Understanding the Role of Human Variation in Vaccine Adverse Events: The Clinical Immunization Safety Assessment Network

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KEY WORDS
CISA Network, vaccine safety, adverse events following immunization

ABBREVIATIONS
AEFI—adverse event(s) following immunization
CISA—Clinical Immunization Safety Assessment
CDC—Centers for Disease Control and Prevention
VAERS—Vaccine Adverse Events Reporting System
ISO—Immunization Safety Office
VHC—Vaccine Healthcare Centers
NVAC—National Vaccine Advisory Committee

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(Continued on last page)
Successful implementation of widespread immunization programs in the United States has resulted in a dramatic decline in the incidence of life-threatening vaccine-preventable diseases. However, at the same time, rare adverse events following immunization (AEFI) have received increased attention from parents, health care providers, and the news media. Clinically significant AEFI are so uncommon that it is difficult for health care professionals to provide standardized evaluation, diagnosis, and management for an individual patient’s AEFI. The Clinical Immunization Safety Assessment (CISA) Network was conceived in response to the need for vaccine-safety risk assessment to investigate the role of individual variability and host risk factors in the occurrence of an AEFI as well as for clinical guidance on complex vaccine-safety questions from health care providers and the public.

The Centers for Disease Control and Prevention (CDC) created the CISA Network in 2001 to improve the scientific understanding of vaccine safety at the individual “patient” level. A network comprising clinical academic centers in partnership with the CDC serves as a source of clinical expertise in evaluating and treating AEFI and conducting clinical research on immunization-associated health risks.

The primary goals of the CISA Network include (1) developing research protocols for clinical evaluation, diagnosis, and management of AEFI, (2) improving the understanding of AEFI at the individual level, including determining possible genetic and other risk factors for predisposed people and subpopulations at high risk, (3) developing evidence-based algorithms for vaccination of people at risk of serious AEFI, and (4) serving as subject-matter experts for clinical vaccine-safety inquiries (see Table 1).

The CISA Network advises clinicians on the evaluation, diagnosis, and management of AEFI. The network conducts research through establishment of working groups for clinical consultations; for study of specific adverse events using institutional review board–approved, standardized protocols; and for evaluation of overarching immunization-safety issues such as hypersensitivity and causality. These data will be used to improve the scientific understanding of AEFI and develop protocols or algorithms for health care professionals that will assist in evaluation, diagnosis, and management of patients.

The CISA Network actively collaborates with the Vaccine Adverse Events Reporting System (VAERS) and Vaccine Safety Datalink (VSD) within the Immunization Safety Office (ISO) at the CDC.1 Simply put, the VAERS identifies signals of potential AEFI, the VSD investigates the epidemiologic and statistical significance of those signals, and the CISA Network conducts clinical research studies to evaluate these adverse events, including their pathogenesis and possible causal relationships with vaccine, and provides advice and algorithms regarding management and administration of subsequent doses of vaccine.

The Vaccine Healthcare Centers (VHC) Network, established initially as a collaborative program between the Department of Defense and the CDC, is a comparable entity within the military health system to the CISA Network in the civilian sector and has been described in a Government Accountability Office report (www.gao.gov/new.items/d07787r.pdf). The VHC was developed to support improved evaluation, treatment, and reporting of AEFI in service personnel.

In this report we review the accomplishments of the CISA Network to date in understanding the role of human variation in vaccine adverse events.

### METHODS

#### Academic Centers

The clinical academic centers include Johns Hopkins University Bloomberg School of Public Health (Baltimore, MD), University of Maryland (Baltimore, MD) (2001–2005), Northern California Kaiser Permanente, Kaiser Permanente Vaccine Study Center (Oakland, CA), Stanford University School of Medicine (Palo Alto, CA), Vanderbilt University Medical Center (Nashville, TN), Boston University Medical Center (Boston, MA), and Columbia University (New York, NY).

#### Working-Group Model

The CISA Network is structured around a series of working groups for specific immunization-safety topics (outlined in Table 2). Current CISA working groups address general immunization-safety issues (eg, clini-

### TABLE 1 CISA Network Initiative

<table>
<thead>
<tr>
<th>Objective</th>
<th>Description</th>
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<tr>
<td>Mission</td>
<td>Design and conduct research of immunization-associated adverse events and individual variation</td>
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<td>Supply providers and the public with evidence-based algorithms when considering vaccination of those at risk for AEFI</td>
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<tr>
<td>Goals</td>
<td>Study the pathophysiologic basis of AEFI by using hypothesis-driven protocols</td>
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<td></td>
<td>Study risk factors associated with developing an AEFI by using hypothesis-driven protocols including genetic host risk factors</td>
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<tr>
<td></td>
<td>Provide clinicians with evidence-based algorithms when evaluating AEFI</td>
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<tr>
<td></td>
<td>Provide immunization algorithms and clinical management protocol for patients at high risk</td>
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<tr>
<td></td>
<td>Serve as subject-matter experts for clinical vaccine-safety inquiries</td>
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1. Larussa et al. (2006).
Each working group convenes monthly conference calls, during which a complex vaccine-safety question/concern/issue is addressed in a structured format. For example, on the monthly Clinical Case Consult Review and Hypersensitivity working-group calls, an investigator presents a case, which includes the history of present illness (the AEFI) and detailed physical and diagnostic (laboratory and other) findings. A literature review on this subject and a summary of the VAERS data are also presented. The experts discuss the findings and formulate a general assessment and plan. When appropriate, these conclusions are shared with the concerned provider, and the provider frequently participates in the call. Vaccine-safety questions come from a variety of sources including the CDC information hotline (1-800-CDC-INFO), e-mail, and calls to the ISO and individual CISA sites. Although the CISA Network cannot address all vaccine-safety concerns, it makes every effort to provide support for these important questions.

The mechanism for a CISA Network consultation is outlined in Fig 1. Cases can be referred either directly to individual CISA investigators or indirectly through referrals from the CDC. CISA Network personnel contact the referring physician, obtain informed consent from the vaccine recipient or parent, collect relevant clinical and laboratory data, and see the person in consultation, if needed, at one of the CISA Network centers. Cases are then presented to the Clinical Case Consult Review Working Group or other relevant working groups. The working-group conference calls are composed of CISA Network investigators, subspecialists in allergy and immunology and neurology affiliated with CISA Network agencies/institutions, and outside experts if needed. Issues such as whether the event was causally related to the immunization, the medical management of the event, and the advisability of revaccination are discussed, and recommendations are made. Information is transmitted to the requesting physician or health care provider in a written communication.

Special Studies
The CISA Network has developed an infrastructure for proposing, evaluating, and initiating multicentered immunization-safety projects. Proposals are considered from both within and outside of the funded CISA Network centers. A concept sheet is submitted, internal and external expert reviewers are chosen, and the initial proposal is presented, discussed, and accepted or rejected by a majority vote of the CISA Network investigators. Accepted proposals are more fully developed and then resubmitted for final approval. It is typical for several CISA Network centers to participate in approved protocols. All of the centers have developed local and regional networks of collaborating health care providers who can refer patients to the local CISA Network center for evaluation or participation in an ongoing study. Subjects with conditions that are under investigation can be referred to a CISA Network center to discuss participation in an ongoing study. Other referred patients have conditions that may be vaccine related but...
for which there is no relevant ongoing study. All CISA Network centers have an institutional review board–approved protocol for maintaining a deidentified electronic vaccine consult registry and central specimen repository to allow for collection of clinical data and relevant biological specimens from subjects with AEFI. These data and samples will be available for future investigations, which will use newer diagnostic methods (see below).

Collaborations
Regular CISA Network collaborators include the VHC Network, Health Services Resource Administration, the US Food and Drug Administration, the National Vaccine Program Office, and the National Institutes of Health. These collaborations have been a valuable source of additional expertise to allow the CISA Network to better study emerging risks.

RESULTS
CISA Working Groups
Clinical Case Consult Review
The primary goal of this working group is to provide expert consultation for physicians caring for people who have had an adverse event that was temporally associated with immunization. More than 100 cases were evaluated in the first 3 years of the project (2004–2006). The main reasons for referral included causality assessment, management of the adverse event, and questions about revaccination. The results of these CISA Network clinical case consults have been useful in building a collective knowledge base about adverse events potentially associated with vaccination.

Hypersensitivity
The Hypersensitivity Working Group reviews clinical cases to evaluate the strength of the causal relationship between the hypersensitivity reaction and vaccination, the need for intradermal skin testing, and the advisability of revaccination. To date, >50 patients have been evaluated, and some of their cases have also been reviewed by the Clinical Case Consult Review Working Group (see above).

The Hypersensitivity Working Group developed standardized algorithms for evaluating and managing persons who have suspect or definite immediate hypersensitivity reactions such as urticaria, angioedema, and anaphylaxis after vaccines. This review presented background information on vaccine hypersensitivity and incorporated a detailed algorithm that provided a rational and organized approach for the evaluation and management of patients with suspected vaccine reactions. The Hypersensitivity Working Group is currently working on developing similar standardized algorithms for evaluating and managing persons suspected to have experienced a delayed hypersensitivity reaction.

The development of these algorithms indicated the need to assess the appropriate dilution of vaccines to be used for intradermal (intracutaneous) skin testing, if such testing is indicated. A clinical trial was conducted and revealed that prick (puncture) skin testing with full-strength vaccine is unlikely to be complicated by irritant effects and that irritant effects are uncommon when a 1:100 dilution is used by the intradermal route but that undiluted intradermal testing can result in irritant effects that result in false-positive test results for some vaccines.

Causality
CISA Network investigators have published a summary of the scientific method for review of causal associations between vaccines and adverse events and provided critical reviews of the assessment of adverse events after anthrax vaccine.5,6 The Causality Assessment Working Group has developed an algorithm to assist with the standardized and transparent evaluation of potential causal relationships between an adverse event and a preceding immunization. The Causality Assessment Working Group has developed an algorithm to assist with the standardized and transparent evaluation of potential causal relationships between an adverse event and a preceding immunization. An algorithm with illustrative cases is in preparation for publication.

Ongoing and completed projects of the CISA Network are listed in Table 3. The following describes selected examples.

Examples of CISA Studies

Active Telephone Surveillance to Evaluate Adverse Events Among Civilian Smallpox Vaccine Recipients
To characterize and actively monitor adverse events after Dryvax (Wyeth Laboratories, Marietta, PA) vaccinia vaccination in civilian health care workers and first responders, 825 recipients of Dryvax vaccine were interviewed by telephone. Although 12.5% reported missing work because of vaccine adverse events, most adverse events were anticipated and of short duration. This approach was used as a model for active surveillance of adverse events during the influenza A (H1N1) 2009 monovalent vaccine campaign.

Adverse Events Reported After Trivalent Inactivated Influenza Vaccine in Children Aged 6 to 23 Months
In October 2003, the Advisory Committee on Immunization Practices recommended universal influenza vaccination for children aged 6 to 23 months. In collaboration with the Food and Drug Administration, Vanderbilt

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University, and the University of Maryland, the CISA Network evaluated the safety of the expanded influenza vaccine recommendations.7 One-hundred and four serious AEFI were identified in the VAERS database after trivalent inactivated influenza vaccine (TIV); 60% of the reports occurred after TIV administration with other vaccines. The 2 most common serious AEFI were fever (n = 52) and seizure (n = 35). No new or unexpected safety concerns were identified with expanded TIV use.

**Transverse Myelitis and Vaccines**

Working with a team of neurologists, CISA Network investigators developed a standardized algorithm for identification and assessment of possible causes of acute transverse myelopathy. An ongoing study will determine if there is an association between vaccines and idiopathic transverse myelitis and will compare the clinical characteristics of idiopathic transverse myelitis with onset in the 6-week period after vaccines with transverse myelitis not temporally associated with vaccines.8

**Role of Genetics in the Immune Response to the Varicella Vaccine**

This assessment of immune responses to varicella vaccine within sibling pairs was conducted by CISA Network investigators. The evaluation revealed that post–varicella immunization antibody titers within sibling pairs clustered more often than in nonsibling pairs, which supports the hypothesis that genetic factors play a role in the antibody response to the varicella vaccine.9

**Recurrent Sterile Abscesses After Immunization**

This study examined 3 children with recurrent sterile abscesses after immunization and proposed a role of aluminum adjuvant in the development of sterile abscesses after immunization.10

**Collaborations**

CISA Network investigators have participated in the development of Brighton Collaboration’s case definitions for encephalopathy,11 nodules at the injection site,12 generalized convulsive seizures,13 and smallpox vaccine–associated adverse events.14–18 The Johns Hopkins CISA site participated in the comparison of 6 Brighton case definitions of AEFI with expert clinicians. This site recruited and supervised the clinical specialists and subspecialists in pediatrics, neurology, and gastroenterology who reviewed several hundred VAERS reports as part of the validation process.19 CISA Network investigators have played a key role in coordinating the assessment of the validity of Brighton case definitions for intussusception, seizures, and hypotensive hyporesponsive episodes.

Although use of smallpox vaccine in the civilian sector was limited, as of January 2008, >2 million US Department of Defense personnel have been vaccinated (personal communication, Military Vaccine Agency and Immunization Registry, updated January, 2011). A partnership was established between the CISA Network, the VHC Network, and the University of Washington to develop and implement a study to explore the possibility of a genetic predisposition to developing myopericar-

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**TABLE 3 CISA Network Key Accomplishments and Ongoing Projects**

<table>
<thead>
<tr>
<th>Ongoing projects</th>
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<tr>
<td>Clinical risk assessment of new cases of GBS after immunization, including immune response and DNA studies</td>
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<tr>
<td>Clinical risk assessment of myopericarditis after smallpox vaccination, including immune responses and DNA studies</td>
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<tr>
<td>Retrospective Review of Safety and efficacy of live attenuated viral vaccines in patients with DiGeorge syndrome</td>
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<tr>
<td>Ongoing registry that allows for enrollment of persons who experience an AEFI and the ability to store specimens for future studies</td>
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<tr>
<td>Ongoing centralized immunization-safety repository of biological specimens</td>
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<tr>
<td>Ongoing 2-year fellowship in vaccine safety</td>
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<tr>
<td>Genetics of GBS: investigation of vaccine-associated and non–vaccine-associated GBS</td>
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<tr>
<td>The genomics of wheezing and variable immune response after influenza vaccination in infants</td>
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<tr>
<td>Review of immunization practices and safety among children with mitochondrial and metabolic disorders</td>
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<tr>
<td>Acute disseminated encephalomyelitis after immunization</td>
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<tr>
<td>Encephalitis/encephalopathy and measles-mumps-rubella vaccine</td>
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<tr>
<td>Gelatin case-control study to evaluate immediate hypersensitivity after immunization Bell’s palsy after immunizations</td>
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</table>

**Key accomplishments**

Developed an evidenced-based algorithm for managing individuals with vaccine hypersensitivity reaction following vaccination7

Developed and evaluated an algorithm for assessing causality in the evaluation of AEFI1

Evaluated adverse reactions after the fifth dose of DTaP25

Assessed the role for genetics in the immune response to the varicella vaccine3

Evaluated adverse events among civilian smallpox vaccine recipients via telephone surveillance26

Evaluated cases of viscerotropic and neurotropic illness after yellow fever vaccine32

Determined via case-control study of SV40 and non-Hodgkin lymphoma that past infection with SV40 is not associated with increased risk of developing non-Hodgkin lymphoma37

Evaluated risk factors for developing apnea after immunization in the NICU25

Studied immunogenicity and safety of vaccines administered to premature infants34

Evaluated AEFI after yellow fever vaccine via active surveillance12

Evaluated cases of disseminated encephalitis/encephalopathy and measles-mumps-rubella vaccine13

Studied alopecia associated with hepatitis B vaccination by using a mouse model19

Evaluated immunization rates and safety among children with inborn errors of metabolism9

Evaluated hyperammonemic events are not associated with a 21-d postvaccination window in 90 children with urea cycle disorders31

GBS indicates Guillain–Barré Syndrome; IRB, institutional review board; SV40, simian virus 40; DTaP, diphtheria-tetanus-acellular pertussis.
Few studies have been published on the genetic risk factors for AEFI. The CDC has lead responsibility for monitoring the safety of vaccines licensed for use in the United States and for performing research to inform safe vaccination practices. The CDC is working with partners to study the relationship between human genetics and vaccine safety. Identifying genetic associations and risk of serious AEFI eventually may allow

- screening for markers of susceptibility;
- improved guidance for vaccination; and
- development of safer vaccines.

The CDC’s ISO has begun a genomics initiative to (1) develop a scientific approach to understanding the genetic basis for vaccine adverse events and their proper public applications, (2) increase cooperation between federal agencies, academia, and industry, (3) perform studies to identify genes that may be associated with an increased risk for AEFI, and (4) identify strategies for integrating genomics into vaccine safety. On January 30 through 31, 2008, the ISO held a conference, “Understanding the Genomic Basis of Vaccine Safety,” that brought together representatives of the CDC, the Food and Drug Administration, the VHC Network, research universities, and vaccine manufacturers. Those who attended the conference discussed a systematic approach to research into the genetics of immunization safety.

**Immunization Safety BioBank Initiative**

Because many AEFI are rare, it is difficult to have a sufficient number of cases to have the power to adequately evaluate risk factors, including genetic risk factors. Thus, the CISA Network began a postimmunization adverse-event clinical registry and specimen repository (ie, the Immunization Safety BioBank) to "bank" sufficient biological specimens and associated clinical information in anticipation of future studies to assess genetic and immunologic host factors that may predispose people to selected AEFI. A steering committee is currently being formed that is composed of CDC/ISO staff and other government officials, CISA Network investigators, and consultants. The steering committee will refine which AEFI will be included in the repository, review protocols for collecting specimens and medical histories, develop a long-term strategy to guide access for researchers, enhance coordination with existing assets, and advise on an outreach program to collect and transfer biological specimens in persons with AEFI, including recruitment from specialty clinics and from the VAERS.

**Training of Future Investigators With Expertise in Vaccine Safety**

To date, 2 CISA Network–funded, 2-year, postdoctoral vaccine-safety trainees have completed their fellowships. Both have published articles that resulted from their CISA Network–related fellowship investigations23,24 and are pursuing academic careers in vaccine safety. A third 2-year CISA fellowship was recently awarded in the 2008–2009 academic year with the main goal of performing a self-controlled case-series study of the pediatric population within the California Encephalitis Project to determine the relative incidence of encephalopathy/encephalitis that occurs after immunization with pertussis- or measles-containing vaccines. In addition to the formal CISA-fellowship program, the CISA Network centers have actively involved pediatric infectious diseases fellows in CISA Network–related projects and provide supplementary funding for their participation with the CISA Network. Pediatric infectious dis-
CONCLUSIONS
The CISA Network of 6 vaccine-safety centers has accomplished much over the first 9 years of its existence. The infrastructure and expertise are in place to evaluate new potential vaccine-related adverse events and advise clinicians and vaccine recipients on the management of known AEFI and the advisability of revaccination if appropriate. Vital collaborations with other vaccine-safety programs have been initiated and will need to be strengthened. Finally, a new generation of vaccine-safety experts is being trained by the CISA Vaccine Safety fellowship program to be able to address future vaccine-safety concerns. Current information about the CISA Network can be found online (www.cdc.gov/vaccinesafety/Activities/CISA.html).

Vaccine-safety surveillance for many years has used epidemiologic methods to assess causality, but these methods cannot address rare but serious adverse events or provide the clinical expertise to evaluate individual complex causality assessments. As demonstrated by the World Health Organization Causality Assessment Guidelines (www.who.int/vaccines-documents/DocsPDF05/815.pdf), there is international interest and concern about the issues that may affect vaccine trust and the credibility of safety surveillance in particular. The CISA Network represents a credible national commitment to tackle the many issues that are not so easily addressed by epidemiologic database studies and is well positioned to respond to new questions as they arise with the release of new vaccines or new questions about older vaccine combinations.

In response to a 2005 Institute of Medicine recommendation (www.iom.edu/CMSS3793/21144/25184.aspx) and to guide the ISO’s scientific direction, the office developed a 5-year scientific research agenda to guide its vaccine-safety science in 3 areas: research; surveillance (monitoring); and guidance for health care providers. This ISO scientific agenda was developed with input from federal, academic, and vaccine manufacturer scientists as well as a group of vaccine-safety stakeholders. The Department of Health and Human Services conducted an external review process, with oversight of the National Vaccine Advisory Committee (NVAC), to provide advice on the most important research topics on which the ISO should focus during the next 5 years. To better understand the biological mechanisms of action responsible for AEFI, the NVAC recommended that the CISA Network conduct clinical research on the pathophyslogic basis of adverse events. There were several identified research needs that specifically fall under the purview of the CISA Network: (1) study of the molecular immune responses to vaccinations, including common adverse events such as fever or rash, as subclinical correlates that might predict severe adverse events; and (2) the NVAC further recommended that the ISO create an expert advisory group on genomics and vaccine safety to assist with developing a focused genomics research agenda and protocol development. The NVAC recommended that the ISO create a single written guide dedicated to comprehensive clinical guidance, including identification, reporting, and treatment, for AEFI. The NVAC recommended that the ISO include the vaccination of children with mitochondrial disease, mitochondrial dysfunction, and other metabolic diseases as a priority scientific area for research to develop clinical guidance. In addition, the NVAC recommended periodic external review of the Vaccine Safety Datalink and CISA research and the ISO scientific agenda more broadly. The ISO is currently preparing a response to the NVAC recommendations. The CISA Network findings assist domestic and global vaccine-safety policy-makers and thereby enhance public confidence and sustain immunization benefits for all populations. The CISA Network is uniquely suited to study postlicensure vaccine safety in special populations because of its access to both the special populations and the specialists who care for them.

In addition, people with rare and serious AEFI can be referred to the CISA Network for collection of clinical data and relevant biological specimens for inclusion in the institutional review board—approved CISA Vaccine Safety BioBank to facilitate future, yet-to-be-defined investigations.

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