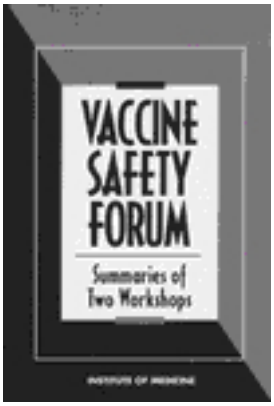

Vaccine Safety Forum: Summaries of Two Workshops

Board on Health Promotion and Disease Prevention, Institute of Medicine

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Vaccine Safety Forum

Summaries of Two Workshops

Vaccine Safety Forum
Board on Health Promotion and Disease Prevention
INSTITUTE OF MEDICINE

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religious since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

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VACCINE SAFETY FORUM

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Vaccine Safety Forum: Summaries of Two Workshops
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Preface

The Institute of Medicine's (IOM's) Vaccine Safety Forum was established in 1995 to examine critical issues relevant to the safety of vaccines used in the United States and to discuss methods for improving the safety of vaccines and vaccination programs. Government agencies, vaccine manufacturers, health professionals, and vaccine consumers share a responsibility for vaccine safety. Members of the forum thus include individuals representing parent or consumer groups with an interest in immunization, individuals representing vaccine manufacturers, physicians, representatives from federal agencies responsible for regulating vaccines and implementing vaccine policies, and academic researchers with expertise in vaccine-related issues.

The Vaccine Safety Forum's activities are a continuation of discussions undertaken by other IOM committees over the past 7 years. Previous IOM work on the subject resulted in the volumes *Adverse Effects of Pertussis and Rubella Vaccines* (1991), *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (1994a), *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* (1994b), and *Research Strategies for Assessing Adverse Events Associated with Vaccines: A Workshop Summary* (1994c). The first workshop of the Vaccine Safety Forum resulted in the publication *Options for Poliomyelitis Vaccination in the United States: Workshop Summary* (1996). On November 6, 1995, the Vaccine Safety Forum convened a workshop on detecting and responding to adverse events following vaccination. Workshop speakers and participants discussed the difficulties in detecting adverse events, current adverse events detection and response methods and procedures, suggestions for improving the means of detecting and responding to adverse events following vaccination, and future areas of research. On April 1, 1996, the

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Vaccine Safety Forum convened a workshop entitled Research to Identify Risks for Adverse Events Following Vaccination: Mechanisms and Possible Means of Prevention. The workshop discussed the various immunologic and genetic factors that might influence individuals' responses to vaccines, current research aimed at assessing what populations are at increased risk for experiencing adverse events from vaccines, and some research avenues that could be pursued in this regard. A number of known and hypothetical vaccine adverse effects were discussed at the workshop; their mention in this document does not imply that Forum members of the IOM regard them as scientifically established risks. This document represents a summary of both workshop.

The purpose of a forum at IOM is to foster dialogue and discussion across sectors and institutions. Forum activities offer a mechanism for convening individuals from a variety of government, academic, industry, and citizen groups in connection with a particular theme. Such activities provide a structured opportunity for regular and open communication among representatives of these groups. The objective, however, is to illuminate issues, not to resolve them. Unlike study committees of IOM, forums cannot provide advice or recommendations to any government agency or other organization. Similarly, workshop summaries or other products resulting from forum activities are precluded from reaching conclusions or recommendations but, instead, are intended to reflect the variety of opinions expressed by the participants. The discussion is intended to be speculative and thought-provoking, not definitive.

The comments in this report represent the views of the workshop participants, as indicated in footnotes for each section and generically in the text. The identification of a speaker as a "vaccine manufacturer's representative" or a "CDC representative" is not intended to suggest that any particular organization holds the same views.

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Contents

Detecting and Responding to Adverse Events Following Vaccination
EXECUTIVE SUMMARY 1
INTRODUCTION 2
DIFFICULTIES IN DETECTING ADVERSE EVENTS FOLLOWING VACCINATION 3
CURRENT ADVERSE EVENT DETECTION AND RESPONSE PROCEDURES 5
Vaccine Adverse Event Reporting System 5
Large Linked Databases 6
Surveillance by Vaccine Manufacturers 7
Food and Drug Administration 8
IMPROVING DETECTION OF AND RESPONSE TO ADVERSE EVENTS 9
Increasing Reporting to VAERS 9
Improving the Quality of Information in VAERS 11
Improving Vaccine Lot Information 13
Improving the Usefulness of LLDB Data 15

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Clinical Trials 15
Comparison Studies 17
ADDITIONAL AREAS FOR RESEARCH 18
REFERENCES 21
WORKSHOP AGENDA 23

Research to Identify Risks for Adverse Events Following Vaccination: Biological Mechanisms and Possible Means of Prevention
EXECUTIVE SUMMARY 29
INTRODUCTION 30
IMMUNE RESPONSE TO VACCINE ANTIGENS 31
Premature Infants 33
GENETIC FACTORS AFFECTING DEVELOPMENT OF AUTOIMMUNITY 35
RESEARCH ON IDENTIFYING POPULATIONS AT RISK FOR ADVERSE EVENTS 37
Arthritis and Rubella Vaccine 37
Anaphylaxis and Measles, Mumps and Rubella Vaccine 38
Convulsions and DPT 39
High-Titer Measles Vaccine 40
Multiple Sclerosis or Guillain-Barré Syndrome and Vaccines 42
Multiple-Antigen Vaccination and Adverse Immune Responses 43
RESEARCH OPPORTUNITIES 44
REFERENCES 51
WORKSHOP AGENDA 57

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Detecting and Responding to Adverse Events Following Vaccination: Workshop Summary

Cynthia J. Howe, Richard B. Johnston, and Gerald M. Fenichel, Editors

EXECUTIVE SUMMARY

On November 6, 1995, the Institute of Medicine's Vaccine Safety Forum convened a workshop on detecting and responding to adverse events following vaccination. Workshop speakers and participants discussed the difficulties in detecting adverse events, current adverse events detection and response methods and procedures, suggestions for improving the means of detecting and responding to adverse events following vaccination, and future areas of research. This document represents a summary of that workshop.

The detection of adverse events following vaccination includes a range of activities. At one extreme it involves the realization that a specific event might be associated with vaccination and the reporting of that case to appropriate authorities. At the other extreme, detection of adverse events includes the assessment of a statistical pattern that suggests that a particular adverse event might be associated with or caused by a particular vaccine. A number of factors make it difficult to detect adverse events associated with vaccination and to determine whether the event is causally associated with the administration of a vaccine: (1) the need to study multiple exposures and multiple outcomes, (2) the lack of unique vaccine-associated syndromes, making it difficult to establish causality, (3) the need for large sample sizes and lack of large computerized immunization databases with individual level data including vaccine lot number, (4) brief exposure periods for each individual, (5) high vaccination coverage makes unvaccinated individuals highly selected.

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Adverse events associated with vaccines are currently detected through the Public Health Service's Vaccine Adverse Event Reporting System (VAERS), the Centers for Disease Control and Prevention's (CDC's) Large Linked Data Base (LLDB),[1] and through surveillance measures undertaken by vaccine manufacturers. The federal agencies primarily responsible for responding to the adverse events associated with vaccines are the Food and Drug Administration (FDA) and CDC. the efforts made by CDC, FDA, and vaccine manufacturers to detect and respond to adverse events following vaccination have been effective in many cases, but there are limits to the detection and response systems currently in use Workshop participants expressed a wide diversity of opinions on priorities for change and improvements and on the scientific basis for some of the suggestions presented. Participants suggested that efforts can be made to improve the quantity, quality, accessibility, and usefulness of VAERS reports. Routine, systematic screening of data, as well as other procedures, can be developed to make LLDB data more useful. The use of larger and better-designed clinical trials conducted both before and after a vaccine's licensure for general use could also be considered to improve the rate of detection of rare adverse events. Such trials could be designed to help separate out the effects of vaccines used in combination and to determine whether certain vaccine combinations pose more risk than vaccines given separately. Vaccine recall procedures could be improved as well.

More research could be done on potential long-term adverse effects from vaccines as well as the potential of vaccines to induce or worsen immune disorders. Research also could usefully address such questions as whether age is a factor in the adverse events experienced following vaccination and whether some groups of individuals are more prone to such adverse effects than others.

INTRODUCTION

The detection of adverse events following vaccination includes a range of activities. At one extreme it involves the realization that a specific event might be associated with vaccination and the reporting of that case to appropriate authorities. At the other extreme, detection of adverse events includes the assessment of a statistical pattern that suggests that a particular adverse event might be associated with or caused by a particular vaccine. These and other aspects of vaccine safety were discussed by the workshop participants. These issues were also covered in an earlier IOM report *Research Strategies for*

[1] Now called the Vaccine Safety Datalink (VSD). LLDB is a generic term for this methodological approach.

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Assessing Adverse Events Associated with Vaccines: A Workshop Summary (1994c).

DIFFICULTIES IN DETECTING ADVERSE EVENTS FOLLOWING VACCINATION[2]

A number of factors make it difficult to detect adverse events associated with vaccination and to determine whether the event is causally associated with the administration of a vaccine: (1) the need to study multiple exposures and multiple outcomes, (2) the lack of unique vaccine-associated syndromes, making it difficult to establish causality, (3) the need for large sample sizes and the lack of large computerized immunization databases with individual level data including vaccine lot number, (4) brief exposure periods for each individual, (5) high vaccination coverage makes unvaccinated individuals highly selected.

Individuals are often given several vaccines simultaneously, making it hard to assess which vaccine exposure might be causing an adverse event. In addition, several possible adverse events can occur following a single vaccination. Traditional public health surveillance measures are usually aimed at detecting a single specific disease outcome or event following exposure to a single agent or disease entity (for infectious diseases, this follows exposure to an etiologic factor such as human immunodeficiency virus). Postmarketing surveillance of vaccines, in contrast, must be structured to detect multiple outcomes, should they occur, following multiple exposures. In addition, surveillance for adverse events associated with vaccination requires the ability to detect both an increase in the frequency of previously known adverse events and the emergence of new, unanticipated adverse events. It is difficult to detect both types of events with a single surveillance system. Traditionally, separate surveillance systems have been established for each purpose, each optimized for its particular objectives.

The lack of a unique laboratory diagnosis or unique clinical syndrome for most of the adverse outcomes investigated in relation to vaccination also makes it difficult to detect adverse events following vaccination. At present, no laboratory diagnosis or clinical description can differentiate a seizure that is caused by a vaccination, for example, from one that is caused by another factor. The lack of a unique syndrome or diagnosis makes it difficult to assess whether the adverse event is coincidental to vaccination (but not caused by it) or a true adverse reaction to the vaccine itself. Most childhood vaccines are given at an

[2] The material in this section is adapted from a presentation by Robert Chen and from comments by other workshop speakers and participants.

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age when medical problems due to genetic or congenital factors are first manifesting themselves. Therefore, it is difficult to assess whether these medical problems are caused by the vaccine or are coincidental to vaccine administration.

Often, it is not possible to assess how many individuals have been given a vaccine of interest, which creates an additional surveillance difficulty. This information is needed to determine what proportion of people receiving the vaccine are experiencing adverse events. Usually, the only data easily available are the number of doses of vaccine distributed, not the number of doses actually administered at any given time. In addition, for individuals who have had an adverse reaction to vaccination, the vaccine lot and manufacturer may not be known, making it difficult to trace potential problems with a particular lot or batch of vaccine.

Another challenge to detecting adverse events is that only a few doses of a single vaccine are usually given to an individual. If the risk of an adverse event is dose related, the likelihood that an adverse reaction occurs after vaccine administration is therefore much lower than after the administration of drugs because drugs are given several times a day for a period of weeks or months. In addition, large populations are needed to conduct epidemiologic studies designed to detect rare adverse events. Studying such large populations can be difficult to do in a timely manner and can be very expensive.

Finally, the fact that large numbers of children in the United States receive vaccinations during childhood presents problems in detecting adverse events following vaccination. In particular, it is difficult to find a comparable control population that has not received the vaccine to help assess potential causality and to determine how often adverse events occur in the absence of vaccination. Those individuals who, voluntarily or otherwise, do not receive vaccines may be different in other respects from those who do. They therefore are not a suitable control population. For example, children who are not vaccinated may be in poorer health, may receive different types of health care in general, or may be part of a restricted gene pool if they are members of religious groups that decline vaccines. In addition, the unvaccinated population may not be large enough to allow for the study of background rates of rare medical events. Although some researchers express ethical concerns about conducting a controlled trial that would require large numbers of individuals not to receive a vaccine from which they might benefit, some parents and consumers express ethical concerns about assuming that the benefit of a tested vaccine will outweigh its risks.

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CURRENT ADVERSE EVENT DETECTION AND RESPONSE PROCEDURES

Adverse events associated with vaccines are currently detected through the Public Health Service's Vaccine Adverse Event Reporting System (VAERS), the Centers for Disease Control and Prevention's (CDC's) Large Linked Data Base (LLDB),[3] and through surveillance measures undertaken by vaccine manufacturers. The federal agencies primarily responsible for responding to the adverse events associated with vaccines are the Food and Drug Administration (FDA) and CDC.

Vaccine Adverse Event Reporting System[4]

Under the aegis of CDC and FDA, VAERS was established in 1990. VAERS requests physicians to report any adverse events observed following vaccination of their patients. Health care providers are required by law[5] to report specific serious events occurring within 30 days after vaccination with a particular set of vaccines, as outlined in a published reportable events table. Patients, parents, or even nonrelatives who witnessed or who are aware of a reaction can also submit a report to VAERS. Although some VAERS reports can include symptoms that occurred years after a vaccine was given, most VAERS reports are of adverse events tightly linked in time to vaccination—usually occurring within a few days after the vaccination.

The narrative description of an adverse event reported on a VAERS form may include a discussion of the symptoms, the time course, the laboratory tests that were performed, and the treatment provided for the adverse event. This description is coded and entered into a computer database. Adverse events are also categorized as to whether they were fatal, serious but nonfatal (i.e., those that were life-threatening, required or prolonged hospitalization, or involved permanent disability), or less serious.

VAERS is a passive surveillance system, and thus, adverse events are likely to be underreported. In addition, it lacks much of the information needed for an epidemiologic study to assess whether a specific vaccine caused a specific adverse event. It can, however, generate signals of potential new adverse events

[3] Now called the Vaccine Safety Datalink (VSD). LLDB is a generic term for this methodological approach.

[4] The material in this section is adapted from presentations by Robert Chen and Miles Braun and from comments by other workshop speakers or participants.

[5] National Childhood Vaccine Injury Act of 1986, P.L. 99-660.

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(e.g., hair loss following receipt of hepatitis B vaccine) or a change in the rate of reporting of previously known adverse events associated with vaccines (e.g., decreased numbers of reports of both serious and less serious events after receipt of the acellular pertussis vaccine versus receipt of the whole-cell vaccine. Confusing peaks in the reporting of adverse events can also stem from recent publicity about an adverse event associated with a vaccine. It is difficult to ascertain whether these peaks in adverse event reports are due to a true increase in adverse events related to the vaccine or result only from increased awareness of a potential problem. Spurious peaks in VAERS reports may also occur from changes in the background rate of adverse events. A recent study has shown, for instance, that an increase in VAERS reports of Guillain-Barré syndrome (GBS) during the 1993–1994 influenza vaccination season was due largely to an increase in the rate of GBS in the general population (Lasky, 1997).

Large Linked Databases[6]

To improve detection of adverse events associated with vaccination and to conduct more active surveillance studies to assess the causality of adverse events, CDC established LLDB in 1990. This database is a CDC-coordinated linkage of large databases of four large health maintenance organizations. Comprising automated data from more than 500,000 children (ages 0 to 6 years) in Oregon, Washington, and California, LLDB enables researchers to link vaccine exposures to medical outcomes and thereby to estimate the rates of occurrence of adverse events following vaccination as well as the background incidence. An elevated rate following vaccination, in comparison with the rate at other times, would suggest a possible causal relation to vaccination. Over the next 5 years, LLDB will also be expanded to include adolescents and adults. Unlike VAERS, LLDB contains all of the information necessary for epidemiologic studies of vaccine adverse effects (vaccination exposures, outcomes among vaccinated and unvaccinated person times, and potential confounders).

The large size of LLDB improves the ability to detect rare adverse events, and extensive quality control of the clinical and immunization data in the system increases its reliability. LLDB also allows for the study of confounding variables and for the exploration of groups at risk for adverse events following vaccination.

[6] The material in this section is adapted from a presentation by Robert Davis.

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Surveillance by Vaccine Manufacturers[7]

Vaccine manufacturers, which share a responsibility for detecting adverse events associated with vaccination, described their procedures as follows. Adverse event reports are reviewed by a team representing safety surveillance, clinical research, regulatory affairs, and quality control. The review team examines events individually and with an eye to repeated reports. The review committee may use a threshold level of, for example, 10 reports during a vaccine's lifetime as a signal that follow-up is needed. Manufacturers also monitor the pattern of adverse event reports for particular lots or batches of vaccine over time. Any atypical patterns are carefully reviewed. The entire surveillance process is carried out in close collaboration with and regular reporting to FDA, and thereby VAERS.

In addition to conducting periodic in-house investigations of vaccines for which a company and VAERS have received large numbers of adverse event reports, local investigations are sometimes necessary. An evaluation of the large numbers of adverse events reported from immunization clinics in South Africa, for example, revealed that the vaccines were improperly administered and that some of the reactions were labeled inaccurately.

Manufacturers noted that postmarketing reporting is voluntary and consequently represents incomplete reporting of the true numbers of adverse events that are actually occurring in the population. Furthemore, these reports are coded in the terminology used by the reporter, and there are no standard case definitions for various adverse events. If a health care provider reports a case of encephalitis, for example, it is recorded as a case of encephalitis.

Because of these limitations and because the standard premarketing clinical trials are not sufficiently large to detect rare adverse events, manufacturers also conduct postmarketing surveillance studies. These studies either search for a particular adverse event in a specific population or scrutinize a large number of vaccines for general safety issues. As an example, an epidemiologic analysis of selected reported neurologic adverse events associated with the administration of the hepatitis B vaccine was presented. The manufacturer reported that, although a causal association could not be entirely ruled out, it found no evidence from the analysis of postmarketing reporting data to suggest that Guillain-Barré syndrome, myelitis, transverse myelitis, multiple sclerosis, optic neuritis, or peripheral neuropathies were causally associated with the administration of the hepatitis B vaccine.

[7] The material in this section is adapted from presentations by Luc Hessel, Robert Levine, and Robert Sharrar.

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Food and Drug Administration[8]

FDA monitors adverse event reporting rates for individual vaccine lots on the basis of crude estimates of lot size and the amount of time that the vaccine lot has been in distribution. The information available to the FDA includes VAERS data and manufacturers' reports, as described above. At weekly meetings, FDA personnel review all the data for lots for which a report of a serious adverse event (any event that requires hospitalization, results in permanent disability, is life threatening, or prolongs hospitalization) has been made during the past week. At these meetings the individual reports are discussed, as are the patterns of reporting, that is, the number of reports made during a specific time frame. Particular scrutiny is given to lots for which there have been relatively large numbers of adverse event reports early in their circulation.

At FDA, further investigation of lots with which adverse events have been associated includes a detailed review of individual reports to look for clusters of similar cases, syndromes that connect the reports, or other patterns. Additional information is sometimes collected from the reporter, primary physician, or medical examiner. The adverse event reporting patterns for other final lots filled from the same bulk vaccine are also considered. Of greater concern is if elevated adverse event reports are received for several final lots from the same batch bulk material than if the number of reports for one lot is higher and that for the others is lower. Lot release data are reviewed to ensure that the lots in question have passed all the required tests.

According to FDA representatives, reports of fatal events and reports of certain serious events are routinely followed up by FDA physicians or by VAERS personnel. Some consumer representatives, however, expressed discontent with the followup that they are aware of. Follow-up includes assessment of the current condition of the patient for nonfatal reports, confirmation of the information provided by the reporter, and requests for additional information, including a more detailed chronology of events and relevant facts about the child or family of the child who experienced the adverse event. Sometimes, additional laboratory results, hospital discharge summaries, or autopsy reports are requested. Sometimes the patient or family is contacted directly; at other times the medical records suffice. Reports of less serious events are occasionally investigated for unusual events or patterns.

Once the review process is complete, FDA has several options. The agency may determine that the vaccine lot in question is not likely to be faulty but will

[8] The material in this section is adapted from presentations by Susan Ellenberg and Frederick Varricchio and comments by other workshop speakers or participants.

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continue to monitor it carefully; this is the action most often taken. Less commonly, more information is obtained, an on-site facility inspection is requested, or lot samples are retested. The review process may lead to changes in the required labeling.

IMPROVING DETECTION OF AND RESPONSE TO ADVERSE EVENTS[9]

VAERS, LLDB, vaccine manufacturer surveillance measures, and FDA response procedures have several limitations. Speakers and participants voiced several suggestions and discussed measures being undertaken to improve the detection of and response to adverse events associated with vaccination.

Increasing Reporting to VAERS

A CDC study indicated that, as with all passive surveillance systems, underreporting occurs with VAERS; however, reporting efficiency is higher for severe events than for mild ones (Rosenthal and Chen, 1995). An FDA study found that the reporting rate to VAERS varies substantially by state, but those states that reported the most serious events also reported the most events of lesser severity (Braun, 1997).

The concern of some physicians about potential legal liability for an adverse event following vaccination was cited by some participants as a reason for underreporting in VAERS. Theoretically, this should no longer be the case, because the existence of the National Vaccine Injury Compensation Program (established by federal statute in 1986) has resulted in very few suits filed against physicians for vaccine-related injuries since that time. To the extent that physicians are unaware of these circumstances, however, it was suggested that increased education of physicians about the compensation program would help to allay their concerns about reporting adverse events as required.

As another way to increase the number of reports filed with VAERS, representatives from the VAERS contractor, CDC, and FDA will be presenting results obtained from VAERS at professional meetings and in journal articles.

[9] The material in this section is adapted from the discussion among panelists Bart Classen, Robert Chen, Linda Cowan, Susan Ellenberg, Gerald Fenichel, Barbara Loe Fisher, John Glasser, Marie Griffin, Luc Hessel, Robert Kohberger, John Martin, James Singleton, Paul Stolley, Gina Terracciano, Frederick Varricchio, and Robert Wise, and from comments by other speakers and participants.

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Such efforts are intended to increase the reporting rate to VAERS by conveying to physicians the value and usefulness of the reports that they submit.

To help raise adverse event reporting rates by physicians further, a consumer representative suggested that a course on vaccine risks and benefits, adverse event reporting, and educating parents be introduced into medical and nursing school curricula. The speaker also suggested using funds from the U.S. Department of Health and Human Services to create a public education campaign designed to educate physicians and the public about the importance of monitoring children after vaccination, reporting adverse events following vaccination to the government, and screening children for factors that would place them at higher risk of experiencing adverse events following vaccination. (However, specific risk factors for most adverse events are not known.) CDC is working with several universities to develop materials for both physicians and parents that the explain adverse events that may occur after vaccination and how to report them. It was also suggested that more efforts be made to educate adult vaccines about the possible adverse effects of vaccines. A vaccine researcher noted that physicians have vaccine information statements that they can give to the parents of children being vaccinated, but that such statements for adults about to be vaccinated are less common and not as readily available.

More easily accessible means for reporting adverse events to VAERS were also suggested. A consumer representative suggested that, in addition to existing toll-free telephone numbers,[10] an Internet address or World Wide Web site could be instituted to allow physicians, parents, and patients to report adverse events easily and quickly; issues of confidentiality, however, would have to be addressed before such a procedure could be implemented. The Internet contains a vaccine safety information sharing system for people who are actively involved in vaccine research. It is not available to the general public, however, but functions as an alerting mechanism containing, among other things, press reports of vaccine safety issues, newly published research, and study results presented at conferences or meetings, so that researchers are informed and able to respond to the inquiries that they receive.

Noting that most pediatricians lack the time to fill out long forms, a physician suggested that the number of reports to VAERS could be increased by placing the burden of such reporting on the parents of vaccinated children. He suggested that parents be given two cards at the time of vaccination, one for reporting acute reactions to the vaccine and the other for reporting chronic reactions.

[10] The toll-free telephone number for the National Vaccine Injury Compensation Program is (800) 338-2382. The number for the Vaccine Adverse Events Reporting System is (800) 822-7967.

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A consumer representative suggested that, as part of the legal requirement for physicians to report serious adverse events following vaccination, failing to report such events should result in penalties. Parallel to mandatory vaccination laws that keep children out of school if they are not vaccinated, such laws could prevent physicians from administering vaccines if they neglect to report hospitalizations, deaths, and injuries following vaccination.

Improving the Quality of Information in VAERS

A frequent problem encountered with VAERS is misclassification. An FDA representative pointed out that serious events can be misclassified as nonserious if the reporter does not recognize the seriousness of the event or if a serious event is treated on an outpatient basis. (The current definition of a "serious" event requires that the individual be hospitalized.) He indicated that he has seen reports of paralyzing disorders such as Guillain-Barré syndrome and Bell's palsy incorrectly labeled as nonserious.

Another criticism of VAERS is that the description of the adverse event is often inaccurate—that is, the reporter inaccurately labels the adverse event. An FDA study found that for nearly one-quarter of the fatalities reported to VAERS, the final cause of death was significantly different from the cause initially reported (Wise, 1994). A CDC study, however, found that nearly 90 percent of the reports of Guillain-Barré syndrome in VAERS were accurate (Haber et al., 1994).

To improve the accuracy of the information reported to VAERS, several speakers or participants suggested developing more standardized case definitions for evaluating the adverse events reported. Under the direction of CDC and FDA, the VAERS staff is currently undertaking several efforts to improve the quality of the data. Among these are improving the automated screening procedures designed to detect reporting or transcribing errors in VAERS data; improving-the consistency in entering, tracking, and analyzing VAERS data; and improving the detection of duplicate VAERS reports entered into the database. CDC, FDA, and Health Resources and Services Administration Division of Vaccine Injury Compensation are establishing a panel of medical experts to provide advice on analyses of difficult cases and are continuing to conduct studies to evaluate the biases present in the system, examining such issues as reporting delays and how they affect the analysis and validity of the data.

To facilitate the VAERS reporting process and to increase the likelihood that physicians will complete VAERS forms, a vaccine manufacturer's representative suggested that the form might be made more specific. Rather than

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asking doctors to report all adverse events following vaccination, he suggested that it be limited to reporting only those conditions that are of most concern. A CDC representative noted, however, that if VAERS forms were made too specific, the system would lose the ability to detect previously unknown adverse events. Specificity is best achieved, he said, with more active surveillance measures, such as the standard follow-up protocol of certain VAERS reports or through LLDB.

To improve further the quality of information in VAERS reports, a consumer representative suggested that the person assigned to follow up death reports speak to both the parent of the child and the child's physician to obtain more details about the adverse event. Death reports are currently followed up by seeking additional information from the individual who submitted the report. Therefore, if the report was submitted by someone other than the parents the parents might not be aware that an investigation was undertaken. For example, a parent noted that no government representative had ever contacted him personally seeking more information about his son's death following vaccination with the hepatitis B vaccine. This death was misclassified as sudden infant death syndrome (SIDS) in the VAERS report, despite subsequent autopsy findings that strongly suggested cardiac causes. A consumer representative further suggested that deaths labeled as being caused by SIDS, especially when they occur in infants under 1 month of age, in whom SIDS is rare, should be thoroughly investigated so that they can be correctly reclassified if necessary. The criteria developed by the National Institute of Child Health and Human Development to classify a death as being caused by SIDS could be used to verify SIDS deaths reported to VAERS.

A CDC representative suggested that for those reported adverse events for which there are established diagnostic criteria (e.g., anaphylaxis or multiple sclerosis), a standard follow-up protocol should be sent to the reporter and the physician. FDA and CDC are working on improving follow-up to the reports made to VAERS. On a trial basis, letters will routinely be sent to request more follow-up information for certain adverse events, and more telephone follow-up has been implemented. FDA and CDC also plan to assess how to obtain more information from VAERS forms as well as how to make the forms easier to complete.

A public health policy analyst suggested linking infant mortality reviews, which are conducted extensively in the United States, with VAERS data to help detect and provide more information on vaccine-related deaths among infants. Other participants suggested reviewing other existing databases (e.g., the Medicare database) to seek significant information on immunization status and adverse events.

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A consumer representative suggested monitoring the outcomes of serious events, such as seizures, with follow-up at 6 months, 1 year, and 2 years to gather data on persistent sequelae. VAERS currently requests information on recovery status at 60 days and 1 year after selected serious adverse events.

One criticism of VAERS is that its data are not easily accessible either to the medical and research communities or to the public. A physician noted that to obtain VAERS data, he had to employ the Freedom of Information Act, and then the information that he received was not readable by his computer. He suggested that VAERS data be put into a form that can be easily read on a personal computer.[11]

To help improve accessibility, the publicly releasable, nonconfidential component of VAERS data is being converted to a more user-friendly form. Both the hardware and the software used by VAERS are being updated to make it easier and more efficient to conduct analyses of the data. To improve the public's use of the data in VAERS, FDA also plans to update and clarify the explanatory information that accompanies a VAERS data set. A physician suggested that the accessibility of VAERS data be further improved by regularly publishing summaries of the data in CDC's *Morbidity and Mortality Weekly Report*.

A participant suggested that VAERS be made more effective by committing more U.S. Department of Health and Human Service funds to increase the staffing and other resources needed to detect and respond to adverse events more expeditiously. A balance could be struck between the resources spent on VAERS and other mechanisms for gathering data on vaccine safety (e.g., LLDB), each of which has its own inherent strengths and weaknesses.

Improving Vaccine Lot Information

Frequent problems encountered by those monitoring VAERS data include the lack of identification of vaccines and the lot numbers of the vaccines associated with the adverse events reported, inaccurate reporting of the lot numbers of vaccines associated with adverse events, and imprecise estimates of the usage of particular lots over time. Lot sizes are needed as denominators for calculating adverse event rates.

A parent of an injured child reported that she had obtained information about the vaccine lot from which her child's dose came and discovered that a number of other children had died or had been injured following receipt of

[11] VAERS data are available electronically in standard ASCII format by contacting NTIS at (703) 487-4650 or http://www.ntis.gov.

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vaccine from that lot. She wondered whether there is a threshold of such events that triggers recall of a vaccine lot. FDA officials indicated that because lots are highly variable in size, it is not possible to set a specific number as a trigger for recall. FDA officials reported that they monitor carefully the number of serious events reported relative to the size of each lot. However, they are precluded by federal statute from making public the size of any lot; this information is considered proprietary by vaccine manufacturers.

A physician suggested that FDA establish standard criteria for the recall of vaccine lots as well as effective procedures for ensuring that all recalled vaccine materials are collected. He recommended that whenever FDA recalls a vaccine lot, it notify the media as well as pharmacies, pediatricians, and family practice and internal medicine physicians. FDA officials indicated that such notification does occur.

A vaccine manufacture's representative reported on two pilot programs being planned or conducted in Europe to improve the recording of vaccine lot and identification numbers. One program records on a computerized card an individual's immunization information, including the identification and lot numbers of each vaccine received. The information is entered and updated by computer with software in physicians' offices. Another program plans to add bar codes on each vaccine vial to identify not only the product but also the batch number. An optical scanner at immunization clinics can then easily record and enter into a computer database the information each time that a vaccine is given.

To measure the rate of occurrence of rare adverse events for specific vaccine lots, researchers must know the number of vaccine doses administered. A researcher at the CDC has developed a mathematical model to estimate the number of doses of specific lots of vaccine administered and rates of adverse events (Glasser et al., unpublished). He illustrated two applications of this methodology: (1) identification of lots for which rates of reporting of adverse events exceed the average, and which should be scrutinized if many doses remain to be administered and (2) validation of prelicensure testing standards. This approach was developed in collaboration with scientists in the biological laboratories of the Massachusetts and Michigan public health departments, and the underlying model was validated with information about diphtheria and tetanus toxoids and pertussis vaccine administration inferred from vaccine inventories in county and regional public health departments throughout Michigan, which in turn distribute vaccine to the private sector. Although the observed and expected numbers of administrations of specific vaccine lots were concordant, an epidemiologist suggested that further work with vaccine manufacturers was needed to assess the accuracy of the predicted numbers of doses a particular lot administered. Manufacturers could test the model by

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directly monitoring lots to see how well the predicted and actual number of doses in particular lots matched.

To better assess vaccine lot administration, a CDC representative suggested that vaccine manufacturers include postcards in some of the boxes of vaccines distributed. The cards would request that the provider, on the day that the box is opened and vaccine from that box is first given to a patient, write the date on the card and return it by mail. However, a manufacturer who had attempted such an approach believed that studies done in this manner do not generate reliable data because vaccine administration is extremely variable, making vaccine administration impossible to track through indirect methods such as this.

Improving the Usefulness of LLDB Data

The main problem with LLDB is that it is limited by how medical events are captured in their computer data systems during routine visits. It is difficult to discriminate between new events and chronic or recurrent conditions. For example, some databases do not distinguish among a visit for a first seizure, a visit for a recurrent seizure, or a follow-up or check-up visit. By using certain data screening techniques, however, it is possible to subcategorize visits. By limiting seizure reports only to those that occurred in the emergency room and that were separated by 30 days, for example, researchers were able to distinguish visits for actual seizure events from seizure follow-up visits or checkups (Davis, unpublished data). Such screening techniques might make the LLDB more useful, a vaccine researcher suggested.

An FDA representative suggested developing computerized screening methods to identify clusters of potentially related events. Researchers could also develop statistical methods that could more effectively evaluate adverse events following vaccination.

Clinical Trials

To further identify adverse reactions to vaccines, an FDA representative suggested that larger clinical trials of vaccines be performed before the vaccines are licensed for general use. Those studies would need to be large enough to detect rare serious adverse effects such as death or seizures. The speaker suggested the development of procedures for conducting such trials in an effective and efficient manner, noting that studies of this size have been done to evaluate agents used to reduce mortality following heart attacks.

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A speaker raised two related questions: (1) Can the effects of individual vaccines be discerned even though vaccines are usually given in combination; and (2) Does the simultaneous administration of vaccines pose more risk than the administration of vaccine separately? A representative of a manufacturer stated that it is possible to answer these questions by designing a randomized trial in which, for example, one group is given three vaccines simultaneously, another group receives each of those vaccines at separate times, and other groups receive two of the three vaccines simultaneously. One could then assess whether there are any statistically significant differences in the risk of adverse events when these groups are compared. Such studies would be large, cumbersome, and expensive to run, he noted, but theoretically, they can be done.

One participant expressed concern that large prelicensure trials that take several years to conduct and analyze would place too much of a financial burden on vaccine manufacturers and could delay the availability of new vaccines. An epidemiologist commented that large-scale clinical trials, although potentially valuable, would not obviate the continued need for systems such as VAERS to detect the adverse effects of the vaccines. Even if a vaccine is shown to be safe in a large clinical trial, the potential for lot and batch variability and for variability in the use of vaccines require continual surveillance for adverse events.

Several speakers suggested conducting more focused, powerful, larger, and better-designed postlicensure clinical studies to detect *serious* , rare adverse events of vaccines that are not possible to detect in a clinical trial. FDA continues to work with manufacturers in this regard but recognizes that such studies, without randomized control groups, will be far less valid than the randomized trials that can be done prelicensure.

A vaccine manufacturer's representative suggested that each manufacturer should contribute money to a pool that could be used to establish a state-of-the-art, large, linked database system rather than doing its own small-scale postmarketing studies to detect adverse effects from vaccines. This would create a standard system for the detection of rare adverse events, that might go undetected in the smaller studies conducted by individual companies. Manufacturers could pay a maintenance fee for receiving data from such a large linked database system. To improve further the detection of rare adverse events, a vaccine manufacturer's representative suggested establishing an international network of databases of adverse events following vaccination. Such a network would require strict standardization of the information entered into it, however.

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Comparison Studies

Noting that VAERS primarily receives reports of adverse events that occur shortly after vaccination, several speakers suggested developing procedures to detect longer-term or more subtle adverse events that might be associated with vaccination, such as learning disabilities or chronic fatigue syndrome. It was suggested that retrospective studies, as well as prospective studies that use nonvaccinated individuals as controls over a period of 10 or 20 years, be conducted for this purpose. A consumer representative suggested that there be more government funding for studies designed to detect long-term adverse effects of vaccines or to identify individuals at high risk for adverse effects. It was also suggested that children given vaccines in clinical trials be followed for 5 to 10 years to help assess long-term adverse events that do not become apparent until children reach later stages of development. Other participants commented that such studies would be extremely difficult to design, especially if a vaccine comes into general use so that it is given to large numbers of children.

Several speakers suggested that more studies be done using LLDB or other methods to compare vaccinated children with unvaccinated children. There is concern, however, that children who are not vaccinated are different in important ways from those who are vaccinated and therefore are not a suitable control population. To avoid the problem of controls who differ from cases in unmeasured ways, a CDC representative described a method that uses cases as their own controls (Farrington et al., 1996). He illustrated this methodology with a hypothetical example, in which the adverse events and vaccinations that an infant experienced during each month are monitored, and then applied this methodology to seizures after vaccination with the measles-mumps-rubella vaccine reported in CDC's LLDB study. By comparing the rates of occurrence of adverse events during periods immediately following vaccination and at all other times, the risk of adverse events with short latencies can be determined.

To better separate the adverse effects of a vaccine from background adverse events that occur in the age group vaccinated, a vaccine researcher suggested that different vaccine schedules be used for different groups of children in a random manner. This would not be unethical, the speaker noted, if the schedules were devised such that some children received a vaccine only a month or two later than other children.

To improve assessment of the frequency of occurrence of rare adverse events, a vaccine manufacturer's representative suggested that more effort be made to improve general surveillance of specific disorders that could potentially be associated with vaccination, such as Guillain-Barré syndrome or transverse myelitis. The likelihood of these disorders occurring as a result of vaccination

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cannot be assessed until studies firmly establish the incidence of these disorders in the general population. LLDB can be used to help establish such background rates for acute events.

ADDITIONAL AREAS FOR RESEARCH

A number of additional areas in detecting and responding to adverse events following vaccination warrant further research, according to workshop participants. One question is whether the age at which a vaccine is given is a factor in the adverse events experienced. For example, experience with vaccination with the pertussis vaccine in Japan suggested that very young infants were more susceptible to neurologic complications from the whole-cell pertussis vaccine than slightly older infants. However, younger infants have a higher background rate of neurologic diseases than older infants, making assessment of the role of vaccines difficult. Two examples discussed at the workshop suggested to some that later immunization is possibly associated with an increased risk of adverse reactions. A participant presented preliminary findings that earlier administration of BCG vaccine[12] was associated with a decreased risk of developing diabetes, a condition known to have a complex, multifactorial etiology (Classen, 1996). A vaccine manufacturer's representative mentioned evidence of an association (temporal but not necessarily causal) of hepatitis B vaccine with multiple sclerosis (another condition for which etiology is not well understood) in adults but not children.

Related to whether age is a factor in developing adverse events from vaccines is whether some groups of individuals are more predisposed to experiencing such adverse events than others. Immunodeficient individuals are clearly more susceptible to adverse events following vaccination with live viruses. Consequently, these vaccines are not given to them. Some studies also suggest that influenza virus or pneumococcal vaccines given to HIV-infected individuals with advanced disease can increase the amount of HIV in their bodies (Janoff et al., 1995; O'Brien et al., 1995; Tasker et al., 1995). In addition, one study that used LLDBs reported that neurologically impaired children were at a much greater risk of having seizures following childhood vaccinations than a healthy control group (Davis, unpublished data). Such children are at increased risk of having seizures even in the absence of vaccination.

An FDA representative suggested that large clinical trials of a new vaccine be performed in a heterogeneous population before the vaccine is licensed for

[12] Bacillus Calmette-Guérin, a vaccine against tuberculosis, is used extensively in many parts of the world, but not in the United States.

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general use to attempt to detect groups that might be at greater risk of experiencing adverse events. Others commented that this would be difficult and costly, however, because of the increased sample sizes required. Currently, because of the need for close monitoring, accessibility to health care, and data analysis, as well as exclusion criteria for the study of experimental vaccines, clinical trials of vaccines are usually done with a homogeneous population of healthy individuals least likely to experience adverse reactions to the vaccines. Because 2 subpopulations can differ both in their risk of experiencing adverse reactions to a vaccine and in their risk of the disease that the vaccine is designed to prevent, studies to evaluate risks in specific subpopulations could provide needed information.

A consumer representative suggested that VAERS data be used to identify categories of children at higher risk of experiencing adverse events following vaccination. Once identified, these children could be screened out of vaccination programs. She also suggested using the database of the federal Vaccine Injury Compensation Program to detect common denominators among individuals who were injured or who died following vaccination. Analysis of that information could be useful for researchers to identify high-risk children who should not be vaccinated in the future. A CDC representative suggested that the large linked databases are best suited to identifying those at risk of adverse events following vaccination, once the association has been established. This individual believed that VAERS does not have the data necessary for a complete epidemiologic study to assess risk factors (i.e., information on vaccinated children who did not experience the event and on children who experienced the event but who were not vaccinated). The use of Vaccine Injury Compensation Program data would be too expensive if laboratory data were required and too imprecise if history alone were used.

An additional question that was addressed is the extent to which vaccines can trigger disorders through an immune reaction. It is known, for example, that some vaccines can trigger the Guillain-Barré syndrome, which is immune mediated. There is thus justification in studying other immune disorders to evaluate whether they could be related to vaccines. A full assessment of the safety of vaccines requires long-term studies that include controls at low risk for developing the disease prevented by the vaccine being tested, a physician suggested.

A final important question is whether there are long-latency adverse events following vaccinations. A vaccine researcher has studied several adults who have experienced deteriorating brain function over a period of years that in some cases has left them permanently comatose (Martin et al., 1994, 1995). Tests of their brain tissues, blood, and the fluid circulating in their brains and spinal cords have ruled out known causes of brain deterioration. According to

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the speaker, genetic studies suggest that their illness is caused by a newly identified cytomegalovirus closely related to a type that infects African green monkeys. Although there is no evidence of the possible source of the genetic material identified, because the kidney cells of these monkeys are used to culture the viral strains used in the live-virus polio virus vaccine, the speaker hypothesized that at least some lots of this vaccine might harbor a strain of cytomegalovirus that can cause severe brain deterioration decades after vaccination. Although the monkey kidney cells currently used in oral polio virus vaccine production come from laboratory monkeys that are not thought to be infected with viruses and that are screened for viral contamination, previously unsuspected (and therefore not screened for) viruses or viruses present at very low levels could theoretically contaminate the vaccine. A consumer organization representative suggested that FDA regulations for vaccine safety be reviewed and updated to reflect the state of the art in scientific technology so that vaccines are more thoroughly tested for adventitious agents. This testing should include evaluations of the possible roles of additives such as aluminum and formaldehyde in adverse events.

A CDC representative noted that a large number of possible long-term adverse effects could be considered. Given the limited resources at hand, he suggested limiting studies to those effects that seem to be biologically plausible. According to workshop participants, these findings reinforce the need for long-term studies to determine late-onset adverse effects of vaccines. They also suggest that newly devised laboratory tools for virus detection such as the polymerase chain reaction should perhaps be applied even to those vaccines that have historically been accepted as safe to detect adventitious viruses that might cause long-term adverse effects. Such research findings might help to narrow the search for the long-term adverse effects of vaccines.

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WORKSHOP AGENDA

INSTITUTE OF MEDICINE VACCINE SAFETY FORUM

Workshop on Detecting and Responding to Adverse Events Following Vaccination

November 6, 1995

Washington, D.C.

I. Introduction to Adverse Events: The Questions

8:30–8:45 a.m.	*Gerald Fenichel* (Workshop Chair) Vanderbilt University School of Medicine

II. Detecting Adverse Events

8:45–9:45	Surveillance for Vaccine Adverse Events *Rohert Chen*, Centers for Disease Control and Prevention
9:45–10:00	Description of Data in the Vaccine Adverse Event Reporting System (VAERS) *Miles Braun*, Food and Drug Administration
10:00–10:15	**BREAK**

III. Responding to Adverse Events

10:15–10:45	Epidemiologic Methods and the Study of Adverse Events *Samy Suissa*, McGill University
10:45–11:15	Epidemiologic Methods Applied to Vaccine Adverse Events *Marie Griffin*, Vanderbilt University Medical Center

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11:15–11:45	Detection and Response Activities of Vaccine Manufacturers *Luc Hessel*, Pasteur Mérieux Connaught *Robert Levine*, Lederle-Praxis Biologicals *Robert Sharrar*, Merck Research Laboratories
11:45–12:15 p.m.	Experiences of Consumers with Adverse Event Detection and Response *Barbara Loe Fisher*, National Vaccine Information Center *Mark Geier*, Medical/Legal Consultant *Kathy Schaus*, Little Rock, Arkansas *Jack Sexton*, Woodbridge, Virginia
12:15–1:15	**LUNCH**
IV. Examples of Methodologies Applied to Research on Vaccine Adverse Events	
1:15–1:30	Vaccine Lot Surveillance *Susan Ellenberg*, Food and Drug Administration
1:30–1:45	Reviewing Case Reports *Frederick Varricchio*, Food and Drug Administration
1:45–2:00	Analysis of Seizure Reports in LLDBs *Robert Davis*, Group Health Cooperative, Seattle
2:00–2:15	Studying Immune-mediated Disorders *John Martin*, University of Southern California School of Medicine
2:15–2:30	**BREAK**
V. Panel Discussions	
2:30–3:15	Panel 1—Reporting and Data Collection **Moderator**: *Linda Cowan*, University of Oklahoma Health Sciences Center **Panelists**: *Barbara Loe Fisher*, National Vaccine

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	Information Center*; Luc Hessel*, Pasteur Mérieux Connaught*; Gina Terracciano*, Centers for Disease Control and Prevention*; Frederick Varricchio*, Food and Drug Administration
3:15–4:00	Panel 2—Detection Methodologies **Moderator**: *Paul Stolley*, University of Maryland School of Medicine **Panelists**: *Bart Classen*, Classen Immunotherapies*; Susan Ellenberg*, Food and Drug Administration; *Barbara Loe Fisher*, National Vaccine Information Center; *James Singleton*, Centers for Disease Control and Prevention; *Robert Wise*, Food and Drug Administration
4:00–4:45	Panel 3—Response Methodologies **Moderator**: *Paul* Stolley, University of Maryland School of Medicine **Panelists**: *Barbara Loe* Fisher, National Vaccine Information Center ***; John Glasser, Centers for Disease Control and Prevention; Marie Griffin*, Vanderbilt*; John Martin*, University of Southern California**
4:45–5:30	Panel 4—Summation Panel: Where do we stand? **Moderator**: *Gerald Fenichel* (Workshop Chair), Vanderbilt University School of Medicine **Panelists**: *Robert Chen*, Centers for Disease Control and Prevention; Susan Ellenberg, Food and Drug Administration; *Barbara Loe Fisher*, National Vaccine Information Center; *Robert Kohberger*, Lederle-Praxis Biologicals

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Research to Identify Risks for Adverse Events Following Vaccination: Biological Mechanisms and Possible Means of Prevention

Cynthia J. Howe, Richard B. Johnston, and E. Russell Alexander, Editors

EXECUTIVE SUMMARY

On April 1, 1996, the Vaccine Safety Forum convened a workshop entitled Research to Identify Risks for Adverse Events Following Vaccination: Mechanisms and Possible Means of Prevention. The workshop discussed the various immunologic and genetic factors that might influence individuals' responses to vaccines, current research aimed at assessing what populations are at increased risk for experiencing adverse events from vaccines, and research avenues that could be pursued in this regard. This document represents a summary of that workshop.

As discussed at the workshop, a number of immunologic and genetic variables are likely to foster diverse responses to vaccines. Certain populations may be more susceptible to adverse events following vaccination because of some of these variables.

Studies aimed at assessing which groups of individuals may be at most risk for experiencing adverse events from specific vaccines were also addressed. These studies include those that examine the potential link between the following: arthritis and rubella vaccine; anaphylaxis and the measles, mumps, and rubella vaccine; convulsions and the diphtheria and tetanus toxoids and pertussis vaccine (DPT); high-titer measles vaccines and mortality; multiple sclerosis or Guillain-Barré syndrome and vaccination; multiple-antigen vaccinations and adverse events; and adverse events following vaccinations among premature infants.

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Researchers are currently conducting studies aimed at assessing which populations are at risk for certain adverse events, including determining the allergies that make people prone to anaphylactic reactions following vaccination against measles, mumps, and rubella, identifying the neurologic impairments that may make infants more prone to convulsions following vaccination with DPT, assessing premature infants' responses to vaccines, and determining the underlying cause for the increased mortality observed in some populations of girls given high-titer measles vaccine.

A number of questions remain unanswered regarding risks for adverse events following vaccination and ways to lower such risks. Several speakers suggested research avenues that might prove fruitful in this regard, including studies that assess the risk of adverse events after vaccination in specific genetic populations; on a molecular biology level, the impact over time of multiple vaccinations; whether there is a link between learning disabilities and vaccination; whether autistic children have different immune responses than nonautistic children; whether health care workers vaccinated with the hepatitis B virus vaccine (HBV) experience more autoimmune disorders; and whether the antigens in vaccines are likely to cause demyelinating disorders. Although several forum members and other workshop participants voiced concern that some of these studies would be difficult to design or impractical to conduct, the information that they would provide, if the studies are successfully carried out, might be valuable in determining risks for adverse events following vaccination.

INTRODUCTION

As discussed at the workshop, a number of immunologic and genetic variables are likely to foster diverse responses to vaccines. Because vaccines work through their effects on the human immune system, some scientists who study vaccine adverse effects have concentrated on allergic reactions or autoimmune processes as potential causes of adverse effects. Reflecting these ideas, the first session of the workshop addressed research on immune responses to vaccine antigens. If adverse reactions to vaccines are autoimmune reactions, as discussed in the previous section, then susceptibility to adverse events after vaccination might depend in part on an inherited or genetic susceptibility to such reactions. If so, the study of such disorders might provide insight into genetic susceptibility and expression. Reflecting these issues, the second session of the workshop addressed genetic variability in immune factors, and the interaction of these factors with environmental agents.

Certain populations may be more susceptible to adverse events following vaccination because of some of these variables. The third section of the report

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discussed a selected number of these populations. The final section presents a preliminary research agenda of possible or putative links in these areas.

IMMUNE RESPONSE TO VACCINE ANTIGENS[13]

Infection-causing microbes and the vaccines designed to combat them have portions of proteins called antigens. These antigens stimulate a number of cells in the immune system, including macrophages, T cells, and B cells. An immune response begins when macrophages ingest antigens such as proteins entering the body and digest them into antigen fragments. A molecule called MHC (major histocompatibility complex) carries certain of these fragments to the surface of the cell, where they are displayed but they are still locked into the cleft of the MHC molecule. These displayed antigen fragments are recognized by T cells, which stimulate B cells to secrete antibodies to the fragments as well as prompt other immune defenses. According to Berkower, studies suggest that because T cells only recognize antigen fragments from proteins predigested by macrophages, they cannot distinguish between a specific antigen fragment that comes from an infecting microbe and the same antigen fragment that comes from a vaccine (Chisari and Ferrari, 1995).

Stimulated immune cells secrete a variety of chemical substances called cytokines, which determine which class of antibodies are generated. The cytokine interleukin 4, for example, can prompt B cells to secrete immunoglobin E (IgE) antibodies, which trigger allergic reactions. Other cytokines cause B cells to preferentially secrete IgG, which is mainly found in the blood, or IgA, most of which is found in body fluids.

Different MHC molecules bind to different antigen fragments; the set of MHC molecules and the genes that commandeer their production vary widely from one individual to another. Therefore, although the immune systems of two people may respond to the same protein in a vaccine, their T cells may respond to different portions of that protein. This diversity fosters differences in responses to vaccine antigens.

There are at least nine chemically distinct classes of immunoglobulins, and the balance of the various types of cytokines that stimulate antibody secretion determines the final response to a vaccine. Consequently, vaccine responses can differ between individuals because the same vaccine stimulates different individuals to generate different amounts of the various cytokines. Vaccine responses might not only differ in the short term, but they could also vary in the

[13] This section is based on information presented by Ira Berkower, Hira. Nakhasi, Henry McFarland, and Burton Waisbren.

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long term if they trigger a predominantly IgE response. This response could trigger an allergic reaction to future immunizations with the same antigens (IOM, 1994a).

To prevent the body's immune system from destroying its own tissues in what is known as an autoimmune response, immature T cells that react against self-antigens are thought to be destroyed in the thymus gland, creating what is known as central tolerance. Peripheral tolerance might also occur, whereby those T cells that could potentially react to self-antigens and that are not destroyed in the thymus are somehow prevented from causing an autoimmune reaction. Although studies suggest that peripheral tolerance exists, at least in experimental animals, the mechanism for the process is not yet known. If peripheral tolerance exists in people, an autoimmune response might occur in response to vaccination if the vaccine somehow disrupts that peripheral tolerance or if peripheral tolerance is not strong on the day of vaccination (Miller et al., 1989).

Some people have suggested that vaccines can stimulate autoimmune reactions if some of the antigen fragments in vaccines resemble a person's self-antigens. However, it is unclear why an immune system that is tolerant of its own self-antigens would respond to a self-antigen mimic in a vaccine. Berkower speculated that vaccines might counter peripheral tolerance and foster an autoimmune reaction if they contain molecular mimics of self-antigens that are usually not exposed to T cells, because peripheral tolerance seems to depend on the continuous presence of an antigen.

Nakhasi suggested that an autoimmune response might be instigated by a vaccine or by natural infection if the microbial antigens bind to self-antigens in infected cells and change the antigens' shape such that they are no longer tolerated and can elicit an immune response.

According to McFarland, researchers suspect that molecular mimicry, which could possibly lead to an autoimmune disorder, might be occurring between self-antigens and antigens from microbes or vaccines if the two antigens share much of the same chemical structure. Recent studies suggest, however, that they need to have a similar structure only in the narrow region that binds to the T-cell receptor (Vogt et al., 1994; Wucherpfennig et al., 1994). In addition, the amino acids in this region do not have to be identical; rather studies suggest that they must have the same basic chemical and charge properties (Vogt et al., 1994; Wucherpfennig et al., 1994; Vergelli et al., 1996).

Some researchers have hypothesized that autoimmune diseases may be stimulated by viruses (Fujinami et al., 1985; Westall and Root-Bernstein, 1983). Westall and Root-Bernstein have postulated that this may occur if three criteria are met. The first one is that antigens are present that have molecular structure similar to self antigens found in certain human tissue (Westall and Root

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Bernstein, 1983). The second one is that an adjuvant derived from walls of the bacterial cells used in the vaccine's manufacture is present. The third one is that antigens exhibiting complimentarity are present. When these three criteria are present an antigenic challenge to the host evokes autoimmunity. This hypothesis has been named Multiple-Antigen-Mediated-Autoimmunity (MAMA) Syndrome. Root-Bernstein has presented evidence that it exists in AIDS patients who develop encephalomyelitis (Sela and Arnon, 1992). Waisbren suggested that the MAMA Syndrome might be a mechanism that induces autoimmunity in susceptible individuals after vaccination with virus components that are also present in human tissue. These antigens may be associated with other complimentary viral antigens and bacterial cell wall components present in the patient who has been vaccinated.

Premature Infants[14]

Each year about 300,000 premature infants are born in the United States, and most of these survive past infancy (Ventura et al., 1996). Preliminary studies suggest that premature large birthweight infants have the same or less risk of experiencing the usual adverse effects reported for full-term infants following vaccination with HBV or DPT (Bernbaum et al., 1989; Koblan et al., 1988; Ramsay et al., 1995; Losonsky, unpublished data). However, recent data with DPT immunization in very low birth weight infants suggest that moderate to severe adverse reactions can occur following routine vaccination with DPT in infants born less than 1,000 grams (Sudhakarow et al., 1996). Routine immunization of extremely premature infants is associated with significant adverse events. According to Losonsky, larger studies that cover the full range of vaccines given to infants need to be done to assess the risk of common adverse events in premature infants.

Current vaccine schedules are based largely on the immune responses seen in full-term rather than premature infants. The human immune system matures throughout fetal life and up until about 2 years of age, however, so even full-term infants do not develop an adequate protective immune response to most vaccines administered in the first weeks of life. Losonsky expressed concern that premature infants given vaccines at the standard times may not develop adequate immunity to the diseases against which the vaccines are designed to protect. There is also speculation that some premature infants might develop immunologic tolerance to the viral or bacterial antigens in vaccines such that

[14] This section is based on information presented by Gene Losonsky.

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they do not develop an immune response to subsequent vaccines given later in life.

According to Losonsky, 98 percent of full-term infants achieve protective immune responses after receiving the third dose of HBV (Losonsky, unpublished data). A study of HBV given to premature infants, however, found that only 54 percent of infants with birth weights of less than 1,000 grams and 70 percent of infants with birth weights of 1,000 to 1,500 grams attained protective immune responses after receiving the third dose of the vaccine. Thirteen of the premature infants with little or no detectable antibody responses to the three doses of HBV were given a fourth dose of the vaccine at 9 to 12 months of age. Only 46 percent of these revaccinated infants achieved protective antibody levels (Losonsky, unpublished data).

These data suggest, Losonsky noted, the possibility that tolerance develops in some premature infants. Researchers are following those infants who did not respond to the fourth HBV dose to see if their lack of response is permanent. Other studies suggest that the immune systems of premature infants given DPT and oral polo vaccine at standard times respond as well as those of full-term infants (Koblin et al., 1988; Conway et al., 1993; D'Angio et al., 1995). However, a decreased immune response to some enhanced-potency inactivated polio-oral polio vaccine combinations and to certain *Haemophilus influenzae* type b conjugate vaccines was seen in premature infants. The response depended on gestational age and weight at the time of the first immunization (Munoz et al., 1995; D'Angio et al., 1995).

According to Losonsky, these findings suggest that vaccine schedules, dosages, and combinations for preterm infants may have to differ from those for full-term infants. She added that the best schedule and dosage for each vaccine cannot be predicted on theoretical grounds but can only be determined by further study. Care must be taken, she said, not to leave premature infants vaccinated but unprotected from disease. A representative of the National Institute of Allergy and Infectious Diseases (NIAID) pointed out, however, that the risk of inducing tolerance to vaccination for a specific disease must be balanced with the risk of the infant dying or suffering long-term consequences from natural infection. Premature infants, for example, are more likely to have respiratory abnormalities that may put them at greater risk for complications from the respiratory disease pertussis (whooping cough).

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GENETIC FACTORS AFFECTING DEVELOPMENT OF AUTOIMMUNITY[15]

If adverse reactions to vaccines are autoimmune reactions, as discussed in the previous section, then susceptibility to adverse events after vaccination might depend in part on an inherited or genetic susceptibility to such reactions. If so, the study of such disorders might provide insight into genetic susceptibility and expression. Autoimmune disorders, which affect between 10 and 20 percent of the population (Miller, 1995) are thought to be caused by many different genetic and environmental factors acting together. Reflecting these issues, the second session of the workshop addressed genetic variability in immune factors, and the interaction of these factors with environmental agents.

According to Miller, the genes likely to be involved in the development of autoimmune disorders are those that code for the production of MHC molecules, those that encode other proteins involved with antigen processing, and T-cell receptors. Genes that code for or regulate the production of immunoglobulins or cytokines are also likely candidates, as are genes that regulate the metabolism of drugs and toxins. Because most autoimmune disorders are more prevalent in women than men, sex chromosome genes also likely play a role in their development.

Much of the research documenting genetic risk factors associated with autoimmune disorders have focused on the MHC genes, which in humans are known as human leukocyte antigen (HLA) genes. Different HLA gene subtypes have been shown to be associated with an increased risk for different autoimmune disorders.

The interaction of genes can also influence the risk for autoimmune disorders. Researchers have shown that people who have the HLA genetic marker called DQ2 in conjunction with a gene for a certain subtype of immunoglobulin have a much increased risk for autoimmune-mediated myositis, a muscle destroying condition with many etiologies, compared with the risk if they have just one of those genes (Miller, 1995)

Environmental triggers of autoimmune disorders (as discussed above) can also interact with genetic factors. Environmental agents that have been implicated in some autoimmune diseases include infectious organisms, foods, dietary supplements, drugs, toxic agents and other substances, occupational exposures, foreign cells, and medical devices. It is not known for certain how these factors trigger autoimmune disorders. Hypothetical mechanisms include the following: These agents could foster an increased or altered expression of self-antigens, they could cause direct inhibitory or stimulatory effects on

[15] This section is based on information by Frederick Miller and Howard Urnovitz.

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components of the immune system, or they could cause a combination of these effects. Studies suggest that the duration and number of exposures to the same or different agents, as well as the dosage and route of administration of the agent, affect the risks of developing specific autoimmune disorders (Miller, 1997).

Research suggests that the same autoimmune syndrome can be induced by different environmental agents, even though each agent is associated with different HLA risk factors. In contrast, a similar syndrome induced by different agents can sometimes be associated with the same genetic risk factor (Love and Miller, 1993). A lupus-like syndrome can be caused by the heart medication procainamide in association with the HLA subtype DR6, for example, or by the high blood pressure drug hydralazine in association with the HLA subtype DR4. In contrast, two scleroderma-like syndromes, one due to contaminated rapeseed oil and another associated with ingestion of certain manufacturing batches of L-tryptophan, are both associated with the HLA subtype DR4 (Miller, 1997).

Genetic factors that also might influence the risk of developing autoimmune disorders and other possible adverse reactions from vaccines are human endogenous retroviruses (HERVs). HERVs are genetic sequences that resemble retroviruses and that may either be a precursor or a product of viruses whose genes have become inserted into all human DNA. HERVs usually cannot actively infect cells, like viruses can, but evidence suggests that their genes can be expressed, possibly to the point of generating proteins, in certain tissues under certain circumstances. Factors proposed to possibly influence HERV expression include hormones, X rays, compounds generated by the immune system in response to infection, viruses, and steroids (Urnovitz and Murphy, 1996).

A mouse model also suggests that certain genes can influence the expression of specific endogenous retroviruses (ERVs). In this mouse model, mice that have a gene that fosters expression of ERVs develop an age-dependent paralyzing disorder when they are infected with a virus that, without ERV expression, is normally harmless (Murphy et al., 1983).

The possibility that ERVs can be part of the disease process, as in the previously mentioned mouse model, has prompted one workshop speaker to consider the possibility that HERVs play a role in certain human diseases or in adverse events following vaccination. Because HERVs have the enzyme needed to copy and incorporate viral genetic material into human DNA, HERVs theoretically might copy and incorporate the viral genetic material presented in vaccines or natural infections (Urnovitz et al., 1996). Urnovitz hypothesized that these fragments normally would not be expressed but that an infection by another organism, certain hormones, or injury might activate them.

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HERVs might also alter immune responses to infection or a vaccine. Laboratory studies of a synthetic molecule similar to a mouse ERV have found that the compound can alter the cytokine balance, which affects T-cell responses to infections (Haraguchi et al., 1995).

In general, the genetics of autoimmune diseases makes it difficult to determine whether these syndromes could be induced by vaccines. The facts that multiple genes and environmental factors can cause a single autoimmune disorder and that the genetic markers for susceptibility may not be the genes causing the increased risk but are only closely linked on the DNA strand to the genes for those risk factors complicate the process of determining causation. These risk factors can also differ among ethnic and racial groups. The hypothesis that some adverse effects of vaccines are caused by viral vaccine-related HERV gene expression is a reasonable hypothesis. However, the current lack of experimental research confirming or refuting the hypothesis makes it impossible at this time to attribute vaccine effects to this type of genetic influence.

RESEARCH ON IDENTIFYING POPULATIONS AT RISK FOR ADVERSE EVENTS

Individual susceptibility to vaccine adverse effects may be associated with population risk factors of various sorts. The following sections represents topics chosen by the Forum members, based on their knowledge of potentially promising research. These studies include those that examine the potential link between the following: arthritis and rubella vaccine; anaphylaxis and measles, mumps, and rubella vaccine; convulsions and DPT; high-titer measles vaccines and mortality; multiple sclerosis or Guillain-Barré syndrome and vaccination; multiple-antigen vaccinations and adverse events; and premature infants and adverse events following vaccination.

Arthritis and Rubella Vaccine[16]

Rubella (German measles) infections are associated with arthritis in some patients, and there is concern that the rubella vaccine, which consists of a live weakened strain of rubella virus, might instigate an autoimmune response that results in arthritis (Institute of Medicine, 1991). Research has uncovered two cellular host proteins to which the rubella virus needs to bind in order to

[16] This section is based on information presented by Hira Nakhasi.

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replicate (Singh et al., 1994; Pogue et al., 1996). Antibodies to these two self-antigens have been found in the serum of patients with rheumatoid arthritis, an autoimmune disorder (Pogue et al., 1996). Nakhasi hypothesized that when the rubella virus binds to these self-antigens, it changes their shapes such that they are no longer tolerated and can elicit an immune response.

Investigators are assessing whether people given the rubella vaccine develop autoantibodies to the two self-antigens needed for viral replication and whether such autoantibody production is associated with the development of non-rheumatoid arthritis in the long term. Another recent study, however, has not found a correlation between arthritis and rubella vaccination (Slater et al., 1995). A geneticist from the National Institute of Child Health and Human Development (NICHD) suggested assessing whether genetic variation in the genes that code for the two self-antigens to which rubella virus binds might explain differences in susceptibility to arthritic complications of rubella or rubella vaccination.

Anaphylaxis and Measles, Mumps, and Rubella Vaccine[17]

Anaphylaxis is a life-threatening allergic reaction whose symptoms include itching, hives, low blood pressure, abnormal fluid retention that causes swelling of tissues, and difficulty breathing. According to a report by the Institute of Medicine, the evidence established a causal relation between measles, mumps, and rubella vaccine and anaphylaxis. Estimates of the risk range from 1 per 20,000 to 1 per 1,000,000 per doses distributed (Institute of Medicine, 1994a).

Measles, mumps, and rubella vaccine consists of measles, mumps, and rubella antigens, gelatin, sorbitol, neomycin, and residual egg proteins. Because egg proteins can stimulate an anaphylactic reaction in individuals severely allergic to eggs, it has been assumed that the egg-related antigens in the vaccine were responsible for the rare cases of anaphylaxis that occur following vaccination. Consequently, the American Academy of Pediatrics (AAP) has recommended that children with severe egg allergies be skin tested for allergy to the vaccine. If they test positive, they must then receive a series of allergy shots to desensitize them to the vaccine. It is also recommended that they be observed by trained medical personnel for 20 minutes after vaccination (American Academy of Pediatrics, 1994).

Recent studies suggest that the AAP guidelines may not be appropriate or sufficient. In one study of 224 children with a history of egg allergy, only 29 skin tested positive to measles, mumps, and rubella vaccine. Of these children,

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only three also reacted to the vaccine (James et al., 1995). Furthermore, preliminary findings of several investigators also suggest that the gelatin and not the egg component of the vaccine may be the cause of some anaphylactic reactions. A Japanese study found, for example, that the blood of 10 out of 11 patients who had an anaphylactic reaction after vaccination against measles, mumps, and rubella reacted to the gelatin used in the vaccine (Sakaguchi et al., 1995). Another study found that 38 patients who had an anaphylactic reaction to the vaccine were not allergic to eggs (James et al., 1995). According to Phillips, these findings suggest that screening for egg allergy alone may not be fully effective in preventing anaphylaxis and that most children who are allergic to eggs can safely receive the vaccine.

Future research on the food allergies of patients who have anaphylactic reactions to vaccines should help discern the cause of these reactions. Once the component of the vaccine responsible for the reaction is determined, improved screening protocols for patients at risk for such reactions can be developed. Alternatively, vaccine manufacturers may be able to eliminate the allergenic component of a vaccine.

Another study of the reports of anaphylaxis occurring following vaccination against measles, mumps, and rubella indicated that the time to the onset of the anaphylaxis reactions was less than 20 minutes in fewer than half of the subjects (Phillips, unpublished data). These data suggest that 20 minutes may not be an adequate time for observing a patient after vaccination with the vaccine. In addition, most of the reports were of anaphylaxis that occurred after receipt of the second dose of the measles, mumps, and rubella vaccine, so a history of receipt of the vaccine without adverse consequences may not indicate a low risk of adverse consequences in the future.

Convulsions and DPT[18]

A recent study by the Centers for Disease Control and Prevention (CDC) found that infants with a history of convulsions were about 10 times more likely to experience convulsions or other neurologic adverse events following vaccination with DPT than infants without a personal history of convulsions (Haber et al., 1993). CDC researchers also found that infants with a family history of convulsions were about three times more likely to have convulsions or other neurologic adverse events after vaccination with DPT than infants without such a family history (Chen et al., 1993).

[18] This section was based on information presented by Robert Chen and Robert Davis.

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According to Chen, these findings confirm the results of previous studies and suggest that the AAP recommendations regarding vaccination with DPT are still valid. These recommendations are that infants with a history of convulsions not receive DPT until their neurologic conditions are clearly determined. Once determined, they should then receive diphtheria and tetanus toxoids (DT) unless the seizure disorder is controlled, in which case they should receive DPT. ACIP has concluded that a family history of febrile convulsions should not deter infants from receiving DPT (CDC, 1993). More rigorous controlled studies need to be conducted, however, to assess firmly the risk of convulsions following vaccination with DPT in infants with a personal or family history of febrile or afebrile convulsions.

CDC is conducting a large controlled study of the risk of convulsions following vaccination with DPT in infants who are neurologically impaired or considered at risk of being neurologically impaired because of a number of factors, including being born prematurely, deprived of oxygen during birth, or developmentally delayed. This study will use data in the Large Linked Database (LLDB), a CDC-coordinated linkage of four large health maintenance organizations' databases. Comprised of automated data for nearly 500,000 children in Oregon, Washington, and California, the LLDB includes information on hospital, outpatient and emergency department utilization. Using these files, researchers can identify children who are neurologically impaired or at risk of such impairments, and assess their response following vaccination with DPT in comparison with children not recently vaccinated. According to Davis, the number of children in the study is large enough to determine with relatively high statistical confidence whether children with neurologic impairments or at risk for neurologic impairment are at increased risk for experiencing convulsions following vaccination with DPT.

High-Titer Measles Vaccine[19]

In most developing countries, infants receive the measles vaccine at 9 months of age. Because there is a high rate of transmission of measles in infants younger than this among certain populations in developing countries, the World Health Organization (WHO) recommended in 1989 that infants in these populations receive a high-titer, live attenuated measles vaccine at 6 months of age. To prompt a protective immune response in younger infants, the high-titer measles vaccine has more measles antigen than the standard measles vaccine.

[19] This section is based on information presented by Elizabeth Holt, Maria Elena Leon, Brian Wahl, and Robert Chen.

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According to Holt, initial tests of this vaccine indicated that infants at 5 to 6 months of age had immune responses similar to those found among children who received standard-titer measles vaccine at 9 months of age. Adverse events associated with the vaccine, such as rash and fever, occurred at rates similar to those among children who received the standard measles vaccine.

More long-term studies in Haiti, Guinea-Bissau, and Senegal, however, found that girls who received the high-titer vaccine were more likely to die before the age of 3 years than those who received the standard vaccine (Aaby et al., 1993a; Garenne et al., 1991; Holt et al., 1993). The two most common causes of death in the Haiti study were diarrhea and malnutrition. On the basis of these findings, WHO recommended in 1992 that high-titer measles vaccine not be given to children (WHO, 1992).

Natural measles infection has been associated with some suppressed T-cell functions that can persist for months after complete recovery from the acute illness (Aaby et al. 1990a, 1990b, 1993b). Thus, there was concern that the high-titer measles vaccine might also be inducing long-term immune suppression. A cross-sectional study conducted in Peru, however, found that although children who received the high-titer vaccine an average of 27 months earlier had slightly lower values for a number of immune function parameters evaluated, the values were within the normal range (Leon et al., 1993). Girls who received the high-titer vaccine, however, had a significantly lower proportion of a type of T cell known as CD4 in their blood than did girls who received the low-titer vaccine. Recipients of the high-titer vaccine responded less well to tetanus, diphtheria, and pertussis antigens, but the differences were not statistically significant in a multiple linear regression model. However, recipients of the high-titer vaccine had lower proliferative responses to mitogen (PHA) and girls who received the high-titer vaccine had a lower proportion of CD4+ T cells in the peripheral blood. Girls who received the high-titer vaccine also had smaller size skin test responses (delayed type hypersensitivity responses) to tetanus antigens.

Two studies conducted in Sudan and Haiti 4 to 5 years after high-titer vaccination evaluated a variety of immunologic parameters and found no consistent major differences between the high-titer vaccine recipients and the low-titer vaccine recipients (Bertley et al., 1997a and 1997b; Libman et al., 1997). There were minor differences in a number of immunologic parameters between all children who received the high-titer and low-titer vaccines, and between girls who received the high-titer and low-titer vaccines. However, the differences were not in excess of what would be expected by chance when a large number of immunologic tests is performed. The Sudan study found that during a 5-year period, children who received the high-titer measles vaccine

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were not ill more often than those who received the low-titer vaccine. This was also true for girls.

Ward noted that all children in both studies had measles antibodies by age 5, even though 10 to 20 percent of these children had not developed antibodies to measles shortly after they received the measles vaccine when they were infants. These initially seronegative children were likely to have been infected with natural measles, which was circulating in Sudan and Haiti, between the time that these children were vaccinated and the time that they were followed up. This suggests that any effects observed in the study may be due, in part, to natural infection with measles and not to the measles vaccine received.

Chen noted that one study indicates that there may be delayed mortality after a natural measles infection (Hull et al., 1983). This delayed mortality might be mimicked by the measles vaccine with a high antigen titer. The delayed mortality associated with measles infection might occur more often in girls, Ward said, because studies suggest that measles causes more deaths in girls than in boys (Garenne et al., 1991). Such excess delayed mortality is not seen in all outbreaks (Chen et al., 1994).

Multiple Sclerosis or Guillain-Barré Syndrome and Vaccines[20]

Both multiple sclerosis (MS) and Guillain-Barré syndrome (GBS) are thought to be associated with certain vaccines (IOM, 1994) but the causal mechanisms of these adverse effects are not known and somewhat speculative. On the presumption that there is an association, some possible mechanisms worth exploring were discussed at the workshop.

The hallmark of MS, which affects between 250,000 and 350,000 people in the United States (Kurtzke, 1997), is patchy destruction of the fatty sheath, called myelin, that envelops and insulates the nerves in the brain and spinal column. This destruction of myelin disrupts the passage of messages along these nerves, causing a number of symptoms that include weakness, tingling, numbness, loss of coordination and balance, dizziness, muscle spasms, slurred speech, and blurred or double vision. The cause of MS is unknown, although it is thought to be an autoimmune disorder that afflicts a subgroup of people who are genetically susceptible. According to McFarland, studies have failed to demonstrate that MS is caused by a molecular mimicry mechanism.

The symptoms of MS tend to wax and wane over time, and magnetic resonance imaging (MRI) studies suggest that patients have central nervous

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system damage several years prior to the appearance of symptoms that present at time of diagnosis (Stone, 1995). The only factor shown definitively to trigger exacerbations of MS is an acute viral infection. MS patients who have acute viral infections are at greater risk for an exacerbation than those who are not infected (Sibley, 1997). Several studies have found that vaccination does not increase the risk for an exacerbation of MS (Miller et al., 1997). One study using MRI found there was no evidence of increased nerve damage in MS patients after vaccination against influenza virus (Ropper, 1992).

Another autoimmune disorder, GBS, causes progressive paralysis due to a loss of myelin around nerves. A majority of GBS patients report some kind of "trigger" event (infections, surgery) shortly before the onset of GBS (Ropper, 1992). Studies of swine influenza vaccine recipients indicated that they had approximately 8 fold increase risk of GBS during the weeks immediately post-vaccination compared to nonrecipients (Schonberger et al., 1979; Safranek et al., 1991). It is not clear whether a contaminant or the virus itself in these batches made people more susceptible to GBS. Subsequent influenza vaccines prepared from other virus strains have not been clearly associated with an increases risk of GBS (Hurwitz et al., 1981; Kaplan et al., 1982; Chen et al., 1992). During five of six seasons studied since 1976, the point estimates of the relative risks of GBS after influenza vaccination were slightly elevated; however, in none of these studies was the overall elevation in relative risk statistically significant (CDC, 1997). This may be due to either a low barely detectable risk or by uncontrolled confounding or bias. Another study found that those individuals who reported experiencing GBS following vaccination against swine flu were not more likely than those without the syndrome to have a family or personal history of autoimmune disorders (Ropper, 1992).

Multiple-Antigen Vaccination and Adverse Immune Responses[21]

Some people have expressed concern that individuals vaccinated for several diseases simultaneously might be at increased risk for experiencing adverse effects, such as abnormal immune system responses (Peeler et al., 1958; Peeler et al., 1965; White et al., 1974). Although people are constantly exposed to multiple antigens, the presentation (injection into skin or muscle, for example) of vaccine antigens is different from the way common antigens, such as food or naturally-occurring viruses and bacteria, are encountered. Many employees at the USA Medical Research Institute of Infectious Diseases at Fort Detrick in Frederick, Maryland, receive multiple vaccinations to protect them from the

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microbes being researched at the institute. Studies comparing these employees with a control group found a few significant differences in immunologic parameters, including elevated levels of antibodies in their blood. These differences increased as more time passed following immunization, but the findings are of questionable clinical significance. Researchers are conducting another study that will evaluate a number of immunologic parameters in retired and current employees at the institute, most of whom received a half dozen vaccines over a 6to 9-month period.

RESEARCH OPPORTUNITIES[22]

A number of questions remain unanswered regarding risks for adverse events following vaccination and ways to lower such risks. Several speakers, including a parent representing a consumers organization focused on vaccine safety, suggested research avenues that might prove fruitful in this regard.

Hanson pointed out that although children with genetic disorders or other chronic conditions represent between 5 and 15 percent of all children (Warkany, 1971), the effects of vaccination on these children are not known because they were either excluded from or not present in large enough numbers in the studies that initially tested the effects of vaccines. He suggested that researchers assess the risk of adverse events associated with vaccination in populations with specific genetic makeups.

Identifying families with several members who experience similar adverse events after vaccination, the speaker added, could provide a highly enriched sample of families suitable for studies of genetic factors associated with the adverse effects of vaccines. These families could be identified by using the LLDB, which could also be used to identify twins useful in the study of genetic differences associated with the risk of adverse events following vaccination. To prioritize which genetic populations should be studied, the speaker suggested creating ranked categories of conditions on the basis of the most frequent claims under the Vaccine Injury Compensation Program, and among those, the conditions most likely to have a genetic susceptibility component worthy of study. These studies could use genetic markers of development of disease identified from other studies. The use of such markers, however, requires researchers to develop ways to protect research subjects from discrimination on the basis of their genetic makeup, the speaker noted.

[22] This section is based on information presented by James Hanson, Marcel Kinsbourne, Burton Waisbren, Barbara Loe Fisher, and other forum members.

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A CDC epidemiologist noted that no unique laboratory diagnosis or clinical syndrome has been identified for most of the rare, serious outcomes associated with vaccination. Without the ability to define uniquely such adverse events, it will be difficult to link them to specific genetic markers. He added, however, that such analysis is feasible for adverse events that are more common, such as seizures, with the use of the LLDB. By genetically analyzing tissue or blood samples from those individuals who developed seizures following vaccination with DPT, for example, and comparing them with samples from matched controls who did not react adversely to vaccination, researchers might discern a genetic marker for susceptibility to seizures following vaccination with DPT.

Fisher delineated five research areas that she felt, from a parent's perspective, were important to pursue. One was research to evaluate, on a molecular biology level, the impact over time of repeatedly manipulating the human immune system with single and multiple antigens. Parents who are being asked or required by law to vaccinate their children with increasing numbers of vaccines, she pointed out, want it known what exactly is happening in the human body at the molecular level when several vaccines are given simultaneously or over a short period of time, compared to physiologic responses to naturally-presented antigens, such as those found in the viruses or bacteria against which the vaccines are directed.

The way in which an antigen is presented to the body, including whether in a vaccine or through natural infection, could affect the immune response. The route of immunization with DNA vaccines, for instance, could influence the type of cytokine response elicited by the vaccine.[23] In addition, the immune response to multiple antigens given simultaneously could be different than the response to the same antigens given individually (Goldenthal et al., 1995). A representative of a vaccine manufacturer said that studies are being conducted to assess some of the short-term immunologic effects of vaccines given separately versus the effects of those given simultaneously.

Consumer advocates also question whether there are differences in long-term immunologic function and health status between children who receive vaccinations and those who do not. Several vaccine manufacturer representatives and biomedical researchers noted that it would be a challenge to conduct studies aimed at assessing the long-term immunologic effects of vaccination versus nonvaccination. It is difficult to find for such studies a group of nonvaccinated children who are similar in all relevant aspects to vaccinated children, an epidemiologist pointed out. Other researchers noted that even if immunologic differences are detected between vaccinated and nonvaccinated

[23] Based on data presented at the International Meeting on Nucleic Acid Approaches for the Prevention of Infectious Diseases, Bethesda, Md., February 5-7, 1996.

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children, it would be difficult to assess whether those differences are due to the dozen or so antigens encountered in vaccines or to the myriad of antigens a child encounters through infections or diet.

There are several immunologic parameters that one could study, a vaccine manufacturer pointed out, and it is not known which are of the highest priority for documenting potential changes with respect to vaccination. It is not practical and there are not enough resources, he said, to evaluate all immune parameters. Ultimately, the immune parameters selected should relate to protection from the agent as well as related to adverse events. One researcher noted that vaccines have mainly been evaluated in terms of their ability to generate antibodies. She suggested conducting more studies that determine T-cell response or other immune parameters besides antibody response, as is already being done for AIDS vaccines. Even if immunologic differences were found when individuals are exposed to an antigen via a vaccine versus via natural infection, a researcher noted, those differences will be difficult to interpret in terms of their implication for susceptibility to disease or the development of subsequent disease.

The second important area of research, Fisher said, is to assess whether vaccinations in conjunction with antibiotic use and exposure to environmental toxins make people more vulnerable to new and more virulent viruses and bacteria or more prone to adverse effects from vaccines or infections. Others questioned the scientific basis for this hypotheses.

Third, she suggested that studies be conducted to investigate the possible link between vaccination and learning disabilities or attention deficit disorder. More than 2.5 million children with specific learning disabilities have been identified in the United States (U.S. Dept. of Education, 1996). She and Kinsbourne, a pediatric neurologist, noted that a vaccine that might, in rare cases, cause severe brain damage might more frequently cause milder forms of brain damage that could manifest itself as a learning disability or attention deficit disorder. This hypothesis is based on evidence that some causes of brain damage, such as low oxygen conditions during birth, not only cause severe mental retardation or cerebral palsy but are also associated with an increased risk of the hyperactive impulsive behavior that is seen in children with attention deficit disorder (Nichols and Chen, 1981; Astbury et al., 1987).

If a vaccine causes mild brain damage, the effects of such damage may not be apparent for several years following vaccination, Kinsbourne pointed out. Deficits in such skills as learning to read, spell, write, or concentrate, for example, will not become apparent until the child has reached a level of development where such skills are expected. Kinsbourne also noted that there are several different kinds of learning disabilities and that there are no established causes for any of them.

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Kinsbourne suggested conducting a study to assess whether learning disabilities occur more frequently in vaccinated children who suffered adverse reactions (particularly neurological) as compared to those who did not. The other logical comparison of vaccinated with unvaccinated children might be more difficult in terms of obtaining a sufficiently large unvaccinated sample matched for age, sex. and SFS. Such a study would, in particular, focus on pertussis vaccine, the well recognized adverse reactions of seizures, hypotonic/ hyperesponsive episodes and prolonged inconsolable crying within 72 hours of the vaccination. Potential outcome variables of particular interest would be attention deficit-hyperactivity disorder, selective learning disabilities, and clumsiness with motor soft signs.

Fisher's fourth research priority was that researchers conduct studies to investigate the possible link between vaccines and autism. Autism affects 1 in 1,000 children (Bryson, 1996). Some autistic children have been found to have abnormally high levels of rubella antibodies. When these children were given intravenous immune globulin (known as IVIG), their rubella antibody levels fell and their autism seemed to improve (Gupta et al., 1996).

It was suggested that a study comparing a number of measures of immune function in autistic versus nonautistic children would be worthwhile. Others pointed out, however, even if an immunologic abnormality is found in autistic children, it will be difficult to establish whether vaccines rather than other factors such as infectious diseases or toxic exposures trigger this abnormality.

Fisher's fifth research priority was studies that will, on a continuing long-term basis, scientifically reevaluate each of the 10 vaccines being given to children. These would include full evaluation of the safety of the growth media, adjuvants, preservatives and other additives, as well as identification of genetic and other risk factors, to screen out children at high risk for experiencing an adverse event after vaccination. She expressed concern that viruses in the animal tissues used to produce some vaccines might be introduced into the body via vaccines, and some of these might cause disease. Vaccine manufacturers currently screen the tissues that they use in vaccine production for known infectious agents, but it is possible, Fisher pointed out, that viruses previously unknown might be present in the growth media used in vaccine production.

A practicing internist had several suggestions of ways to assess whether particular disorders can be stimulated by specific vaccines and, if so, ways to avoid such stimulation. Because there have been several reports the development of MS or other syndromes characterized by a loss of myelin following vaccination with HBV (Shaw et al., 1988; Herroelen et al., 1991; Nadler, 1993), he suggested contacting 1,000 hospitals and having each of them determine whether a randomly selected sample of 100 of their nurses vaccinated with HBV developed any symptoms suggesting a demyelinating autoimmune

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disorder. A workshop participant noted that any findings from such a study would not be applicable to the general population because, by the nature of their occupation, health care workers have different exposures than the general public. In addition, health care workers are adults, and thus may not be informative to the infant immunization issues.

It was noted that because HBV was initially given predominantly to health care workers, if there is a link between the vaccine and demyelinating disorders such as MS or GBS, the incidence of these disorders should be significantly greater in health care workers than in the general public. This could be relatively easily assessed with epidemiologic studies with data collected in other established studies of health care workers. A CDC representative pointed out, however, that MS initially occurs most often in young women. A higher frequency of the disorder in vaccinated nurses, who are predominantly young women, may reflect a higher incidence of the disease in this population and may not be directly due to vaccination.

Waisbren also suggested testing all present and projected vaccines for antigens that are similar in molecular structure to human myelin and assessing whether these antigens induce in an animal model a demyelinating condition called allergic encephalomyelitis (EAE). If they do, he suggested their removal from present and future vaccines with the use of genetic engineering or other techniques (Sela and Amon, 1992). A FDA representative noted that although it would be relatively easy to remove antigens from genetically engineered vaccines and assess whether those antigens can induce EAE, it is more difficult to do so in vaccines made up of live whole viruses, in which all the antigenic components are not clearly isolated.

A drug company representative noted that the three-dimensional structure of an antigen is often critical to the effects that it can have on the body. This three-dimensional structure is dependent on the connections that the antigen has to other components in the vaccine. Consequently, whether or not the antigen, in isolation, induces EAE may not indicate whether it would be able to do so in the three-dimensional conformation that it would have in the vaccine. However, such an analysis may be useful for some antigens whose functions are not as dependent on their three-dimensional structures. Other forum members voiced concern about the applicability of the EAE model because it uses an adjuvant that stimulates the immune system to a greater degree than most adjuvants used in vaccines.

Waisbren also suggested testing the MAMA hypothesis as an explanation for why some people develop GBS or MS after vaccination with HBV by determining if vaccinated patients showed an increase in the number of antimyelin T cells in their circulating blood (Shaw et al., 1988; Herroelen et al., 1991; Zhang et al., 1994). Vaccines could also be checked for homology

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between their polypeptides and human myelin and for complimentarity of their antigens with other viruses or bacterial cell wall substances that might be present in vaccine recipients (Westall and Root-Bernstein, 1983).

In summary, a number of questions remain unanswered regarding risks for adverse events following vaccination and ways to lower such risks. Several speakers suggested research avenues that might prove fruitful in this regard, including studies that assess the risk of adverse events after vaccination in specific genetic populations; on a molecular biology level, the impact over time of multiple vaccination; whether there is a link between learning disabilities and vaccination; whether autistic children have different immune responses than nonautistic children; whether health care workers vaccinated with the hepatitis B virus vaccine (HBV) experience more autoimmune disorders; and whether the antigens in vaccines are likely to cause demyelinating disorders. Several forum members and other workshop participants voiced concern that some of these studies would be difficult to design or impractical to conduct because of a lack of standard definitions or reactions, rarity, and lack of clear diagnostic tests for risk states such as autism. Others felt that information that they would provide, if the studies are successfully carried out, would be valuable in determining risk for adverse events following vaccination.

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WORKSHOP AGENDA

INSTITUTE OF MEDICINE VACCINE SAFETY FORUM

Workshop on Research to Identify Risks for Adverse Events Following Vaccination: Mechanisms and Possible Means of Prevention

April 1, 1996

Washington, D.C.

8:25 a.m.	Introduction *Russell Alexander*, Seattle-King County Health Department; Workshop Chair
8:30	Challenges for Vaccine Safety Research: Creating a Comprehensive System *James Hanson*, NICHD
8:45	Immune Response to Vaccine Antigens *Ira Berkower*, FDA
9:15	Anaphylaxis *Lynelle Phillips*, CDC
9:35	Personal and Family History of Convulsions *Robert Chen*, CDC
9:55	Using LLDBs to Identify Children at Risk *Robert Davis*, University of Washington
10:15	Adverse Effects of Immunization of the Premature Infant *Genevieve Losonsky*, University of Maryland
10:35	BREAK

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10:50	High-Titer Measles Vaccines: Gender, Mortality, and Immunologic Profile *Elizabeth Holt*, Johns Hopkins University *Maria Elena Leon*, Johns Hopkins University *Brian Ward*, McGill University
11:40	Discussion
12:15 p.m.	LUNCH
1:15	Rubella and Arthritis *Hira Nakhasi*, FDA
1:35	Genetic Risk Factors for Environmentally Associated Autoimmune Diseases *Frederick Miller*, FDA
1:55	Jumping Genes, Genetics, and Molecular Memory *Howard Urnovitz*, Calypte Biomedical Corporation
2:15	Research Needs, Perspective from Parents *Barbara Loe Fisher*, National Vaccine Information Center
2:35	Methodologic Considerations in Studying People Receiving Multiple Antigens *Philip Pittman*, USAMRIID
3:05	BREAK
3:20	Autoimmune Demyelinating Diseases *Henry McFarland*, NINDS
3:40	Hepatitis B Vaccine and Autoimmune Demyelinating Diseases *Burton Waisbren*, Waisbren Clinic
4:00	Learning Disorders and Vaccines *Marcel Kinsbourne*
4:20	Discussion
5:00	ADJOURN

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Vaccine Safety Forum: Summaries of Two Workshops
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