenda, previously reviewed by the NVAC
19 VSWG, contains a call for the development of evidence-based clinical guidance protocols for managing
20 AEFI⁵³ but there does not currently appear to be a central repository of such clinical guidance.

21 22 **4.2.6. Feedback mechanisms: From practice to bench**

23
24 To improve our understanding of the biological mechanisms underlying adverse events, more robust
25 communication and collaboration is needed between basic scientists conducting laboratory research,
26 epidemiologists conducting population-based research, and other partners, such as scientists within the
27 vaccine industry. It is important to recognize the role that manufacturers play in biological mechanisms
28 research. The vaccine industry has a strong incentive to ensure that their products are safe and effective
29 and thus has invested significant resources into determining the biological mechanisms of adverse
30 reactions, not only during the pre-licensure phase, but also post-licensure.

31
32 When a significant adverse reaction is observed in epidemiological/surveillance studies, communication
33 with laboratory scientists may help to understand potential underlying mechanisms; similarly, if
34 laboratory research uncovers mechanisms through which a severe adverse event may be triggered,
35 targeted surveillance and epidemiologic studies may be helpful to assess whether there is an actual
36 association of immunization with the event. This two-way communication between epidemiologic and
37 basic biomedical science research is critical to ensuring that all parties involved in studies related to
38 vaccine safety are aware of concurrent research that may impact their own studies. A model for the flow
39 of information and collaboration among these various scientific disciplines is the Clinical and
40 Translational Science Awards (CTSA), now awarded to 46 institutions nationally, with a mission to
41 accelerate technology development from the lab to the clinic. Investigator initiated research is an
42 important mechanism for innovation and enhancing scientific understanding. The general format for this
43 flow and feedback of information is displayed in Figure 2

44 45 **4.3. Stakeholder and public input**

46
47 Information obtained from the public comment period and a stakeholder's meeting on June 13, 2011 will
48 be included in the final report.

1 **5. Discussion/Conclusions**

2
3 **5.1. System framework and general discussion**

4
5 The current charge of the NVAC VSWG, in the most distilled sense, is to review the current vaccine
6 safety system, identify possible opportunities for improvement within the current system and suggest
7 potential steps to meet those opportunities.

8
9 The quest to improve our understanding of vaccines and appropriately balance the benefit/risk
10 comparisons for vaccines, involves – in fact, requires – the efforts of a diverse array of entities and
11 individuals. This includes the biomedical research and healthcare communities; the pharmaceutical
12 industry; federal, state, and local governments; advocacy organizations; and the general public. Because
13 immunization programs are the corner stone of the national public health enterprise, the federal
14 government necessarily is the focal point for vaccines in general and for managing the vaccine safety
15 system in particular. These myriad groups comprising the United States vaccine safety system has
16 worked in concert to effectively identify and address a variety of safety signals (e.g., intussusception and
17 Rotashield®, GBS and MCV4).

18
19 **5.2. Conclusions from review of the vaccine safety system**

20
21 The VSWG finds that the US vaccine safety system is a fundamentally sound system for monitoring
22 vaccine safety that has functioned well since the enactment of the NCVIA. This does not, however,
23 preclude efforts of CQI. Given recent advances in technology and research methodology, it is appropriate
24 to look for and pursue opportunities to make this good system better. Following the information
25 gathering efforts undertaken by the VSWG and corresponding stakeholder and public engagement
26 sessions, the VSWG has come to the following conclusions.

27
28 **5.2.1. Coordination of the system**

29
30 In accord with the charge to address “... the infrastructure needs for a federal vaccine safety system ...”
31 the VSWG, initially through its Structure and Governance Subgroup and later as a working group of the
32 whole, considered the current infrastructure. The VSWG determined that the National Vaccine Program
33 includes all the requisite functions for a vaccine safety system (i.e., research, regulation, post-licensure
34 surveillance, guidance for immunization programs, guidance for clinicians, injury compensation, and
35 oversight) and that the organizational placements of these functions are consistent with the missions of
36 the respective participating agencies and offices. However, the VSWG believes that, while fundamentally
37 sound, the current vaccine safety system can and should be improved considerably by stronger central
38 leadership, coordination, and ongoing assurance.

39
40 The need for improved coordination of components of the vaccine safety system parallels an ongoing
41 NVAC theme of increased coordination within the US vaccine enterprise^{46,62}, as well as being cited in a
42 number of earlier reports^{44,46,110,111}. During the working group’s information gathering phase, interviews
43 with representatives from different Federal agencies within the vaccine safety system reflected room for
44 improvement with respect to coordination within the National Vaccine Program, and between its complex
45 mix of governmental and non-governmental partners and stakeholders¹⁰¹. There is recent evidence that
46 this type of coordination is possible and can pay dividends for public health. The rapid response of the
47 NVPO in implementing the NVAC recommendations of July²⁰ and August¹¹² 2009 related to H1N1
48 influenza vaccine safety monitoring provides support for this concept. When the IOM made
49 recommendations related to coordination in their report “Priorities for the National Vaccine Plan”, they
50 cited these H1N1 safety monitoring recommendations as an example of what could be accomplished
51 through these coordinated efforts⁴⁶.

1 Overall, as seen with the National Vaccine Program in general, there is need for improved coordination
2 among relevant Departments, Agencies and partners on vaccine safety issues. Recommendations
3 stressing coordination in the National Vaccine Plan^{46,113} highlighted the need for coordination across all
4 components of the vaccine enterprise, including the vaccine safety system. There are some examples of
5 strong coordination, including VAERS, co-administered by the CDC and the FDA¹¹⁴, and bi-weekly
6 conference calls between the leadership of ISO and CBER (FDA and CDC, personal communication,
7 2011). It is important to identify and build on the best practices of collaboration and coordination that
8 occurred in recent years, primarily in response to public health emergencies (e.g.,
9 rotavirus/intussusception and H1N1 influenza), including steps to ensure the most efficient use of
10 resources in basic, clinical and surveillance research, as well as communications to external stakeholders
11 and the public. Additionally, agencies with a role in immunizations, such as IHS, AHRQ and VA should
12 have adequate representation through NVP-related task forces, advisory committees and working groups.
13

14 The need for coordination extends to the research realm. Basic research, clinical research, and
15 epidemiological research must all be well-coordinated and inform one another, a feedback loop which is
16 currently underdeveloped. Without formal linkages between vaccine-related entities (such as the National
17 Institute of Allergy and Infectious Disease [NIAID], VTEU, CDC, CISA, and FDA) complimentary
18 expertise and infrastructure cannot be fully leveraged. A mechanism is needed for collaborating with
19 experts outside of the vaccine safety arena when questions arise that would benefit from neurologists,
20 mitochondrial experts, etc. Not only would these linkages aid in understanding the potential adverse
21 events, subspecialists may be sources of cases for study or samples for a vaccine safety repository.
22

23 While the CDC ISO has a 5-year research agenda⁵³ in place, on which the NVAC previously made
24 recommendations⁶², this represents only one component of vaccine safety research. While activities are
25 currently underway in other agencies^{64,97}, they do not represent a consistent enterprise-wide vaccine safety
26 plan. Development and implementation of such a plan would require a coordinated effort to ensure that
27 the goals of the plan are being met. Such reviews were envisioned by IOM in the report “Vaccine Safety
28 Research, Data Access, and Public Trust”, where the NVAC was called on to annually review and
29 provide advice on the research plan for the VSD¹¹⁵.
30

31 Improved coordination is important to ensure that appropriate data related to vaccination and adverse
32 events are collected when opportunities to do so present themselves. Long-term, longitudinal studies,
33 such as the National Children’s Study provide the opportunity for analysis of large cohorts of children,
34 and efforts need to be leveraged to ensure that accurate immunization data are collected. While these
35 studies are not designed solely to address effects, both beneficial and adverse, of vaccination, they do
36 provide an opportunity to improve data retrieval methods (e.g., through medical records or through
37 immunization information system review).
38

39 Acting as the operational arm of the National Vaccine Program, the NVPO is charged with coordinating
40 activities across the Federal government to implement the goals of the National Vaccine Plan¹¹⁶.
41 However, the Director of the National Vaccine Program, the ASH, does not have organizational authority
42 over the agencies that comprise the National Vaccine Program, and is therefore hampered in his/her
43 ability to directly enact change or coordinate activities within these agencies. Instead, this authority
44 resides with the Secretary of HHS and Secretaries of non-HHS Departments involved in vaccination and
45 vaccine safety. It is critical to increase awareness of the functions and activities of the vaccine safety
46 system among these Secretaries, and to increase their role in meeting their respective charges relative to
47 vaccine safety. The coordinating entity for the vaccine safety system therefore needs a clear mandate to
48 perform these coordinating functions. With improved coordination, there is also a greater ability to be
49 flexible with a given program to adapt to an emergent need such as those adapted to assess “real-time”
50 risk during the H1N1 epidemic.
51

1 Outside of the Federal government structure, public advisory committees make recommendations to
2 appropriate agencies. For example, the legislation that established the NVAC listed eight other National
3 Vaccine Program responsibilities, in addition to vaccine safety, that the NVAC was to provide advice on.
4 Given this broad scope, and a limited membership size, with some membership categories prescribed by
5 the NVAC charter¹¹⁷, there is a potential limit to the amount of vaccine safety expertise within the full
6 committee. This need has been addressed by subcommittees and working groups that can enlist non-
7 NVAC members, as needed. Depending on the task at hand, these groups can be task-oriented with
8 specific timelines for completion, possibly precluding long-term evaluation.
9

10 Vaccine safety activities and vaccine science require financial resources and staff support. Substantial
11 investments will be needed to improve the ability to engage in causality assessment and to improve
12 scientific understanding of mechanisms and individual risk. Staffing dedicated to vaccine safety
13 activities is not commensurate with the responsibilities and workload necessary to fulfill their
14 obligations¹¹⁸.
15

16 Funding within the Federal infrastructure for post-licensure vaccine safety has not increased significantly
17 since 2004, despite the addition of four vaccines to the routinely recommended immunization schedule.
18 In general, funding for vaccine safety system partners has remained flat over many years, while the
19 number of vaccines and the number of people vaccinated has increased substantially, though there have
20 been some targeted increases, such as the funding dedicated to development of the Mini-Sentinel
21 program. Because many activities that impact vaccine safety, either directly or indirectly occur without
22 the specific moniker of “vaccine safety”, it is difficult to identify what proportion of agencies’ and
23 Departments’ funding is allocated to vaccine safety-related functions.
24

25 The NVAC previously highlighted the need for additional funding for vaccine safety research, with focus
26 on the CDC ISO⁶², as well as general recommendations addressing the need for additional funding for
27 vaccine safety activities in 1996¹¹⁹, 1997¹²⁰, 1998¹²¹ and 1999⁶⁰. The IOM also recommended funding
28 increases as part of its review of the National Vaccine Plan⁴⁶. Additionally, the increased infrastructure
29 capacity to address the H1N1 influenza pandemic was developed using temporary funding allocations,
30 and there was no clear plan to maintain these improvements. In February, 2010, NVAC resolved that
31 important improvements made in public health infrastructure (including but not limited to vaccine safety)
32 should be maintained¹²². Specifically, NVAC recognized the need to continue funding infrastructure
33 improvements that were put in place to deal with the pandemic.
34

35 Thus, the VSWG provides the following conclusions in the area of Coordination:
36

37 Enhanced collaboration on vaccine-safety initiatives between agencies is needed.
38

39 Leadership within the Office of the Secretary, HHS to exercise its inherent authorities to improve
40 coordination among US government agencies and offices needs to be increased.
41

42 An enterprise-wide agenda for enhancing research in critical subject matters, including both pre-
43 licensure research activities and post-licensure surveillance, needs to be created.
44

45 Public advisory committees and their related subcommittees/working groups would benefit from
46 enhanced expert representation to address vaccine safety issues by inclusion of subject matter
47 experts in areas such as understanding, preventing, and treating vaccine-associated adverse
48 events.
49

50 Resources, including fiscal support and staffing, provided to vaccine safety activities should be
51 increased at levels commensurate with the needs and opportunities that exist.

1 **5.2.2. Basic biomedical research**
2

3 The human immune system is incredibly complex. Many investigators are working to understand the
4 physiologic responses of the immune system and how they change over a person’s lifetime. The
5 knowledge base related to the biological basis of vaccine adverse reactions exhibits substantial gaps and
6 uncertainties and critical opportunities to address them are receiving insufficient attention and funding.
7 There are several ongoing efforts to examine biological mechanisms behind the immune response to
8 vaccination in particular. Such research may also be helpful to better understand and possibly treat or
9 prevent vaccine adverse reactions. However, these efforts for the most part remain insular and not well
10 coordinated with each other. In discussions with scientists, it was determined that no inventory of basic
11 research possibly related to vaccine response and adverse reactions has been formed or maintained. There
12 is no current effort to do this. Important opportunities to link basic research to vaccinology and the study
13 of vaccine adverse reactions are being missed.
14

15 Basic research into the molecular and cellular responses making up the immune response to vaccination
16 that may be related to adverse events, including studies of vaccine antigens, adjuvants and other related
17 components¹²³, needs to be improved and incentivized, as was done with the use of American Recovery
18 and Reinvestment Act funds to begin a study to model the human immune response¹²⁴. NIH activities
19 could also be integrated into existing FDA/CDC studies of vaccine safety to enhance the inclusion of
20 information from basic research. It may be beneficial to develop systematic methods to prioritize which
21 vaccine adverse reactions should be studied or to consider incorporation of public input into the
22 prioritization process.
23

24 There are other entities with great potential to contribute to the scientific base of biological mechanisms
25 but they need to be more actively involved and committed to the vaccine safety research program. NIH
26 has given much attention to immunology research through programs like the Human Immune
27 Phenotyping Research Centers and targeted programs. Genomics research has also increased
28 exponentially, and genome-wide scans have the ability to identify rare variants associated with diseases or
29 conditions. Much of the focus on genomics has stemmed from the notion that biological responses are
30 affected by genetics, and different drugs may be more or less appropriate for different individuals. The
31 concept of personalized medicine is now widespread. In light of the interest and investment being made
32 in these respective scientific disciplines, there is great opportunity to collaborate and inform vaccine
33 safety science through the lenses of immunology and genomics. This will require collaboration among
34 scientists and entities conducting research, funding, and access to specimens through an effective biobank
35 able to capture the necessary samples from patients who experience very rare events. Formalized data
36 sharing will inform a coordinated scientific agenda that includes biological mechanisms, which is critical
37 to ensure that the biological basis behind vaccine adverse events is properly understood. Research cannot
38 be undertaken without a strong vaccine safety science work force, which is currently small and
39 inadequately supported.
40

41 While a substantial amount of basic research with applicability to vaccinology is occurring through NIH
42 support, linkages between these individual research activities, and a broader connection to vaccinology is
43 lacking. Increasing the awareness of the potential interoperability of these research activities within the
44 scope of vaccine safety science is essential to ensure that an appropriately broad array of vaccine-related
45 research is moving towards a common end point. While the VSWG identified lack of a vaccine safety
46 study section at NIH as a gap, there may be other processes that can be refined to meet the goal of
47 improved coordination of vaccine safety related activities. An emphasis on the multi-disciplinary
48 approach to addressing vaccine safety questions, including the development of linkages across funding
49 opportunities is needed. Possible solutions include highlighting the use of particular keywords, such as
50 “vaccine safety”, and requests for targeted review by vaccine safety experts, to ensure that the
51 interdisciplinary benefits of the study are made known. The existing program announcement for vaccine

1 safety-related research⁶⁴ is one step in attracting the desired high-quality, multidisciplinary investigators
2 to this field, but it is critical that there be a mechanism within NIH to track research with applicability to
3 vaccine safety, and work to foster these linkages.
4

5 A consistent funding mechanism for vaccine safety research should be identified, which could support
6 program project grants and investigator-initiated research into vaccine safety under the scope of a national
7 vaccine safety scientific agenda. The development of this scientific agenda, and coordinated research
8 program could also help the development of a National Vaccine Safety Biospecimen Repository.
9 Currently, an IRB-approved specimen repository is maintained through CISA. Expansion into a larger-
10 scale repository could increase the ability to perform necessary biological mechanisms research, but may
11 magnify the logistical issues of maintaining such a repository.
12

13 Thus, the VSWG provides the following conclusion in the area of Basic Biomedical Research:
14

15 Research into the molecular and cellular mechanisms that may be involved in vaccine-associated
16 adverse events is not always linked to the concept of vaccine safety. Coordinating such research
17 efforts and more clearly identifying their possible application to vaccine safety would possibly
18 enhance prevention and treatment of vaccine adverse events.
19

20 Development of a National Vaccine Safety Biospecimen Repository has a number of logistical
21 challenges that need to be addressed, including but not limited to: 1) identification of what types
22 of samples would be banked, 2) what associated information would be needed for the samples to
23 be useful, 3) who would contribute samples to the repository, 4) how would the samples be
24 distributed, 5) who would determine which requests for samples would be approved, 6) who
25 would maintain the samples, 7) who would ship the samples, and 8) how would the repository be
26 funded.
27

28 **5.2.3. Vaccine development/pre-licensure activities/clinical trials**

29
30 Sample size limitations for clinical trials can affect the ability to clearly identify associations between
31 vaccination and adverse events during vaccine development and testing. While it is impractical to attempt
32 to increase clinical trial size to match post-licensure vaccine uptake, increased knowledge regarding
33 biological mechanisms of vaccine adverse reactions and comparisons with known vaccine-adverse event
34 associations can help clarify specific targets for pre-licensure vaccine safety studies. An example was the
35 increased clinical trial size for rotavirus vaccine trials to identify associations with intussusception
36 following the experience with the first licensed rotavirus vaccine¹⁵. This type of coordinated feedback
37 and continuous evaluation between manufacturers, biomedical researchers and the government is a
38 critical component of vaccine development and pre-licensure activities, and needs to be fostered. One
39 key area of for vaccine development and pre-licensure activities is animal and toxicology studies
40 conducted prior to beginning clinical trials.
41
42

43 Thus, the VSWG provides the following conclusion in the area of Vaccine Development/Pre-Licensure
44 Activities/Clinical Trials:
45

46 Vaccine clinical trials have improved, in particular with larger sample sizes to detect rarer AEFI.
47 Ongoing clinical trials offer an opportunity for continuous evaluation and improvement to
48 identify best methods for vaccine safety outcome measures.
49
50

1 **5.2.4. Vaccine licensure**

2
3 Vaccine licensing activities were outside of the scope of this working group, and the VSWG makes no
4 conclusions on this topic, as these considerations are under the purview of the Vaccines and Related
5 Biological Products Advisory Committee.

6
7 **5.2.5. Post-licensure activities**

8
9 5.2.5.1. Surveillance/signal detection

10
11 Because of the lack of sufficient power to detect many rare outcomes that can be temporally associated
12 with immunization (which are needed to evaluate data acquired during the course of immunization), the
13 significance of small increases in risk is difficult to evaluate with confidence. Efforts to estimate
14 background rates of AEFI that may be temporally associated with pandemic influenza vaccination during
15 preparations for the H1N1 influenza vaccination campaign was a key step in increasing this knowledge
16 base⁸⁴.

17
18 The utility of VAERS was well demonstrated following the initial post-licensure period for the first
19 licensed rotavirus vaccine. However, the limitations of a passive reporting system, along with reports
20 containing incomplete data, can affect the strengths of the system, and new technologies should be
21 employed as possible to address these limitations¹²⁵. Additionally, some reports published using VAERS
22 data¹²⁶⁻¹²⁸ included analytic interpretations beyond what is recognized as feasible with these data^{77,78},
23 which can lead to misunderstandings of the value and application of this system.

24
25 Expanded technologic approaches to surveillance of early concerns and “warning signs” among the public
26 have not been widely utilized. While focus groups and town meetings are important for getting more in-
27 depth sense of public concerns and responses to messages, they do not provide a sense of the distribution
28 of the concerns in the general population.

29
30 Thus, the VSWG provides the following conclusions in the area of Surveillance/Signal Detection:

31 Calculation of background rates of potential AEFI in subpopulations is important for proper
32 vaccine safety risk assessment.

33
34 The uses and limitations of VAERS may not be widely understood by its target population (e.g.,
35 physicians, parents), and its uses and limitations are not widely understood by the general
36 population.

37
38 Strategies are needed to enhance the quality of data reported to VAERS. Some potential
39 examples are outreach to individuals who make reports encouraging more complete data
40 reporting and utilization of technology and data abstraction methods from electronic health
41 records to enhance reporting.

42
43 For an increasingly proactive way to measure AEFI, the vaccine safety enterprise needs an
44 expanded array of surveillance approaches to ascertain early concerns through public opinion
45 polling and active monitoring the “new media” such as blogs, etc.

46
47
48 5.2.5.2. Signal assessment/hypothesis testing

49
50 Post-licensure data collection for vaccine safety is required through Title 21, Code of Federal
51 Regulations, Part 600.80, “Post marketing reporting of adverse experiences”¹²⁹ and existing FDA

1 guidance to industry on vaccine safety reporting¹³⁰. However, the extent of post-licensure vaccine safety
2 monitoring may not be readily apparent to the public, potentially leading to concerns about the adequacy
3 of this type of evaluation.
4

5 Post-licensure studies of vaccine safety can require extensive time and effort, and there may be the
6 perception of a trade-off between timeliness and quality of the results. However, as seen with the NVAC
7 H1N1 VSRAWG¹³¹, high quality and rapid evaluation of vaccine safety data can be performed, though
8 the intensive effort required may not be sustainable for all, or even most, vaccine safety examinations.
9 Ad hoc development of systems such as the Meningococcal Vaccine Study¹⁸ and PRISM²³ to supplement
10 the VSD can be effective for defined and targeted analyses, though an evaluation for more widespread
11 application still needs to be performed. Increased sample sizes and increased technological advances
12 (e.g., RCA) can increase the timeliness for detection of significant levels of adverse events^{93,132}.
13

14 A major opportunity to increase sample sizes for study of AEFI comes from the FDA Amendments Act of
15 2007³⁴, which calls for increasing the size of the population under active surveillance for post-licensure
16 examination of adverse events. At this time, the FDA is developing the Sentinel Initiative, a large
17 surveillance system for medical products (including medical devices, drugs and vaccines) safety studies.
18 It is anticipated that by July 1, 2012, the population under surveillance will reach 100 million. The
19 Sentinel Initiative relies on advanced informatics capabilities to efficiently and accurately access
20 information in billing information and electronic health records.
21

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

27 Thus, the VSWG provides the following conclusions in the area of Signal Assessment/Hypothesis
28 Testing:
29

30 Programs for post-licensure surveillance and hypothesis testing for AEFI should be enhanced
31 regarding the quality and timeliness of reports and scope of coverage, while balancing the
32 resources required for such efforts with the potential benefits. New data analysis technologies
33 could assist in improving the timeliness of these findings.
34

35 Even well-developed epidemiological studies of actual or potential vaccine-associated adverse
36 events would benefit from increased sample sizes to be able to more quickly detect rare adverse
37 events.
38

39 5.2.5.3. Biological mechanisms 40

41 While proactive monitoring efforts are used to identify rarer AEFI with more widespread vaccine use, the
42 current system for research into biological mechanisms of vaccine adverse reactions is, by its inherent
43 nature, primarily reactive. While basic research projects such as the NIH's Human Phenotyping Project
44 provide a great opportunity to build and sustain a consortium approach for profiling human immune
45 responses, little has been done to capture potential synergies between these efforts with others such as the
46 development of a biospecimen repository. Indeed, more thought and leadership is needed on approaches
47 to incentivize novel research that will provide critical information to guide vaccine safety policy decisions
48 across all aspects of the life cycle of a vaccine.
49

50 Many opportunities exist to gain new fundamental insights into the molecular and cellular mechanisms
51 that may be involved in vaccine adverse reactions that could improve prevention and treatment of vaccine

1 adverse events. Although the purpose of this report is not to prescribe specific vaccine safety activities,
2 the VSWG would like to reaffirm that NVAC made recommendations related to biological mechanisms in
3 its June 2009 report⁶², including “Consider detailed mechanistic studies of common but mild adverse
4 events such as fever or rash. These might provide insights into mechanisms of severe but rare adverse
5 events”⁶². This prior NVAC recommendation was made to attempt to understand if there are common
6 mechanisms underlying adverse events that are common and mild as well as more severe adverse events.
7 Attempts to understand underlying mechanistic issues for adverse events may allow examination of
8 severe adverse events through the proxy of other, more common, adverse events.

9
10 Efforts to study biological mechanisms of vaccine adverse effects are substantially under-resourced and
11 could contribute more to this effort with additional funding and research staff. The need for solid
12 research to understand biological mechanisms and inform clinical guidance to medical providers is clear,
13 but the resources needed to adequately support these efforts are lacking. As an example, CISA faces
14 challenges in recruiting sufficient subjects for many of their protocols due to limited funding and the
15 difficulties inherent in studying very rare outcomes.

16
17 Thus, the VSWG provides the following conclusion in the area of Biological Mechanisms:

18
19 Research into the molecular and cellular mechanisms that may be involved in vaccine-associated
20 adverse events is occurring but could benefit from increased coordination, planning and
21 resources.

22 23 5.2.5.4. Causality assessment

24
25 The lack of coordination around vaccine safety research described above has left open many opportunities
26 to improve knowledge and understanding of vaccine safety. In 18 of 30 (60%) assessments since 2001,
27 the IOM concluded there was not adequate information to accept or reject a causal association between
28 vaccination and specific adverse events⁵⁰. Part of the problem with vaccine adverse event causality
29 assessments is the lack of statistical power associated with smaller studies. The use of large linked
30 databases has begun to reduce this problem but even in the VSD, the population under active surveillance
31 may still be too small for examination of very rare adverse events (e.g., 1-2 cases / 100,000 for GBS) or
32 events among important subgroups such as pregnant women.

33
34 Thus, the VSWG provides the following conclusions in the area of Causality Assessment:

35
36 Causality assessment, as performed by the IOM, is a useful and robust process. There is a need
37 for institutionalizing a standing causality assessment group.

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

43 44 5.2.5.5. Injury compensation

45
46 The current Vaccine Injury Table became effective November 10, 2008. However, four vaccines
47 (hepatitis A vaccine, trivalent influenza vaccine, meningococcal [polysaccharide and conjugate] vaccines
48 and HPV vaccine) have not undergone full review of adverse events that may be considered for
49 compensation under the VICP¹⁰⁰. An IOM review is underway for these, and other, vaccines¹³³.
50 However, until this review is completed and new entries are made to the Vaccine Injury Table, adverse
51 events following receipt of these vaccines must be proven to be associated with vaccination in order for

1 compensation to be provided. Often claims alleging conditions not listed in the Vaccine Injury Table are
2 compensated on the basis of negotiated settlements between both parties. Since FY 2007, over half of
3 claims adjudicated annually are compensated on the basis of litigative risk settlements.
4

5 While provision of information about VAERS and the VICP to patients is mandated for administration of
6 all vaccines, the extent to which this information may be underutilized by individuals who experience an
7 adverse reaction is unknown. One recent study observing physician-patient interactions did not find any
8 instances of providers specifically referencing the VICP during vaccination visits, though VIS were
9 routinely provided⁸³. Preliminary results of an assessment of provider and public awareness of the VICP
10 presented to the ACCV¹³⁴ indicated a lack of awareness of the existence, functions and role of the VICP.
11 As indicated in the Communications section, improvements in coordinated distribution of vaccine safety
12 information may help provide clarity regarding both VAERS and the VICP.
13

14 Thus, the VSWG provides the following conclusions in the area of Injury Compensation:
15

16 The timeframe for updating the vaccine injury compensation table could be improved
17 commensurate to the pertinent and existing knowledge base.
18

19 Provider and public awareness of the VICP Program could be increased.
20

21 5.2.5.6. Public health response 22

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

32 By definition, public health response activities are primarily reactive. While CDC has an impressive
33 track record of providing support through the Epi-AID system for disease investigation and control, there
34 may be room for coordination of public health response activities across Departments and agencies
35 involved in the vaccine safety system. Additionally, aside from high-profile situations, such as the
36 rotavirus vaccine/intussusception case and the H1N1 influenza vaccination campaign, there does not
37 appear to be broad communication to the public about the public health functions involved in vaccine
38 safety.
39

40 Proactive efforts to assure appropriate public health response were evident throughout the planning that
41 occurred in summer 2009 for the H1N1 influenza vaccine campaign. While activities such as PRISM
42 sought to establish links for immunization data across multiple sources, including health plan data and
43 immunization information systems, there were still challenges in obtaining H1N1 immunization data for
44 individuals vaccinated outside of traditional immunization settings, to link to health outcomes data.
45

46 Thus, the VSWG provides the following conclusion in the area of Public Health Response:
47

48 Recognizing the work of CDC in vaccine safety-related public health response, best practices and
49 collaborative efforts should be promulgated among Federal Departments and agencies that may
50 be involved in these types of public health response activities.
51

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

5 5.2.5.7. Communications

6
7 Information about vaccine safety is primarily disseminated by the CDC¹³⁵, through news releases, press
8 conferences and website postings. However, vaccine safety information is also distributed by other HHS
9 agencies such as NIH and FDA¹³⁶ and other Departments (e.g., Defense^{137,138}), and is often related to
10 more specific topics. The establishment and authorization of a central body within the federal
11 government to coordinate and distribute vaccine safety information would improve communications on
12 vaccine safety.

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

20
21 Thus, the VSWG provides the following conclusion in the area of Communications:

22
23 The provision of a one-stop source of comprehensive information about vaccine safety, for the
24 public and providers, such as how to report adverse events, how the vaccine safety system has
25 successfully identified previous actual adverse events following immunizations, how the vaccine
26 injury compensation program works, what safety-related research is underway, etc. will improve
27 communications to the public on this issue.

28
29 There is room for improved coordination between the different US government Departments and
30 agencies (e.g., CDC, FDA, DOD, DVA) with respect to their outreach about the safety of
31 vaccines.

32 5.2.5.8. Clinical practice

33
34
35 Comprehensive education, particularly for immunization providers, is very important, not only for
36 adverse event identification but also for proper vaccine administration and treatment of adverse events.
37 This will require research and development of treatment algorithms. The DOD VHC has developed
38 related algorithms, more of which are needed for vaccines given in the general population.

39
40 For healthcare providers, as well as individuals who believe that they have experienced a vaccine injury,
41 clinical guidance for managing and coping with vaccine injuries is limited. Even within “Epidemiology
42 and Prevention of Vaccine Preventable Diseases” (aka, “The Pink Book”)¹⁰⁹ there is limited information
43 on clinical guidance for managing adverse events following immunization.

44
45 Thus, the VSWG provides the following conclusions in the area of Clinical Practice:

46
47 Clinical guidance and other support related to identification, evaluation, treatment, management
48 and coping with AEFI should be improved and widely disseminated to vaccination providers,
49 patients and caregivers.

50

1 FDA initiatives on barcoding should be widely adopted, to help surveillance systems capture data
2 more consistently.

3 4 **5.2.6. Feedback mechanisms**

5
6 The findings related to feedback of vaccine safety science and vaccinology described above can primarily
7 be addressed through better coordination of the system. The conclusions presented in Section 5.2.1 are
8 applicable to this area as well.

9 10 **5.3. Goals of an ideal vaccine safety system**

11 The VSWG concluded that the US vaccine safety system should be able to:

- 12 • accurately detect AEFI with high sensitivity and specificity,
- 13 • accurately quantify the risk of AEFI to allow benefit/risk comparisons,
- 14 • assess whether an AEFI is causally linked to vaccination,
- 15 • conduct an appropriate public health response to emerging vaccine safety issues,
- 16 • appropriately communicate results between the scientific community and the public,
- 17 • ensure that system processes and results are transparent,
- 18 • better understand AEFI to develop proactive research into AEFI occurrence and prevention, and
- 19 • perform these tasks in a timely manner.

20
21 The ideal vaccine safety system should consist not only of a responsive arm but also a long-range,
22 proactive research arm.

23
24 During its discussion and deliberations, the VSWG identified nine essential functions of a vaccine safety
25 system. The identified functions are the essential components of the vaccine safety system. They are
26 presented in Appendix 8. It is important to note that the order of the functions does not indicate priority
27 nor does the number of associated items indicate scope.

28
29 Additionally, the VSWG noted ten attributes by which the functions identified could be best performed.
30 The essential attributes of the vaccine safety system functions are presented in Appendix 9. Key
31 attributes are defined as qualities or characteristics the VSWG hopes to maximize for each essential
32 system function. Each of these key attributes is important for all functions of the vaccine safety system,
33 and each was considered on a continuum. Although the VSWG agrees that all attributes should be
34 maximized in each function, participants of the Salt Lake City small stakeholder meeting identified three
35 attributes they felt should be prioritized: evidence-based decision making, objectivity, and transparency.

36 37 **5.4. Public confidence**

38
39 In response to its charge, the VSWG considered whether public confidence in vaccine safety during
40 recent years may impact vaccination coverage and whether the recommended improvements in the safety
41 system could improve public confidence, resulting in higher vaccine coverage. Current coverage levels
42 for many routinely recommended childhood vaccines are at historically high levels in the whole
43 population³, raising the question about whether vaccine safety concerns expressed by parents in some
44 surveys^{8,139} have led to changes in parental vaccine decision-making. However, with the availability of
45 alternative vaccination schedules, some parents may be delaying vaccination or requesting that their
46 children have immunizations spread out more than called for in the recommended schedule. Also recent
47 outbreaks of measles, as well as data on vaccination coverage at the school level, have highlighted
48 pockets of under-immunization in subgroups concerned about vaccine safety. These pockets have
49 adversely affected the health of the larger population by providing an opportunity for introduced diseases
50

1 to take hold in under-immunized populations. In addition, it is possible that safety concerns may impede
2 the uptake of more recently recommended vaccines or will do so in the future.

3
4 A consistent theme in research about attitudes toward vaccination is that patients consider their physician
5 the most trusted source of information about vaccine safety^{8,31,140,141}. Physicians then need to better
6 understand both the safety of vaccines and the vaccine safety system. They must have confidence in the
7 scientific basis for that understanding and efforts need to be undertaken to assess this understanding and
8 related perceptions¹⁴¹. Moreover, they must have adequate methods to communicate with their patients,
9 whether through more face-to-face time or other education tools. This is a difficult goal given the
10 economic pressures in primary care.

11
12 A nationally representative survey conducted in early 2009 among parents of children aged up to 17 years
13 found over half of all individuals surveyed had concerns about serious adverse effects of vaccines⁸.
14 Another study in 2009 sponsored by the Association of State and Territorial Health Officials (ASTHO)
15 found that the most common reason for delaying vaccination was concern about too many vaccines given
16 at once. Nearly a third of those sampled found the statements convincing that vaccines are unsafe
17 because of ingredients such as thimerosal or aluminum and that too many vaccines given too soon can be
18 harmful. Some of those who chose to vaccinate their children and expressed minor concerns or no
19 concerns at all nevertheless expressed concern over ingredients and the number of vaccines²⁶. This may
20 be driven by a lack of awareness of the activities of the nation's vaccine safety system by the average
21 American. Most available data focuses on public perceptions about the safety of vaccines and not
22 perception of the vaccine safety system. However, the ASTHO study suggests parents are also concerned
23 about the vaccine safety system itself, at least as manifest by government guidance for immunization
24 practice. Nearly a quarter of those surveyed found convincing statements that data supporting vaccine
25 safety were unreliable due to bias by pharmaceutical companies and government cover-up²⁶.

26
27 During the 2009 H1N1 influenza pandemic, among 2,994 pregnant women who did not receive the
28 seasonal influenza vaccination, 48% cited safety concerns for their baby and 45% cited safety concerns
29 for themselves. Among the 2,602 who did not receive the 2009 H1N1 vaccination, 64% cited safety
30 concerns for their baby and 61% cited safety concerns for themselves¹⁴². Since the bulk of the H1N1
31 vaccine became available after the fall 2009 wave of H1N1 disease, when public demand may have
32 lessened, it is difficult to determine the impact of these safety concerns on the ultimate H1N1 vaccination
33 coverage: median coverage was 41% for children aged 6 months to 17 years, 38% for adults aged 18 to 49
34 years with high risk conditions, 29% for adults 18 to 49 years without high risk conditions, 46% for adults
35 aged 50 to 64 and 69% for adults aged 65 years and older^{27,143}.

36
37 The VSWG could not determine if improvements in the vaccine safety system will change public
38 attitudes in general. In particular, the VSWG found no data suggesting that, for individuals in specific
39 populations who oppose vaccination for their children, improvements in the vaccine safety system will
40 modify attitudes. The general public is likely largely unaware of the vaccine safety system and its
41 function in ensuring vaccine safety, and it is not clear that knowledge of the system would change these
42 attitudes or behavior. On the other hand, increasing awareness of, and improving appreciation of
43 enhancements to the vaccine safety system by practicing physicians may increase their ability to rapidly
44 communicate vaccine safety information to parents. This is of particular importance with the large
45 amount of information to be communicated, both vaccine-related and not vaccine-related, during routine
46 physician visits where time may be limited⁸³. However, regardless of whether a continuous improvement
47 process in the vaccine safety system will improve public confidence, resulting in increased acceptance of
48 vaccines, these improvement processes must be considered if they will strengthen the system and improve
49 scientific understanding and patient safety.

1 **6. Recommendations**
2

3 The draft recommendations presented here were developed by the National Vaccine Advisory Committee
4 (NVAC) Vaccine Safety Working Group (VSWG). The draft being circulated is a synthesis of the
5 information that the VSWG has obtained since July 2009 for purposes of discussion and comment. No
6 decisions have been made by the VSWG regarding the final outcome of these recommendations or their
7 components. The VSWG will consider all comments made on this draft as they prepare the penultimate
8 draft of the report for discussion and deliberation by the NVAC.
9

10 These recommendations, when finalized by the VSWG, will be deliberated on by the NVAC. The NVAC
11 serves in an advisory role to the Assistant Secretary for Health (ASH), within the United States
12 Department of Health and Human Services (HHS). If approved by the NVAC, they will be formally
13 transmitted to the Assistant Secretary for Health for his consideration and possible implementation, which
14 may include communication with various components of the Department and other interested parties.
15

16 For some of the recommendations below, the VSWG went beyond simply stating the objective to include
17 details regarding either how the objective should be achieved or what the completed objective should
18 include. The VSWG chose this approach for three reasons. First, the VSWG seeks to avoid ambiguity
19 regarding its thinking; absent the associated details, a reader could reasonably interpret the
20 recommendation substantially differently than does the VSWG. Second, the RAND Corporation, in a
21 recent study commissioned by the NVPO, found many previous NVAC recommendations to be lacking
22 sufficient details to guide implementation and called for future NVAC recommendation to be
23 “actionable”.¹⁴⁴ Therefore, the VSWG sought to make its intended actions clear. Third, recognizing that
24 HHS may wish to consider alternative approaches to implementing the recommendations below, the
25 VSWG believes that the details it offers will provide a valuable benchmark against which to compare any
26 given alternative approach and determine whether it is more or less superior to that recommended here.
27

28 The VSWG is mindful that, per its charge, its recommendations need not be constrained by the budgets
29 for the NVP-coordinated agencies and Departments - either current funding levels or projected ones.
30 Nevertheless, in formulating these recommendations, the VSWG was aware of potential budget
31 implications, recognizing that they would have a long-term impact on the vaccine safety system, and not
32 be solely constrained by the current fiscal environment. The VSWG recognizes that some
33 recommendations can be accommodated readily within current operating levels; that other
34 recommendations will require modest increments beyond current spending; and that still other
35 recommendations will require commitment of substantial additional funds. In general, the budget
36 implications of each recommendation are self-evident from the description and associated discussion.
37 Recommendation 9 in this document calls for a costing of all recommendations accepted by the NVAC.
38

39 The VSWG understands that vaccine safety is but one of many worthy claimants for funding as the
40 Executive Branch and the Congress weigh difficult choices throughout the annual budget process. The
41 VSWG also understands that the flexibility inherent in this process is considerable. In particular, the
42 discretionary budget for the Department of Health and Human Services (HHS) for Fiscal Year 2010
43 (October 01, 2009 to September 30, 2010) was almost \$79 billion; and the corresponding item in the
44 President’s Budget Request for Fiscal Year 2011 is over \$81 billion. Reprioritization of a small portion of
45 the annual HHS discretionary budget toward enhancing the vaccine safety infrastructure over the next few
46 years seems realistic.
47
48
49
50
51

1 **Recommendation 1 – Leadership**
2

3 To ensure adequate leadership for vaccine safety-related issues, the VSWG recommends that HHS clearly
4 delineate and update the structural organization, constituted as the National Vaccine Program (NVP),
5 which is responsible for coordinating federal government activities related to vaccine safety.
6

7 ***Recommendation 1.1 – Reaffirmation of the System Structure***
8

9 The Secretary, HHS, should affirm the commitment of the Department of HHS to fulfilling the letter and
10 spirit of the vaccine safety provisions of the National Childhood Vaccine Injury Act of 1986 by issuing a
11 policy statement that includes the following components:
12

- 13 • Reaffirmation that the NVP is a coordinated effort among the Food and Drug Administration (FDA),
14 the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the
15 Health Resources and Services Administration (HRSA), and the Centers for Medicare and Medicaid
16 Services (CMS) and the Departments of Defense (DOD) and Veterans Affairs (DVA) and the United
17 States Agency for International Development (USAID);
18
- 19 • Reaffirmation that the Assistant Secretary for Health (ASH), having been designated as Director,
20 NVP is responsible for the direction of the NVP activities related to coordination of vaccine safety;
21
- 22 • Reaffirmation that the National Vaccine Program Office (NVPO) is charged with advising the ASH
23 regarding implementation of the responsibilities of the NVP and coordinating the vaccine safety-
24 focused activities of the NVP¹ (see related recommendations in Recommendation 2).
25
- 26 • Reaffirmation that the National Vaccine Advisory Committee (NVAC) is responsible for reviewing
27 vaccine safety policy and the vaccine safety-focused activities; developing recommendations based
28 on these reviews; and transmitting its recommendations to the ASH, and to the Secretary pending
29 implementation of Recommendation 1.3;
30

31 ***Recommendation 1.2 – Structural Organizational Changes in the National Vaccine Program***
32

- 33 • Inclusion of the Indian Health Service and the Agency for Healthcare Research and Quality as
34 participants in the NVP.
35
- 36 • Direction to HHS agencies coordinated under the NVP, accompanied by a request to DOD, DVA, and
37 USAID, for the following:
38 ○ to cooperate fully with NVPO vaccine-safety coordination efforts,
39 ○ to identify and pursue opportunities for collaborative projects relevant to NVP vaccine safety
40 objectives with other NVP coordinated agencies,
41 ○ to ensure that they regularly obtain the advice of appropriate subject matter experts and
42 consumers to guide initiatives related to vaccine safety, and
43 ○ to ensure that other governmental agencies, vaccine manufacturers, and appropriate stakeholder
44 organizations and representatives of the public regularly have the opportunity to provide feedback
45 during the planning and implementation of initiatives related to vaccine safety and are apprised of
46 initiatives and outcomes related to vaccine safety.
47 ○ to define performance expectations related to vaccine safety for the NVP-coordinated agencies.
48

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

1 ***Recommendation 1.3 – National Vaccine Advisory Committee Charter***
2

3 The Charter of the National Vaccine Advisory Committee should be modified to reflect the following
4 changes:
5

- 6 • Specify that NVAC advises the Secretary as well as the ASH, thereby defining a relationship between
7 NVAC and the Secretary akin to that which already exists for the Advisory Committee on
8 Immunization Practices and other major HHS public advisory committees;
9
- 10 • Specify additional Federal *ex officio* representation from the Indian Health Service and the Agency
11 for Healthcare Research and Quality.
12

13 Both in response to requests from the Secretary and at its own initiative, the NVAC should evaluate the
14 progress of the NVP-coordinated agencies toward enhancing vaccine safety, especially through NVP-
15 wide initiatives to enhance research, post-licensure surveillance, public information, and stakeholder
16 engagement. To accomplish this, the Assistant Secretary for Health should charge the NVAC to create a
17 standing Working Group on Vaccine Safety. Members of this Working Group should be selected using a
18 similar approach as used for the H1N1 Vaccine Safety Risk Assessment Working Group.
19

20 This Working Group would, at a minimum, be charged with reviewing the following long-term goals and
21 activities:

- 22 • implementation of these and other related NVAC safety recommendations through regular reports
23 from the ISTF, as described in Recommendation 8.2;
24 • agencies' vaccine safety plans and progress in implementing them;
25 • response to emerging vaccine safety issues as they arise.
26

27 **Recommendation 2 – Coordination**
28

29 ***Recommendation 2.1 – Expanded role for the ISTF***
30

31 The Federal Immunization Safety Task Force (ISTF) is a cross-government committee, including
32 representatives from HHS agencies, DOD and DVA; is led by HHS; chaired by the ASH in his/her role as
33 Director, NVP; and supported by NVPO. The ISTF should make regular reports, in accordance with the
34 structure described in Recommendations 8.2. The VSWG recommends increasing the scope of the
35 ISTF's vaccine safety coordinating activities, under the leadership of the ASH and the Director, NVPO, to
36 include establishing subcommittees in the following areas:

- 37 • Research
38 • Post-licensure surveillance
39 • Clinical Practice
40 • Communications
41 • Stakeholder and public engagement
42

43 ***Recommendation 2.2 – Expanded composition of the ISTF***
44

45 The VSWG recommends that NVPO expand the membership of the ISTF to ensure representation from
46 the agencies and Departments specified as contributing to the National Vaccine Program components
47 outlined in P.L. 99-660, or subsequently redesignated or renamed agencies, including the Centers for
48 Medicare and Medicaid Services, the Agency for Healthcare Research and Quality, and the US Agency
49 for International Development.
50

1 **Recommendation 3 – Research**

2
3 ***Recommendation 3.1 – Development of a vaccine safety research agenda***

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

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

20
21 ***Recommendation 3.2 – Building a vaccine safety research community***

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

- 27 • Facilitate a community of vaccine safety researchers that crosses the boundaries from basic research,
- 28 clinical research and epidemiology to ensure continuity of research from different arenas, entities, and
- 29 disciplines.
- 30 • Share vaccine safety-related research findings with all members of the ISTF at regular monthly Task
- 31 Force meetings;
- 32 • Leverage existing infrastructure and investments for vaccine safety research, such as CISA, the
- 33 National Children’s Study, and others.
- 34 • Engage vaccine manufacturers to capitalize on their expertise, large preclinical and clinical databases,
- 35 specimen repositories and scientific resources to inform further vaccine safety studies
- 36 • Coordinate the development, implementation and periodic update of the National Vaccine Safety
- 37 Scientific Agenda, as described in Recommendation 3.1.
- 38 • Ensure there is feedback between stakeholders within the vaccine safety enterprise so that research
- 39 findings translate into safer products and guidelines for their use when appropriate.

40
41 ***Recommendation 3.3 – Research funding and investigator training***

- 42
43 • The NIH should develop processes to identify and link multi-disciplinary intramural and extramural
- 44 vaccine safety research programs and funding, including encouraging researchers to highlight if
- 45 research may have a potential application to vaccinology and vaccine safety through targeted
- 46 applications of keywords and requested reviewers, and through appropriate revisions of “PA-08-256:
- 47 Research to Advance Vaccine Safety” to ensure a wide range of applicability across multiple
- 48 disciplines.

- 49
50 • HHS and its related agencies, along with academic partners and professional organizations, should

- 3
4 • HHS and its related agencies, along with academic partners and professional organizations should
5 support training in vaccine safety for scientists in non-biomedical research areas (e.g. cost/benefit
6 analyses, quality assurance, and policy analysis).
7

8 ***Recommendation 3.4 – Ascertainment of public concerns and perceptions***
9

10 The CDC should evaluate the usefulness of rapidly deployed and analyzed public opinion polling and
11 active monitoring of electronic media to ascertain public concerns and perceptions about vaccine safety.
12 Findings should be used to inform both the vaccine safety research agenda and communications
13 programs.
14

15 ***Recommendation 3.5 – Research directed to clinical practice***
16

- 17 • The NVP, working through the ISTF Subcommittees on Research and Clinical Practice (See
18 Recommendation 2.1) and relevant non-governmental partners (e.g., the CISA Network) should
19 coordinate research to improve clinical guidance and methods for the identification, evaluation,
20 clinical management and reporting of adverse events, including information on clinical follow-up for
21 individuals who experience AEFI. Best practices identified from sources such as the DOD Vaccine
22 Healthcare Centers, AHRQ, and the Brighton Collaboration should be utilized to the greatest possible
23 extent.
24
- 25 • CDC and FDA should develop a consistent and systematic approach, using VAERS or another related
26 reporting mechanism, to characterize the extent to which vaccine administration errors occur and
27 implement strategies for reducing them as appropriate for quality improvement and patient safety.
28 The long-term goal of this approach is to establish a standard mechanism for surveillance of
29 administration errors.
30

31 ***Recommendation 3.6 – Data access***
32

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

- 37 • final data that were used for decisions about vaccine safety (following “reproducible research”¹⁴⁵
38 strategies),
39 • general data that have not been used for a specific adverse event, such as VSD, CISA, and associated
40 specimen banks, to the extent possible, and
41 • preclinical, clinical, and post-licensure data that are part of the application process.
42

43 ***Recommendation 3.7 – Biological specimens***
44

45 CDC and the CISA Network should complete planning and implement recommendations for the
46 enhancement of a National Vaccine Safety Biospecimen Repository linking biological samples to clinical
47 data for unusual AEFI to accelerate studies of biological mechanism and subpopulations at increased risk
48 for adverse events.
49

1 **Recommendation 4 – Post-Licensure Surveillance**

2
3 ***Recommendation 4.1 – Post-licensure surveillance plans for new vaccines***

4
5 The ISTF Subcommittee on Post-Licensure Surveillance (see Recommendation 2.1) should convene
6 relevant Federal agencies and Departments, at appropriate times, to review established proactive action
7 plans for post-licensure vaccine safety evaluations, to ensure coordination of activities and to develop a
8 systematic, integrated approach to post-marketing surveillance plans that includes FDA requests for post-
9 licensure monitoring, CDC commitments to VSD data analysis, and participation from other Federal
10 agencies and Departments that may contribute to coordinated post-licensure surveillance.

11
12 ***Recommendation 4.2 – Post-licensure surveillance data considerations***

13
14 The ISTF Subcommittee on Post-Licensure Surveillance should incorporate the following components
15 into the plans reviewed as in Recommendation 4.1:

- 16
17 • Ensure vaccine safety data are collected on ACIP-recommended vaccine usage not covered by FDA-
18 approved labeling; Utilizing coordination efforts detailed in Recommendation 2 and research
19 coordination efforts detailed in Recommendation 3.2, post-licensure vaccine safety surveillance
20 activities should be informed by manufacturer’s expertise and experience with pre-licensure clinical
21 trials.
22
23 • Utilize and fully take advantage of the FDA Sentinel Project for expanding the population under
24 active surveillance to 100 million by 2012 to do signal detection, validation and confirmation.
25 Special attention should be given to federal initiatives on electronic health and immunization records
26 and alternative ways to link data, and under-represented groups, such as minority populations.
27

28 ***Recommendation 4.3 – Implementation of post-licensure surveillance programs***

29
30 The ISTF, representing the NVP-coordinated agencies and Departments, should lead the efforts to
31 implement the national agenda to enhance post-licensure surveillance (see Recommendation 3.1) and the
32 post-licensure surveillance plans for new vaccines or vaccine formulations/combinations (see
33 Recommendation 4.1)

34
35 **Recommendation 5 – Clinical Practice**

36
37 ***Recommendation 5.1 – Utilizing improvements to clinical practice***

38
39 The ISTF Subcommittee on Clinical Practice should ensure dissemination of information on the following
40 topics:

- 41
42 • Improved clinical guidance to clinicians on the identification, evaluation, clinical management and
43 reporting of adverse events, particularly when advances in clinical practice, as described in
44 Recommendation 3.5 are made and published. An example of this type of guidance is the CISA
45 hypersensitivity algorithm¹⁴⁶.
46
47 • Clinical practice activities that can prevent adverse events associated with vaccine administration
48 errors, particularly when advances are made in examining the occurrence of these errors, as described
49 in Recommendation 3.5.
50

1 ***Recommendation 5.2 – Barcode labeling of vaccines***
2

3 Acknowledging efforts currently underway at FDA, the VSWG is supportive of efforts to create a routine
4 system of barcode labeling of vaccine vials and pre-filled syringes that is compatible, ideally, with
5 international standards.
6

7 **Recommendation 6 – Communications**
8

- 9 • The ISTF Subcommittee on Communications (see Recommendation 2.1) should ensure development
10 and maintenance of a unified program of public information about vaccines, vaccine safety and the
11 vaccine safety system that can serve as a resource to the public and health professionals. This
12 information should be available, at a minimum, through a publicly accessible web site, such as
13 Vaccines.gov. This program, and associated dissemination tools, should focus on establishing and
14 maintaining links to specific agencies information about the safety, efficacy and effectiveness of each
15 licensed vaccine, including:
16 ○ the Vaccine Information Statement;
17 ○ the official package insert, as prepared and issued by FDA and the FDA’s analysis provided to
18 VRBPAC;
19 ○ summaries of the design, scope, and results of the key clinical trials that supported licensure;
20 ○ summaries of the design, scope, and results of any post-licensure clinical trials required by FDA
21 or being conducted under the auspices of one or more of the other NVP-participating agencies;
22 ○ abstracts of product-specific peer-reviewed research reports published after licensure;
23 ○ abstracts of ongoing product-specific research studies funded by HHS or other Departments of
24 the Federal Government; and
25 ○ a clearer public explanation of each agency’s role in post-licensure vaccine safety.
26
- 27 • This communications plan also should focus on utilizing existing mechanisms, and where necessary
28 establishing mechanisms, and publicizing various means by which members of the public can obtain
29 information about vaccines.
30
- 31 • The CDC should utilize and disseminate findings from research into public concerns (See
32 Recommendation 3.4) to develop communications tools applicable to address public concerns and
33 perceptions.
34
- 35 • CDC and FDA should improve methods for communication about the extent to which follow-up to
36 individual VAERS reports may be conducted.
37

38 **Recommendation 7 – Stakeholder and Public Engagement**
39

- 40 • The ASH should direct NVPO to work with NVAC and the ISTF Subcommittee on Stakeholder and
41 Public Engagement (see Recommendation 2.1) to develop and maintain an ongoing and meaningful
42 program of appropriate stakeholder engagement around vaccine safety. This program should focus
43 on ensuring that appropriate stakeholders and the public have the opportunity to regularly provide
44 feedback, through routine stakeholder and public engagement processes, during planning and
45 evaluation of major NVP activities, such as the development of the vaccine safety research agenda
46 (see Recommendation 3.1) and NVAC reviews of NVP activities.
47
- 48 • This program also should publicize various means by which members of the public can share
49 concerns and recommendations about vaccine safety not related to a specific occurrence of a specific
50 AEFI, as would be reported through VAERS.

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

6 **Recommendation 8 – Assurance and Accountability**
7

8 ***Recommendation 8.1 – Enhanced role of the National Vaccine Advisory Committee***
9

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

18 ***Recommendation 8.2 – Relationship between ISTF and NVAC***
19

20 The ISTF should meet at least annually with the NVAC Standing Working Group on Vaccine Safety (see
21 Recommendation 1.3) and file an annual progress report, with an associated presentation at an NVAC
22 meeting, on processes undertaken to monitor and evaluate vaccine safety, including but not limited to,
23 meeting the recommendations specified in Recommendation 3 and 4. These regular meetings with the
24 NVAC standing safety working group may occur through means other than in-person meetings (e.g.
25 teleconference).
26

27 ***Recommendation 8.3 – External assessment of adverse event causality***
28

29 To resolve difficult scientific questions through external scientific review of available evidence and
30 provide regular updates to the Vaccine Injury Table, a mechanism should be developed to conduct
31 causality evaluation of selected vaccine adverse events. On an annual basis, the ISTF, in consultation
32 with the NVAC standing working group on vaccine safety, will conduct a review of potential topics for
33 examination, based on adverse events following immunization for which a review of causality is
34 warranted and there is scientific literature addressing the topic. If serious adverse events that meet these
35 criteria are identified, the Secretary, HHS, should request that an independent panel, such as an IOM
36 Committee, assess the causal relationship between the identified vaccine(s) and suspected adverse
37 event(s).
38

39 ***Recommendation 8.4 – Assurance and accountability of progress in enhancing the vaccine safety***
40 ***system***
41

42 To assure progress in enhancing the vaccine safety system, as highlighted in the above recommendations,
43 there is need for a formal mechanism for review and accountability. Several options were presented to, or
44 identified by, the VSWG through a variety of activities including prior stakeholder and public
45 engagement during the VSWG Task 1, the Task 2 kick-off meeting, the April 2010 “Writing Group”
46 meeting and deliberations by the VSWG and its Structure and Governance subgroup.
47

48 Three options have been discussed for external independent assurance related to vaccine safety, with the
49 second of these options having three potential configurations. No decisions have been made by the
50 VSWG, and the VSWG is still deliberating the options. They do not reflect the conclusions of the VSWG
51 or any individual member, but are presented here for the purposes of discussion. In particular,

1 Recommendation 8.4 Option 3 had limited support on the VSWG but is presented here to get additional
2 input from stakeholders.

3
4 **Option 1: Empower NVAC to be responsible for vaccine safety assurance**

5
6 The Executive Branch would not seek to create a vaccine-safety oversight entity outside HHS. Instead,
7 NVAC would continue to be the advisory entity primarily responsible for evaluating NVP programs and
8 commissioning vaccine-specific investigations. Opportunities exist for HHS to enhance NVAC's
9 standing and authorities, as described in Recommendations 1.1, 1.3, 7, 8.1, and 8.2.

10
11 **Option 2: Establish a fixed-tenure panel outside HHS to monitor the efforts of NVP and NVAC,**
12 **respectively, to improve the vaccine safety system**

13
14 During its defined tenure (e.g., 5 years), the panel would be responsible for evaluating the progress of
15 NVP in implementing enhancements to the vaccine safety system and the effectiveness of NVAC in
16 performing independent evaluations of NVP activities. The panel would have an organizational locus
17 outside HHS. The host administrative entity would have a role in establishing the panel, arranging for
18 funding and other resources as necessary, receiving the panel's reports containing its findings and
19 recommendations regarding the vaccine safety system, and sharing those reports with officials within the
20 Executive Branch, members of the Congress, and the general public.

21
22 Among the questions that the panel might address are a) Are the NVP-participating entities being
23 appropriately responsive to the Secretary and the ASH in enhancing the vaccine safety system? b) Are
24 NVP-wide initiatives properly focused, achieving high quality, and proceeding with appropriate speed? c)
25 Is NVAC receiving the operational flexibility and resources necessary to be effective and credible in
26 evaluating NVP activities? d) Are NVP activities and NVAC evaluations, taken together, sufficient to
27 foster public confidence in the vaccine safety system? Or should an Independent Agency be created to
28 oversee the system?; and e) If such an Independent Agency be needed, what should be its characteristics?
29

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

31
32 Option 2a: Establish the panel as a Presidential Commission

33
34 Under this option, the President would establish the Commission by some appropriate means (e.g.,
35 Executive Order) to carry out the monitoring and reporting activities. Most likely, the President also
36 would designate a senior official with the Executive Office of the President to ensure that the Commission
37 receives requisite support, to receive and disseminate its reports, and to advise the President regarding
38 necessary follow up actions, if any.

39
40 The President would appoint or arrange for appointment of the members of the Commission in accord
41 with whatever process he or his designee deems appropriate, including possible participation the
42 Congress. For example, the Commission could have 8 members – 4 appointed by the President and 4
43 appointed by the key Congressional committees whose purviews include vaccine safety (respectively, the
44 Senate Committee on Health, Education, Labor, and Pensions; the House Committee on Energy and
45 Commerce; the Senate Committee on Appropriations; and the House Committee on Appropriations).

46
47 Option 2b. Establish the panel as an IOM Committee

48
49 The host administrative entity (e.g., a component of the Executive Office of the President) would contract
50 with IOM to carry out the monitoring and reporting activities. IOM would appoint the members of the
51 Committee in accord with whatever process it deems appropriate. The host administrative entity would

1 be responsible for ensuring that the Committee has the requisite support, for receiving and disseminating
2 its reports, and for advising the President regarding necessary follow up actions, if any.

3
4 Option 2c: Create an Independent Agency within the Executive Branch to oversee the vaccine safety
5 system, primarily NVP and NVAC^{2 3}

6
7 A new Independent Agency within the Executive Branch would be responsible for oversight of the
8 vaccine safety system. In particular, the Agency would evaluate NVP programs and commission vaccine-
9 specific investigations by NVP-coordinated agencies (e.g., FDA) or by non-government entities (e.g.,
10 IOM).

11
12 **Option 3: Create an Independent Agency within the Executive Branch to focus on the safety of**
13 **vaccines.**⁴

14
15 A new Independent Agency within the Executive Branch would assume responsibility for operating
16 VAERS and possibly other vaccine-safety related programs (e.g., VSD). In addition, the Agency would
17 have authority to commission vaccine-specific investigations by NVP-coordinated agencies (e.g., FDA)
18 or by non-government entities (e.g., IOM). The Agency would develop findings and recommendations
19 regarding vaccine safety and share them with NVP and the general public.

20
21 **Recommendation 9 – Cost evaluation of recommendations**

22
23 The NVPO should coordinate, across the relevant Departments and Agencies, a cost evaluation of the
24 recommendations in this report approved by the NVAC. This evaluation should be presented to the
25 NVAC at a regularly scheduled NVAC meeting.
26

² 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.

³ 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.

⁴ Footnotes 2 and 3 above apply to Option 4 as well as to Option 3.

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- 2
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1 Table 1. Impact of vaccines on vaccine-preventable diseases in the United States compared to the pre-
 2 vaccine era.

Disease	Reported Illness before Vaccine	Reported cases 2009¹⁴⁷	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%

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1 Table 2. Vaccination coverage estimates for children 19-35 months, National Immunization Survey,
 2 United States, 1994, 2000, 2009.

Vaccine	Dose assessment	1994 ¹⁴⁸	2000 ¹⁴⁹	2009 ³
		% (95% CI)	% (95% CI)	% (95% CI)
DTP/DT/DTaP	3+ doses	93 (±0.7)	94 (±0.5)	95 (±0.6)
DTP/DT/DTaP	4+ doses	77 (±1.1)	82 (±0.8)	84 (±1.0)
Poliovirus	3+ doses	83 (±1.0)	90 (±0.6)	93 (±0.7)
<i>Haemophilus influenzae</i> type b	3+ doses	86 (±0.9)	93 (±0.5)	84 (±1.0)
Measles-containing / MMR	1+ dose(s)	89 (±0.9)	91 (±0.6)	90 (±0.8)
Hepatitis B	3+ doses	37 (±1.2)	90 (±0.6)	92 (±0.7)
Varicella	1+ dose(s)	N/A	68 (±0.9)	90 (±0.8)
PCV	3+ doses	N/A	N/A	93 (±0.7)
PCV	4+ doses	N/A	N/A	80 (±1.2)
Hepatitis A	2+ doses	N/A	N/A	47 (±1.4)
Rotavirus	Vaccine-type appropriate	N/A	N/A	44 (±1.4)
4:3:1 combined series*		75 (±1.2)	78 (±0.9)	N/A
4:3:1:3:3:1 combined series† with Hib excluded		N/A	N/A	78 (±1.1)
4:3:1:3:3:1:4 combined series§		N/A	N/A	64 (±1.2)
4:3:1:3:3:1:4 combined series§ with Hib excluded		N/A	N/A	71 (±1.2)

3 *- DTP/DT; poliovirus; measles-containing

4 †- DTP/DT/DTaP; poliovirus, measles-containing, Hib, hepatitis B

5 §- DTP/DT/DTaP; poliovirus, measles-containing, Hib, hepatitis B; varicella, PCV

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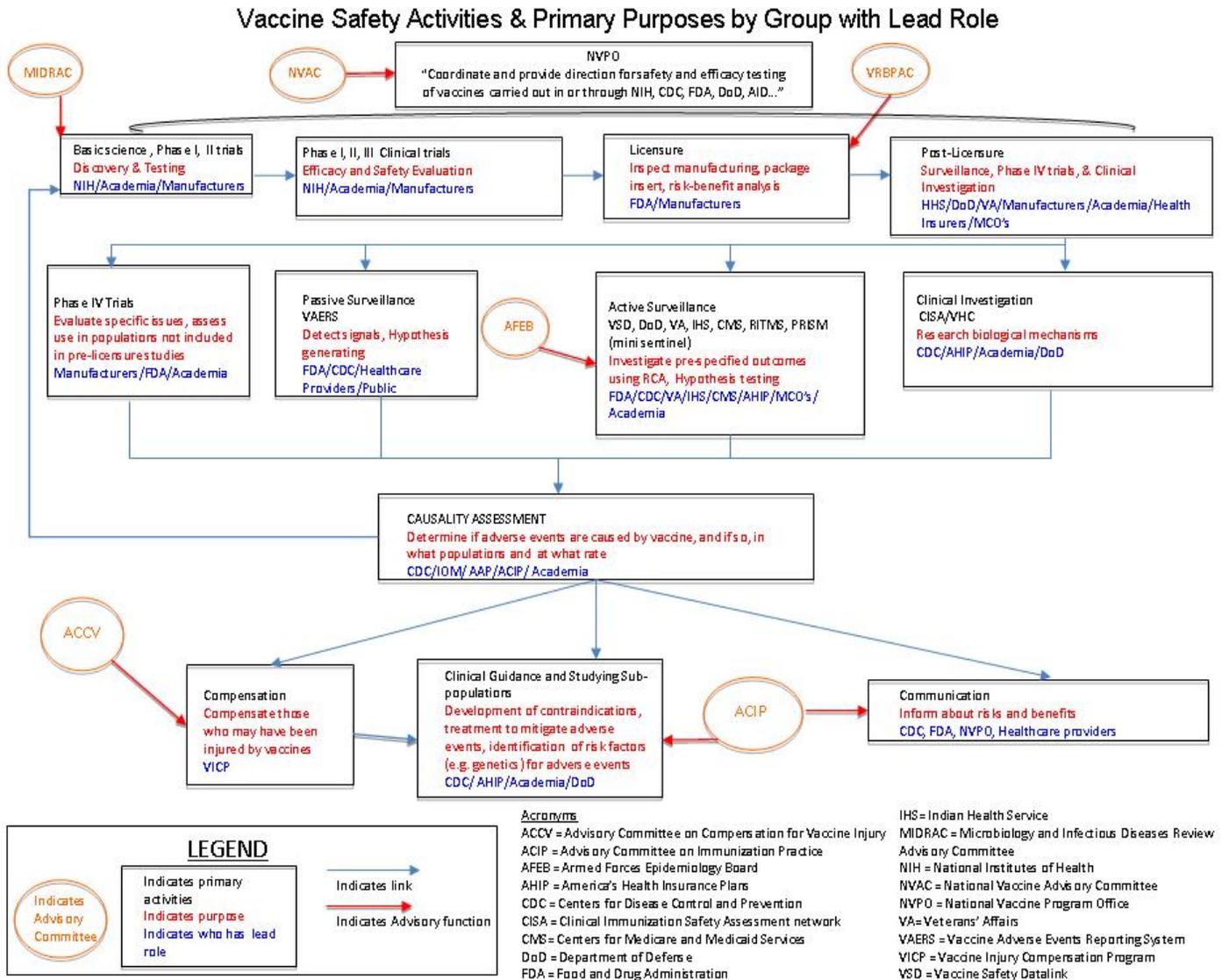
1 Table 3. Vaccination coverage estimates for adolescents and adults, National Immunization Survey-Teen
 2 Module⁶ and National Health Interview Survey⁷, United States, 2009.

Vaccine, dose assessment	Population	% (95% CI)
MMR, 2+ doses	Adolescents, aged 13-17	89.1 (88.3-89.9)
Hepatitis B, 3+ doses	Adolescents, aged 13-17	89.9 (89.2-90.6)
Hepatitis B, 3+ doses	Adults, high-risk, aged 19-49	41.8 (38.4-45.4)
Hepatitis B, 3+ doses	Adults, not high-risk, aged 19-49	33.7 (32.6-34.9)
Varicella (history of disease or 2+ doses of varicella vaccine)	Adolescents, aged 13-17	75.7 (74.6-76.8)
Herpes zoster(shingles), ever	Adults, aged 60+	10.0 (9.1-11.0)
Td or Tdap, 1+ dose since age 10	Adolescents, aged 13-17	76.2 (75.1-77.2)
Td or Tdap, 1+ dose in past 10 years	Adults, aged 19-49	63.1 (61.9-64.2)
Td or Tdap, 1+ dose in past 10 years	Adults, aged 50-64	62.8 (61.3-64.3)
Td or Tdap, 1+ dose in past 10 years	Adults, aged 65+	52.8 (51.0-54.6)
Meningococcal meningitis	Adolescents, aged 13-17	53.6 (52.4-54.9)
Human papillomavirus, 1+dose	Adolescents aged 13-17	44.3 (42.4-46.1)
Human papillomavirus, 1+ dose	Female adults, aged 19-26	17.1 (14.8-19.7)

3 *- DTP/DT; poliovirus; measles-containing
 4 †- DTP/DT/DTaP; poliovirus, measles-containing, Hib, hepatitis B
 5 §- DTP/DT/DTaP; poliovirus, measles-containing, Hib, hepatitis B; varicella, PCV
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1 Figure 1. Design of the current US Federal vaccine safety system.
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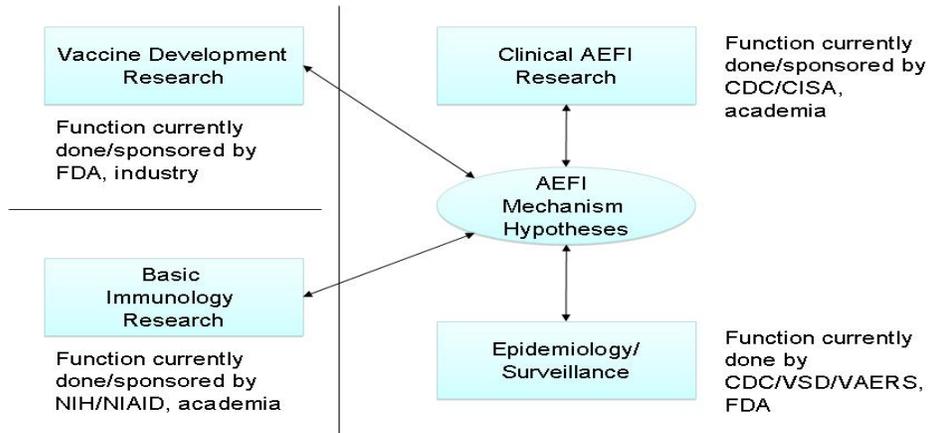


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Figure 2. Proposed feedback loop between research, surveillance and response functions of the vaccine safety system.

Proposed Feedback Loop



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10. Appendices

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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
ASTHO	Association of State and Territorial Health Officials
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
CTSA	Clinical and Translational Science Awards
CQI	Continuous Quality Improvement
DOD	Department of Defense
DTP	Diphtheria/Tetanus/Whole-cell Pertussis vaccine
DT	Diphtheria/Tetanus vaccine
DTaP	Diphtheria/Tetanus/acellular Pertussis vaccine
DVA	Department of Veterans Affairs
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
HMO	Health Maintenance Organization
HPV	Human papillomavirus
HRSA	Health Resources and Services Administration
IAVG	Interagency Vaccine Group
ICD-9	International Classification of Diseases, 9 th Revision
IHS	Indian Health Service
IIS	Immunization Information Systems
IOM	Institute of Medicine
IPV	Inactivated Polio Vaccine
ISO	Immunization Safety Office (of the CDC)
ISTF	Immunization Safety Task Force
LLDB	Large linked databases
MCO	Managed care organization
MCV4	Quadrivalent meningococcal conjugate vaccine
MMR	Measles, Mumps, Rubella vaccine
MMR-V	Measles, mumps, rubella, varicella vaccine
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NCVIA	National Childhood Vaccine Injury Act of 1986
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Program
NVPO	National Vaccine Program Office
ONC	Office of the National Coordinator for Health Information Technology
OPV	Oral Polio Vaccine

Abbreviation	Definition
PCV	Pneumococcal conjugate vaccine
PCV-1	Porcine circovirus type 1
PRISM	Post-Licensure Rapid Immunization Safety Monitoring System
RCA	Rapid cycle analysis
RTIMS	Real Time Immunization Monitoring system
Tdap	Tetanus/Diphtheria/acellular pertussis vaccine
UK	United Kingdom
US	United States of America
VAERS	Vaccine Adverse Events Reporting System
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System
VAPP	Vaccine-associated paralytic polio
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
WHO	World Health Organization

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Appendix 2. National Vaccine Advisory Committee Vaccine Safety Working Group membership, non-Federal Government members.

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

* NVAC Member

† Working Group co-chair

§ NVAC Chair

Appendix 3. National Vaccine Advisory Committee Vaccine Safety Working Group, Federal ex officio representatives*

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

* Principal role was to provide information about aspects of the existing safety system rather than to formulate the Working Group's conclusions and recommendations.

Appendix 4. Agenda, with detailed panelist list, for VSWG kick-off meeting, July 15-16, 2009

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 Baciou, 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

Appendix 5. Information gathering briefings held by the VSWG biomechanisms subgroup

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

Appendix 6. Information gathering briefings held by the VSWG epidemiology and surveillance subgroup

- 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 7. Evaluation criteria

3/ 4/ 10 DRAFT EVALUATION CRITERIA

Note about this document: *These draft evaluation criteria should be used for discussion purposes only. They were prepared as a first draft to be considered by the VSWG and stakeholders more broadly. This document may lack necessary context without explanation. Please contact Heather Bergman of The Keystone Center with questions or comments related to this draft document. Ms. Bergman may be reached at hbergman@keystone.org.*

Draft Evaluation Criteria

The Vaccine Safety Working Group's charge is to review the current federal vaccine safety system and develop a White Paper describing the infrastructure needs for a federal vaccine safety system to fully characterize the safety profile of vaccines in a timely manner, reduce adverse events whenever possible, and maintain and improve public confidence in vaccine safety.

To that end, the criteria below will assist the Vaccine Safety Working Group (VSWG) in evaluating the relative strengths of both the current system and a range of alternatives. The evaluation criteria include three elements:

1. Draft essential functions of a vaccine safety system (*what* the system should do). Each system configuration (or "bundle") is expected to fulfill each of the essential functions.
2. Draft key performance attributes that must guide the execution of a vaccine safety system (*how* the system should work).
3. Draft factors for considering the feasibility of alternative approaches to vaccine safety (whether a given approach is viable at present)

Stakeholder Involvement

The VSWG will seek stakeholder feedback and input on the draft essential functions, key performance attributes, and feasibility factors under consideration. The VSWG is additionally interested in whether there are priority attributes for different system functions. Lastly, the VSWG seeks feedback regarding the system configurations.

Steps to Selecting a System Configuration that Further Strengthens the Vaccine Safety System

In preparation for developing their recommendations, it is proposed that the VSWG would engage in the following steps:

- a) Evaluate the current system or alternative system configurations based on how well each function is or would be performed. The goal of any proposed system should be to maximize the key performance attributes within each function. (Most or all of the key attributes are applicable to each function, although the importance of a given key performance attribute may vary from function to function.)
- b) Once each system configuration is evaluated in terms of the functions and key performance attributes, evaluate the system configuration in terms of the feasibility factors.
- c) The VSWG will seek to share some rationale for their final decisions and recommendations.

The following chart outlines the key performance attributes an ideal Vaccine Safety System would include. In some cases, these key performance attributes have been raised or supported by those external to the VSWG and we have outlined those comments in the third column.

Appendix 7 (cont). Evaluation criteria

KEY PERFORMANCE ATTRIBUTES	EXPLANATION	RELEVANT PUBLIC, STAKEHOLDER, AND IOM COMMENT RAISED DECEMBER 2008-DECEMBER 2009 ^{*5}
Accountability	Includes mechanisms to ensure that promises are kept, duties are performed, and compliance is forthcoming	Is there a way to increase citizen interaction, oversight, and dialogue with decision makers?*
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	Need accountability in the vaccine safety system.^ The National Vaccine Plan should incorporate concrete steps to expand and strengthen vaccine safety research, including: <ul style="list-style-type: none"> • enhanced funding for CDC’s Immunization Safety Office activities, including support of extramural research • enhanced funding for FDA’s safety monitoring activities • expansion of NIH vaccine safety activities to include research portfolios, funding through requests for proposals, program announcements, and creation of a study section dedicated to vaccine safety research Priority. Every effort should be made to fully understand the potential adverse events of vaccines.*^
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	<ul style="list-style-type: none"> • Does race or gender affect how well a vaccine will work, or what any adverse events might be?* • Are people with immune compromised systems more at risk for adverse events?* • Are the elderly at greater risk for adverse events?* • Are pre-mature babies more at risk for adverse events?* • Are pregnant women more at risk for adverse events?*

* Issues marked with an asterisk (*) indicate those that were raised in public and/or stakeholder meetings during Task 1 or through the Request for Information (RFI) issued as part of Task 1.

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⁵ Several issues raised in public meetings during Task 1 as concerns about vaccine safety do not directly relate to issues of governance and structure for a robust vaccine safety system. Although important concerns, these have not been included in this table. The excluded concerns are: manufacturing security, vaccine effectiveness, mandated vaccines, and the role of insurance companies in vaccination.

^ Issues marked with a caret (^) indicate those that were raised by stakeholders at the kickoff meeting on July 14-15, 2009.

KEY PERFORMANCE ATTRIBUTES	EXPLANATION	RELEVANT PUBLIC, STAKEHOLDER, AND IOM COMMENT RAISED DECEMBER 2008-DECEMBER 2009* ⁵
Evidence-Based Decision Making	Applies the best available data from the scientific method to formulate research questions, policies, and practices	How do we identify good, trustworthy information about the benefits, and especially the risks associated with vaccines?*
Initiative	Is self-starting in pursuit of opportunities to fulfill mission requirements	Evidence-based policy. While it is not always possible to know every potential ramification, every effort should be made to ground vaccine policy in vaccine safety evidence.^
Innovativeness	Pursues mission requirements with innovative thinking	
Objectivity	Acts without undue influence from those who have a stake in outcomes of safety assessment (programs promoting vaccines, advocacy organizations, litigants, etc.)	Desire for Independent Science* <ul style="list-style-type: none"> • Who's doing the science? • Is it trustworthy? • Worry about the government/ pharmaceutical connections Independent science. The real and perceived independence of the science is important. Every effort should be made to increase independence. Where this is impossible, additional transparency, peer review and monitoring should be built into the system.*^
Responsiveness	Responds to emerging issues in a timely manner	Agility. Coordination and authorities should enable the government to respond to emerging issues in a timely manner.^
Transparency	Provides access to information about science, process, and rationale for decisions regarding vaccine safety	Concern regarding secrecy of decision making, reporting, and studies* <p>Transparency. Wherever it is possible to increase transparency, this should be done. Thoughtful feedback to the public and others will increase confidence in the reporting system's effectiveness.*^</p> <p>The National Vaccine Plan should include the establishment and scope of work of a permanent NVAC vaccine safety subcommittee to:</p> <p>(a) provide guidance on the activities described in 2-1 and 2-2 in a public and transparent manner;</p> <p>(IOM)</p>

EVALUATION CRITERIA WORKSHEET

Tasks	National Vaccine Plan	Relevant Public, Stakeholder, and Advisory Committee Comments	System Configuration Evaluation
Authority, Oversight, and Leadership			
<ul style="list-style-type: none"> ● Identified 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 	<p>Objective 2.8: Enhance integration and collaboration of vaccine safety activities</p> <p>2.8.1 Improve collaboration, such as data sharing arrangements, across agencies and departments.</p> <p>2.8.2 Improve information and data sharing with international partners (e.g., national vaccine safety programs) as consistent with ethical and human subjects protections.</p>	<ul style="list-style-type: none"> ● Entity should have clear legislated authority (and resources to match) to coordinate and direct vaccine safety activities across government entities.^ ● This function should ensure high-level coordination, oversight, and dialogue from internal (government) and external stakeholders focused on vaccine safety.*^ ● A mechanism for increased coordination and collaboration among immunology, vaccinology, anthropology and other arenas should be required or encouraged.^ ● Multi-Stakeholder Coordination. This function should ensure high-level coordination, oversight, and dialogue from internal (government) and external stakeholders focused on vaccine safety.*^ ● Coordination. A mechanism for increased coordination and collaboration among immunology, vaccinology, anthropology and other arenas should be required or encouraged.^ 	

Tasks	National Vaccine Plan	Relevant Public, Stakeholder, and Advisory Committee Comments	System Configuration Evaluation
Licensing			
<ul style="list-style-type: none"> ● Licenses vaccines with acceptable safety profiles ● Ensures optimal manufacturing processes 	<p>Objective 2.1: Facilitate the continuous modernization of manufacturing sciences and regulatory approaches relevant to manufacturing, inspection and oversight to enhance product quality and patient safety.</p> <p>Strategy 2.1.1: Facilitate the enhancement of vaccine manufacturing sciences and quality systems, including production technologies, in process controls and testing, and identification of best practices in preventive quality systems and oversight.</p> <p>Strategy 2.1.2: Develop, implement and periodically reassess risk-based scientific approaches to identify inspectional priorities and best practices.</p> <p>Strategy 2.1.3: Support new technologies and modernization of both industry and FDA testing of product quality to better prevent and more rapidly detect potential quality or safety issues.</p> <p>Strategy 2.1.4: Evaluate current regulations, guidance documents, policies and procedures that are relevant to manufacturing to determine enhancements that could be made to promote and enhance product safety.</p>	<p>Emphasis should be on safety without regard to effectiveness or disease prevention.^</p>	

Tasks	National Vaccine Plan	Relevant Public, Stakeholder, and Advisory Committee Comments	System Configuration Evaluation
Monitoring			
<ul style="list-style-type: none"> • Detects potential signals of vaccine adverse events • Investigates associations between vaccination and outcomes for potential signals 	<p>Objective 2.2: Enhance timely detection and evaluation of vaccine safety signals.</p> <p>2.2.1: Improve the effectiveness and timeliness of AEFI signal identification and assessment through coordinated use of national Reporting Data: Is the data accurate? Are there ways to improve reporting? passive and active surveillance systems.*</p> <p>2.2.3: Assess lay public and professional questions and concerns about vaccine safety.</p> <p>2.2.4: Improve the process for assessing AEFI signals to determine which signals should be evaluated further in epidemiological and clinical studies.</p> <p>Objective 2.3. Improve timeliness of the evaluation of vaccine safety signals when a high priority new vaccine safety concern emerges, a new vaccine is recommended or vaccination recommendations are expanded, and during public health emergencies such as in an influenza pandemic or other mass vaccination campaign.</p> <p>2.3.1: Increase the size of the population under active surveillance for serious AEFIs that can be included in high quality, rigorously conducted epidemiological studies to test vaccine safety hypotheses.</p> <p>2.3.3: Enhance capacity to monitor immunization safety in the event of a mass vaccination campaign.</p>	<ul style="list-style-type: none"> • Reporting Data: Is the data accurate? Are there ways to improve reporting?* • Reporting metrics. Design metrics to measure quantity and quality of reporting by health practitioners and citizens. Use this information to improve reporting systems.^ • Quality Control. Ensure that active and passive systems are set up to encourage accurate and timely reporting of adverse events.*^ 	

Tasks	National Vaccine Plan	Relevant Public, Stakeholder, and Advisory Committee Comments	System Configuration Evaluation
Research			
<ul style="list-style-type: none"> ● 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 	<p>2.2.2: Enhance collection of medical histories and biological specimens from selected persons experiencing serious AEFI reported to the Vaccine Adverse Event Reporting System (VAERS), petitioning the National Vaccine Injury Compensation Program (VICP), and available through active surveillance to enhance study of biological mechanisms and individual risk factors.</p> <p>2.3.2: Expand collaboration with clinical, laboratory, genetic and statistical experts to conduct clinical research studies to investigate the role of host genetics in AEFI.</p> <p>Objective 2.5: Improve scientific knowledge about the risk of vaccine adverse events and their mechanisms.</p> <p>2.5.1 Identify host risk factors, such as previous or concurrent illness or genetic characteristics that may be associated with increased risk for specific AEFI through basic, clinical, or epidemiological research.</p> <p>2.5.2 Identify the biological mechanism(s) for specific AEFI that, based upon causality assessments (Strategy 2.4.2), are likely to be causally associated with vaccination.</p> <p>2.5.3 Assess whether the risk of specific AEFI is increased in specific populations such as pregnant women, premature infants, elderly persons, those with immunocompromising or other medical conditions, or based on gender or race/ethnicity.</p>	<ul style="list-style-type: none"> ● Potentially harmful ingredients* ● Schedule/number of vaccines given* ● Do vaccines trigger or contribute to other diseases?* ● Combinations of vaccines* ● Combinations of ingredients* ● Side effects (short-term, long-term)* ● Interactions with medicines, allergies, cosmetics, personal care products, environmental factors* ● Do vaccines cause the disease they target?* ● Study of vaccinated vs. un-vaccinated* ● Are some people pre-disposed to having adverse effects?* ● Are people with immune compromised systems more at risk for adverse events?* ● Are the elderly at greater risk for adverse events?* ● Are pre-mature babies more at risk for adverse events?* ● Are pregnant women more at risk for adverse events?* ● Specific questions about MMR, Gardasil, flu* <p>Fostering vaccine safety scientists. Finding ways to entice scientists into this career track is essential to high quality vaccine safety science.^</p> <p>Gaps in science make communication difficult.^</p> <p>There needs to be openness to asking vaccine safety questions. ^</p> <p>Expectations for assessing very rare adverse events are higher. ^</p> <p>Need to understand biologic underpinning, requires</p>	

Tasks	National Vaccine Plan	Relevant Public, Stakeholder, and Advisory Committee Comments	System Configuration Evaluation
	<p>Objective 2.7: Improve cross-cutting scientific capabilities to enhance vaccine safety and the vaccination safety system.</p> <p>2.7.1 Enhance the immunization safety science workforce to recruit and retain additional highly trained scientists and clinicians.</p> <p>2.7.2 Develop additional standard case definitions for AEFI for use in immunization safety surveillance and research, vaccine safety standards such as concept definitions, standardized abbreviations, and standardized study designs.</p> <p>2.7.3 Improve laboratory, epidemiological and statistical methods used in vaccine safety research.</p>	<p>protocols, networks of people, and expertise in those who know how to understand investigations. ^</p> <p>Need to expand systems for tracking and hypothesis testing; there are multiple modalities through which this could occur. ^</p> <p>The National Vaccine Plan should establish a process to identify potential vaccine safety hypotheses for further basic, clinical, or epidemiologic research through annual review of data from the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD) project, the Clinical Immunization Safety Assessment (CISA) network and the Vaccine Injury Compensation Program, and from information available from sources outside the U.S. (IOM)</p> <p>The National Vaccine Plan should emphasize the development and publication of a framework for prioritizing a national vaccine safety research agenda that spans all federal agencies and includes all stakeholders, including the public. (IOM)</p>	
Causality Assessment			
<p>Conducts assessments to determine whether an adverse event is caused by vaccines or vaccination</p>	<p>Objective 2.4: Improve causality assessments of vaccines and related AEFIs.</p> <p>2.4.2 Assess the evidence on a population level for a causal relationship between certain vaccines and specific serious AEFI.</p>		
Injury Compensation			
<p>Compensates individuals who experience vaccine adverse events</p>	<p>2.4.3 Regularly update the Vaccine Injury Table based upon individual and population level causality assessments.</p>		

Tasks	National Vaccine Plan	Relevant Public, Stakeholder, and Advisory Committee Comments	System Configuration Evaluation
Practice			
<ul style="list-style-type: none"> • 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 	<p>2.4.1 As appropriate, develop algorithms and assess the evidence on an individual-level for a causal relationship between certain vaccines and specific serious AEFI.</p> <p>Objective 2.6: Improve clinical practice to prevent, identify and manage AEFIs.</p> <p>2.6.1 Improve training, availability of and access to vaccine safety clinical experts to provide consultation to healthcare providers and public health practitioners.</p> <p>2.6.2 Develop additional evidence-based guidelines for vaccination or revaccination, as appropriate, for persons at increased risk of AEFI. Identify additional contraindications and precautions to vaccination, as needed.</p> <p>2.6.3 Reduce errors in vaccine administration (e.g., wrong vaccine, dose, injection site, or timing) and associated adverse patient outcomes.</p>	<p>More clinical education about vaccines in medical school and questions about vaccines on Board exams is needed. ^</p>	

Tasks	National Vaccine Plan	Relevant Public, Stakeholder, and Advisory Committee Comments	System Configuration Evaluation
Communications			
<ul style="list-style-type: none"> • 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 	<p>Objective 3.3: Enhance delivery of timely, accurate, and transparent information to public audiences and key intermediaries (such as media) about what is known and unknown about the benefits and risks of vaccines and the vaccination program.</p> <p>3.3.1 Enhance communication of scientific findings about vaccine safety and effectiveness studies to the public, partners, and providers in a clear, transparent and timely manner.</p> <p>3.3.2 Consistently and effectively respond in a rapid and coordinated manner to emerging vaccine issues and concerns (e.g. supply, safety or public health emergencies).</p> <p>3.3.3 More rapidly and completely disseminate research findings through peer-reviewed journals, conferences, and partner communications to facilitate implementation of evidence-based strategies.</p>	<ul style="list-style-type: none"> • How do we identify good, trustworthy information about the benefits, and especially the risks associated with vaccines?* • How do we ensure that our doctors can spend quality time with patients talking about the benefits and risks of vaccination?* • Provide accurate, timely information on issues pertaining to vaccine safety. Be clear and honest regarding what is known and unknown.* • Feedback to states, providers, and individuals. Create feedback systems that share information with those that submit reports to the system.*^ <p>Communications should be honest about what we know and what we don't know, and research should be done on how to improve delivery of messages. ^</p> <p>The National Vaccine Plan should include the establishment and scope of work of a permanent NVAC vaccine safety subcommittee to:</p> <p>(c) publish on a biennial basis a review of: potential safety hypotheses; current vaccine safety activities including those of pre- and post-licensure studies, VAERS, VSD, and CISA; and planned priorities for research. (IOM)</p>	

Tasks	National Vaccine Plan	Relevant Public, Stakeholder, and Advisory Committee Comments	System Configuration Evaluation
Engagement			
<ul style="list-style-type: none"> Involves the public and stakeholders in dialogue about issues of concern and priorities for the vaccine safety system 	<p>2.2.3: Assess lay public and professional questions and concerns about vaccine safety.</p>	<ul style="list-style-type: none"> Citizen participation and oversight* Parental and scientific concerns are important, valid, and should be respected* Input on important decisions. Because herd immunity relies on high confidence in the safety of vaccines (and government and pharmaceuticals), it is important to regularly engage stakeholders/thought leaders/public in meaningful dialogue about safety concerns and priorities facing the vaccine safety system.*^ Access to decision makers. It is recognized that government cannot give away its authorities, but an improved vaccine safety system would find mechanisms for ongoing constructive dialogue between high-level decision-makers and key stakeholders or members of the public.* Oversight. To the extent there are ways to increase the number of citizen perspectives on existing boards or to create a separate oversight board with a broad mandate, this may increase confidence in any future vaccine safety system. Involvement and oversight for each functional component of the vaccine safety system will likely contribute to increased confidence in the overall system.*^ <p>The National Vaccine Plan should emphasize the development and publication of a framework for prioritizing a national vaccine safety research agenda that spans all federal agencies and includes all stakeholders, including the public. (IOM)</p>	

FEASIBILITY CRITERIA WORKSHEET

Politically Feasible			
Administratively Feasible			
Fiscally Feasible			

Appendix 8. Key vaccine safety system functions as identified by the Vaccine Safety Working Group.

Function 1. Authority, Oversight, and Leadership

- Identified 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; and
- 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; and
- Ensures optimal manufacturing processes.

Function 3. Monitoring

- Detects potential signals of vaccine adverse events; and
- 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; and
- Assesses individuals who may have experienced vaccine adverse events for additional investigation and analysis.

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

Appendix 9. Attributes of a vaccine safety system identified by the Vaccine Safety Working Group.

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 (programs promoting vaccines, advocacy organizations, litigants, etc.)
Responsiveness	Responds to emerging issues in a timely manner
Transparency	Provides access to information about science, process, and rationale for decisions regarding vaccine safety

Appendix 10. April 11-13, 2010 Salt Lake City meeting memorandum

**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.

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

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

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

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

On June 1, 2010⁶ the VSWG will host an open stakeholder meeting in Washington, D.C., to gain further feedback from interested stakeholders on the vaccine safety system. The Salt Lake City Writing Group has provided valuable feedback that will help the VSWG further refine materials for the June 1 meeting.

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