

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

**AUTHORS:** Philip S. LaRussa, MD,<sup>a</sup> Kathryn M. Edwards, MD,<sup>b</sup> Cornelia L. Dekker, MD,<sup>c</sup> Nicola P. Klein, MD, PhD,<sup>d</sup> Neal A. Halsey, MD,<sup>e,f</sup> Colin Marchant, MD,<sup>g</sup> Roger Baxter, MD,<sup>d</sup> Renata J. M. Engler, MD,<sup>h</sup> Jennifer Kissner, PhD,<sup>b</sup> and Barbara A. Slade, MD, MS<sup>i</sup>

<sup>a</sup>Department of Pediatrics, Division of Pediatric Infectious Diseases, Columbia University, New York; <sup>b</sup>Vanderbilt Vaccine Research Program, Department of Pediatrics, Vanderbilt University, Nashville, Tennessee; <sup>c</sup>Department of Pediatrics, Division of Pediatric Infectious Diseases, Stanford University School of Medicine, Stanford, California; <sup>d</sup>Kaiser Permanente Vaccine Study Center, Oakland, California; <sup>e</sup>Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland; <sup>f</sup>Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; <sup>g</sup>Department of Pediatrics, Boston Medical Center, Boston, Massachusetts; <sup>h</sup>Vaccine Healthcare Centers Network/National Branch, Walter Reed Army Medical Center, Washington, DC; and <sup>i</sup>Centers for Disease Control and Prevention, Atlanta, Georgia

## 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

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the funding agency.

[www.pediatrics.org/cgi/doi/10.1542/peds.2010-1722J](http://www.pediatrics.org/cgi/doi/10.1542/peds.2010-1722J)

doi:10.1542/peds.2010-1722J

Accepted for publication Nov 29, 2010

Address correspondence to Philip LaRussa, MD, Professor of Clinical Pediatrics, Columbia. E-mail: [plarussa@columbia.edu](mailto:plarussa@columbia.edu)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2011 by the American Academy of Pediatrics

**FINANCIAL DISCLOSURE:** Dr LaRussa receives contract funding from the National Institutes of Health (NIH) and the CDC and currently serves on a Novartis data safety monitoring board; Dr Edwards receives contract funding from the NIH and the CDC, has received contract support within the past 3 years from Sanofi Pasteur, Novartis, Wyeth, and CSL for the conduct of clinical vaccine studies, and has served as a consultant to

(Continued on last page)

## abstract

The Clinical Immunization Safety Assessment (CISA) Network is a collaboration between the Centers for Disease Control and Prevention (CDC) and 6 academic medical centers to provide support for immunization safety assessment and research. The CISA Network was established by the CDC in 2001 with 4 primary goals: (1) develop research protocols for clinical evaluation, diagnosis, and management of adverse events following immunization (AEFI); (2) improve 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) develop evidence-based algorithms for vaccination of people at risk of serious AEFI; and (4) serve as subject-matter experts for clinical vaccine-safety inquiries. CISA Network investigators bring in-depth clinical, pathophysiologic, and epidemiologic expertise to assessing causal relationships between vaccines and adverse events and to understanding the pathogenesis of AEFI. CISA Network researchers conduct expert reviews of clinically significant adverse events and determine the validity of the recorded diagnoses on the basis of clinical and laboratory criteria. They also conduct special studies to investigate the possible pathogenesis of adverse events, assess relationships between vaccines and adverse events, and maintain a centralized repository for clinical specimens. The CISA Network provides specific clinical guidance to both health care providers who administer vaccines and those who evaluate and treat patients with possible AEFI. The CISA Network plays an important role in providing critical immunization-safety data and expertise to inform vaccine policy-makers. The CISA Network serves as a unique resource for vaccine-safety monitoring efforts conducted at the CDC. *Pediatrics* 2011;127:S65–S73

Successful implementation of wide-spread 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).

**TABLE 1** CISA Network Initiative

Mission	Design and conduct research of immunization-associated adverse events and individual variation
	Supply providers and the public with evidence-based algorithms when considering vaccination of those at risk for AEFI
Goals	Study the pathophysiologic basis of AEFI by using hypothesis-driven protocols
	Study risk factors associated with developing an AEFI by using hypothesis-driven protocols including genetic host risk factors
	Provide clinicians with evidence-based algorithms when evaluating AEFI
	Provide clinicians with evidence-based vaccination or revaccination algorithms
Objectives	Develop clinical protocols for the evaluation and management of AEFI
	Evaluate patients with similar AEFI by using a standard protocol and assess genetic or other risk factors that may predispose groups at high risk to specific AEFI
	Provide immunization algorithms and clinical management protocol for patients at high risk
	Serve as subject-matter experts for clinical vaccine-safety inquiries

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.<sup>1</sup> Simply put, the VAERS identifies signals of potential AEFI, the VSD investigates the epidemiologic and statistical sig-

nificance 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](http://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 2** CISA Network Working Groups

Administrative
Bell's Palsy
Causality
Clinical Case Consult Review
Diphtheria Tetanus Acellular Pertussis Vaccine
Hypersensitivity
Measles Mumps Rubella Encephalitis/ Encephalopathy
Nurse/Coordinator
Immunization Safety BioBank
Smallpox-Myocarditis
VAERS Case Review
DiGeorge Syndrome
Children With Metabolic/Mitochondrial Disorders
Autoimmunity and Autoimmune Diseases
Guillain-Barré Syndrome
Rotavirus
Yellow Fever

cal case consult review, hypersensitivity, causality assessment) or specific CISA immunization-safety studies (eg, Guillain-Barré syndrome, children with metabolic and mitochondrial disorders, rotavirus vaccines, DiGeorge syndrome). The membership of the working groups varies according to the investigators' particular areas of interest and expertise, and not all sites are members of all working groups. However, all the sites of co-investigators listed in a specific CISA study protocol are automatically represented on the associated working group.

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 pro-

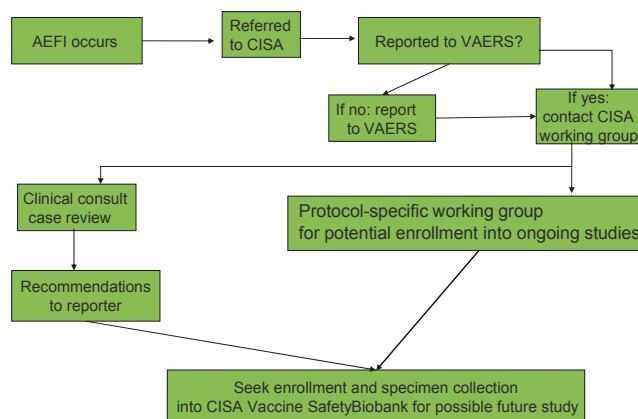
vider frequently participates in the call. Vaccine-safety questions come from a variety of sources including the CDC information hotline (1-800-CDC-INFO), e-mail, and calls to the ISO and individual CISA sites. Although the CISA Network cannot address all vaccine-safety concerns, it makes every effort 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



**FIGURE 1** CISA Network consultation process.

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.<sup>2</sup> 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.<sup>3</sup>

#### *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.<sup>4,5</sup> 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.<sup>6</sup> 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

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

Ongoing projects	
Clinical risk assessment of new cases of GBS after immunization, including immune response and DNA studies	
Clinical risk assessment of myopericarditis after smallpox vaccination, including immune responses and DNA studies	
Retrospective Review of Safety and efficacy of live attenuated viral vaccines in patients with DiGeorge syndrome	
Ongoing registry that allows for enrollment of persons who experience an AEFI and the ability to store specimens for future studies	
Ongoing centralized immunization-safety repository of biological specimens	
Ongoing 2-year fellowship in vaccine safety	
Genetics of GBS: investigation of vaccine-associated and non-vaccine-associated GBS	
The genomics of wheezing and variable immune response after influenza vaccination in infants	
Review of immunization practices and safety among children with mitochondrial and metabolic disorders	
Acute disseminated encephalomyelitis after immunization	
Encephalitis/encephalopathy and measles-mumps-rubella vaccine	
Gelatin case-control study to evaluate immediate hypersensitivity after immunization Bell's palsy after immunizations	
Key accomplishments	
Developed an evidenced-based algorithm for managing individuals with vaccine hypersensitivity reaction following vaccination <sup>2</sup>	
Developed and evaluated an algorithm for assessing causality in the evaluation of AEFI <sup>5</sup>	
Evaluated adverse reactions after the fifth dose of DTaP <sup>25</sup>	
Assessed the role for genetics in the immune response to the varicella vaccine <sup>9</sup>	
Evaluated adverse events among civilian smallpox vaccine recipients via telephone surveillance <sup>6</sup>	
Evaluated cases of viscerotropic and neurotropic illness after yellow fever vaccine <sup>26</sup>	
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 lymphoma <sup>27</sup>	
Evaluated risk factors for developing apnea after immunization in the NICU <sup>23</sup>	
Studied immunogenicity and safety of vaccines administered to premature infants <sup>24</sup>	
Evaluated AEFI after yellow fever vaccine via active surveillance <sup>28</sup>	
Studied Vaccine Acceptance & Risk Perception <sup>22</sup>	
Studied alopecia associated with hepatitis B vaccination by using a mouse model <sup>29</sup>	
Evaluated immunization rates and safety among children with inborn errors of metabolism <sup>30</sup>	
Evaluated hyperammonemic events are not associated with a 21-d postvaccination window in 90 children with urea cycle disorders <sup>31</sup>	

GBS indicates Guillain-Barré Syndrome; IRB, institutional review board; SV40, simian virus 40; DTaP, diphtheria-tetanus-acellular pertussis.

University, and the University of Maryland, the CISA Network evaluated the safety of the expanded influenza vaccine recommendations.<sup>7</sup> 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.<sup>8</sup>

#### *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.<sup>9</sup>

#### *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.<sup>10</sup>

#### **Collaborations**

CISA Network investigators have participated in the development of Brighton Collaboration's case definitions for encephalopathy,<sup>11</sup> nodules at the injection site,<sup>12</sup> generalized convulsive seizures,<sup>13</sup> and smallpox vaccine-associated adverse events.<sup>14–18</sup> 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.<sup>19</sup> 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-

ditis associated with vaccinations. Interim analysis of this ongoing study identified two candidate genes. Validation studies to confirm significant genetic polymorphism associations is ongoing, completion is anticipated by the end of 2011. Preliminary data have shown that although ~2% of influenza vaccine recipients experience new-onset chest pain after vaccination, there was no associated evidence of other objective markers of myocarditis or pericarditis in 186 subjects who underwent prospective evaluation with serial measurement of serial cardiac enzyme levels and electrocardiograms.<sup>20</sup>

CISA Network investigators have collaborated with the CDC's Vaccine Acceptance and Risk Perception (VARP) group to conduct a study to evaluate a newly developed vaccine-information pamphlet.<sup>21</sup>

### **Educational and Outreach Efforts**

CISA Network investigators and their co-investigators have lectured on vaccine-safety issues at national and international scientific meetings<sup>22</sup> provided expert consultation to other branches of government, and participated in the development of case definitions for evaluating vaccine-related adverse events through the Brighton Collaboration and algorithms for the evaluation and management of these events (see above). CISA Network investigators continue to work with responsible members of the general press to help educate health care professionals and the general public about vaccine safety.

Serious health problems after vaccination are rare, although millions of people are vaccinated every year in the United States. Why do only a small number of people develop these AEFI? Do they have genetically determined differences in their immune responses to vaccination compared with those who do not experience adverse events?

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 investigations<sup>8,23,24</sup> 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-

eases fellows at 2 CISA Network centers are leading the effort to better define the shedding of the first dose of live attenuated rotavirus vaccine in healthy vaccine recipients and premature infants. These efforts will increase the pool of high-quality investigators specifically trained to conduct future vaccine-safety research and vaccine-related clinical consultations.

## 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](http://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](http://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/CMS/3793/21144/25184.aspx](http://www.iom.edu/CMS/3793/21144/25184.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 pathophysiologic 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.

## ACKNOWLEDGMENTS

This work was supported by CDC contract 200-2002-00732.

We extend special acknowledgment to Robert Chen, Christine Casey, and John Iskander (CDC), who were instrumental in the establishment of the CISA Network. CISA as a network collaboration has benefited from the contributions of many people both currently and previously associated with the sites, America's Health Insurance Plans, the CDC, the Department of Defense, the US Food and Drug Administration, and other government agencies. All of these people, who are too numerous to mention here, have contributed to the vision, development, and scientific activities of the CISA Network over the years.

## REFERENCES

- Chen RT, Glasser, JW, Rhodes PH. Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. *Pediatrics*. 1997;99(6):765–773
- Wood RA, Berger M, Dreskin SC, et al; Hypersensitivity Working Group of the Clinical Immunization Safety Assessment (CISA) Network. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics*. 2008;122(3). Available at: [www.pediatrics.org/cgi/content/full/122/3/e771](http://www.pediatrics.org/cgi/content/full/122/3/e771)
- Wood R, Setse R, Halsey N; Clinical Immunization Safety Assessment (CISA) Network Hypersensitivity Working Group. Irritant skin test reactions to common vaccines. *J Allergy Clin Immunol*. 2007;120(2):478–481
- Halsey N. Anthrax vaccine and causality assessment from individual case reports. *Pharmacoepidemiol Drug Saf*. 2002;11(3):185–187
- Halsey N. The science of evaluation of adverse effects associated with vaccination. *Semin Pediatr Infect Dis*. 2002;13(3):205–214
- Muralles A, Ray P, Black S, et al. Active telephone surveillance to evaluate adverse events among civilian smallpox vaccine recipients. *Vaccine*. 2006;24(4):476–484
- Rosenberg M, Sparks R, McMahon A, Iskander J, Campbell JD, Edwards KM. Serious adverse events rarely reported after trivalent inactivated influenza vaccine (TIV) in children 6–23 months of age. *Vaccine*. 2009;27(32):4278–4283
- Qiang Y, Krishnan C, Kerr D, Setse R, Quigg M, Halsey N. Idiopathic acute transverse myelitis: comparison of patients with vs. without receipt of a vaccine within 30 days prior to onset. Presented at: 24th International Conference for Pharmacoepidemiology and Therapeutic risk Management; August 17–20, 2008; Copenhagen, Denmark
- Klein N, Fireman B, Enright A, Ray P, Black S, Dekker C. A role for genetics in the immune response to the varicella vaccine. *Pediatr Infect Dis J*. 2007;26(4):300–305
- Klein N, Edwards K, Sparks R, Dekker C; Clinical Immunization Safety Assessment (CISA) Network. Recurrent sterile abscesses following immunization: a possible association with aluminum adjuvant. *BMJ Case Rep*. 2009;
- Ball R, Halsey N, Braun MM, et al; VAERS Working Group. Development of case definitions for acute encephalopathy, encephalitis, and multiple sclerosis reports to the Vaccine Adverse Event Reporting System. *J Clin Epidemiol*. 2002;55(8):819–824
- Rothstein E, Kohl KS, Ball L, et al; Brighton Collaboration Local Reaction Working Group. Nodule at injection site as an adverse event following immunization case definition and guidelines for data collection, analysis, and presentation. *Vaccine*. 2004;22(5–6):575–585
- Bonhoeffer J, Menkes J, Gold MS, et al; Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine*. 2004;22(5–6):557–562
- Graham PL, LaRussa PS, Kohl KS; Brighton Collaboration Vaccinia Virus Adverse Event Working Group for Robust Take. Robust take following exposure to vaccinia virus: case definition and guidelines of data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5763–5770
- Beigel J, Kohl K, Brinley F, et al; Brighton Collaboration Vaccinia Virus Vaccine Adverse Event Working Group for Generalized Vaccinia. Generalized vaccinia as an adverse event following exposure to vaccinia virus: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5745–5753
- Nell P, Kohl P, Graham P, et al; Brighton Collaboration Vaccinia Virus Vaccine Adverse Event Working Group for Eczema Vaccinatum. Eczema vaccinatum as an adverse event following exposure to vaccinia virus: case definition and guidelines of data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5725–5734
- Nell P, Kohl K, Graham P, et al; Brighton Collaboration Vaccinia Virus Vaccine Adverse Event Working Group for Progressive Vaccinia. Progressive vaccinia as an adverse event following exposure to vaccinia virus: case definition and guidelines of data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5735–5744
- Wenger P, Oleske J, Kohl K, et al; Brighton Collaboration Vaccinia Virus Adverse Event Working Group for Inadvertent Inoculation. Inadvertent inoculation as an adverse event following exposure to vaccinia virus: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5754–5762
- Kohl KS, Magnus M, Ball R, Halsey N, Shadomy S, Farley TA. Applicability, reliability, sensitivity, and specificity of six Brighton Collaboration standardized case definitions for adverse events following immunization. *Vaccine*. 2008;26(50):6349–6360
- Slingluff M, Klote M, Hemann B, et al. A pilot study: trivalent inactivated influenza vaccine (TIV) and myopericarditis [abstract]. *J Allergy Clin Immunol*. 2007;119(1 suppl):S96. Abstract 376
- Klein NP, Kissner J, Aguirre A, et al. Differential maternal responses to a newly developed vaccine information pamphlet. *Vaccine*. 2009;28(2):323–328
- Casey C, Campbell S, Iskander J, et al. Clinical assessment of adverse events following immunization (AEFIs): a converging new international paradigm? *Pharmacoepidemiol Drug Saf*. 2004;13(S1):S13–S14
- Klein NP, Massolo M, Greene J, Dekker C, Black S, Escobar G; Vaccine Safety Datalink. Risk factors for developing apnea following immunization in the NICU. *Pediatrics*. 2008;121(3):463–469
- Klein NP, Gans H, Sung P, et al. Preterm infants' T cell responses to inactivated poliovirus vaccine. *J Infect Dis*. 2010;201(2):214–222
- Rennels M, Black S, Woo E, Campbell S, Edwards K. Safety of a fifth dose of diphtheria and tetanus toxoid and acellular pertussis vaccine in children experiencing extensive, local reactions to the fourth dose. *Pediatr Infect Dis J*. 2008;27(5):464–465
- Lindsey NP, Schroeder BA, Miller ER, et al. Adverse event reports following yellow fever vaccination. *Vaccine*. 2008;26(48):6077–6082
- Rollison D, Helzlsouer K, Halsey N, Shah K, Viscidi R. Markers of past infection with simian virus 40 (SV40) and risk of incident non-Hodgkin lymphoma in a Maryland cohort. *Cancer Epidemiol Biomarkers Prev*. 2005;14(6):1448–1452
- Durbin AP, Setse R, Omer SB, et al. Monitoring adverse events following yellow fever vaccination using an integrated telephone and Internet-based system. *Vaccine*. 2009;27(44):6143–6147
- Sundberg J, Silva K, Edwards K, Black B, Jensen A, King L. Failure to induce alopecia areata in C3H/HeJ mice with exogenous interferon gamma. *J Exp Anim Sci*. 2007;43(4):265–270
- Klein NP, Aukes L, Lee J, et al. Evaluation of im-



munization rates and safety among children with inborn errors of metabolism. *Pediatrics*. 2011; In press

31. Schlegel C, Edwards KM, Morgan T, Welch-

Burke T, Lee HS, Summar M; Urea Cycle Consortium. Hyperammonemic events are not associated with a 21 day post-vaccination window in 90 children with urea cycle dis-

orders (UCDs). Presented at: 11th International Congress of Inborn Errors of Metabolism; August 29–September 2, 2009; San Diego, CA

*(Continued from first page)*

*Nexbio and PATH; Dr Dekker receives contract funding from the NIH and the CDC; Dr Klein receives contract funding from the CDC and research support from GlaxoSmithKline, Merck & Co, Sanofi Pasteur, Wyeth (Pfizer), Novartis and MedImmune; Dr Halsey receives contract funding from the CDC and is compensated for serving on safety monitoring committees for studies of vaccines for Merck and Novartis, has received an honorarium for training and support for travel from Sanofi-MSD, a company in France, has research grants through Johns Hopkins University for studies of unrelated vaccines in Guatemala from Berna and Intercel, and has received support for a study of a Merck HPV vaccine in Peru but receives no support for the effort in Peru; Dr Marchant receives contract funding from the CDC and has performed clinical research for GlaxoSmithKline, Sanofi Pasteur, Merck, Wyeth (Pfizer Inc), MedImmune, and Novartis, has served as a consultant to GlaxoSmithKline, Sanofi Pasteur, MedImmune, and Novartis, and has given lectures sponsored by GlaxoSmithKline and Sanofi Pasteur; Dr Baxter receives contract funding from the CDC and research grants from Sanofi Pasteur, MedImmune, Novartis, GlaxoSmithKline, Pfizer, Protein Sciences, and Merck. Drs Engler, Kissner, and Slade have indicated they have no financial relationships relevant to this article to disclose.*

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

Philip S. LaRussa, Kathryn M. Edwards, Cornelia L. Dekker, Nicola P. Klein, Neal A. Halsey, Colin Marchant, Roger Baxter, Renata J. M. Engler, Jennifer Kissner and Barbara A. Slade

*Pediatrics* 2011;127;S65

DOI: 10.1542/peds.2010-1722J originally published online April 18, 2011;

### Updated Information & Services

including high resolution figures, can be found at:  
[http://pediatrics.aappublications.org/content/127/Supplement\\_1/S65](http://pediatrics.aappublications.org/content/127/Supplement_1/S65)

### References

This article cites 26 articles, 3 of which you can access for free at:  
[http://pediatrics.aappublications.org/content/127/Supplement\\_1/S65#BIBL](http://pediatrics.aappublications.org/content/127/Supplement_1/S65#BIBL)

### Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):  
**Infectious Disease**  
[http://www.aappublications.org/cgi/collection/infectious\\_diseases\\_sub](http://www.aappublications.org/cgi/collection/infectious_diseases_sub)

### Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://www.aappublications.org/site/misc/Permissions.xhtml>

### Reprints

Information about ordering reprints can be found online:  
<http://www.aappublications.org/site/misc/reprints.xhtml>

# American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Philip S. LaRussa, Kathryn M. Edwards, Cornelia L. Dekker, Nicola P. Klein, Neal A. Halsey, Colin Marchant, Roger Baxter, Renata J. M. Engler, Jennifer Kissner and Barbara A. Slade

*Pediatrics* 2011;127;S65

DOI: 10.1542/peds.2010-1722J originally published online April 18, 2011;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

[http://pediatrics.aappublications.org/content/127/Supplement\\_1/S65](http://pediatrics.aappublications.org/content/127/Supplement_1/S65)

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2011 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

