

NIAID (Austrian)—San Francisco (Kaiser) Trial, 1975-77

Austrian, with the cooperation of Marvin A. Fried, conducted a large clinical trial involving 13,600 subjects 45 years of age and older enrolled in the Kaiser Permanence Health Plan in San Francisco, California (Austrian, et al., 1976). A total of 6,850 subjects received a 12-valent vaccine (Types 1, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19, 23) produced by Eli Lilly, and 6,750 subjects received a saline placebo.

Data from this study have not been completely analyzed, so there is as yet no conclusive evidence from this study of this vaccine's efficacy in preventing pneumococcal pneumonia. Nonetheless, two findings can be reported. First, no cases of pneumococcal bacteremia caused by the serotypes represented in the vaccine were reported among vaccine recipients, whereas four such cases were reported among controls. Second, about 60 percent of those who received pneumococcal vaccine reported no adverse reactions, about 40 percent experienced discomfort or pain at the injection site, 35 percent developed redness at the injection site, and 3.4 percent developed a mild fever (Austrian, et al., 1976).⁷

NIAID (Ammann)—San Francisco (Univ. of Calif.) Trial, 1974-76

Arthur Ammann tested the safety and efficacy of a Lilly-produced 8-valent pneumococcal polysaccharide vaccine (Types 1, 3, 6, 7, 14, 18, 19, and 23) among children believed to be at high risk of contracting pneumococcal disease (Ammann, 1977). These children, who had either sickle-cell anemia or inadequate spleen function, were vaccinated at the University of California, San Francisco Medical Center.

Ammann administered Lilly's 8-valent pneumococcal vaccine to 96 high risk children: 77 patients with sickle-cell anemia and 19 with inadequate spleen

function. He then measured and compared antibody responses to the vaccine among these unhealthy children with antibody responses elicited by the vaccine among 44 healthy children.

Ammann also immunized another 38 healthy young people and observed them specifically for adverse reactions. Further, during a 2-year postimmunization period, Ammann compared the incidence of pneumococcal infection among the 77 vaccinated sickle-cell patients with that among 106 unvaccinated sickle-cell patients.

Antibody titer responses to pneumococcal vaccine among the 96 high risk children were good and did not differ significantly from the responses among the 44 healthy children. Among the 77 sickle-cell patients, the mean fold increase in indirect hemagglutination titers (i. e., the postimmunization titer divided by preimmunization titer) ranged from 1.65 (Type 19) to 12.55 (Type 3). Among the 19 asplenic children, the corresponding mean fold increase in titers ranged from 1.46 (Type 19) to 18.36 (Type 3). Among both these groups of patients, a mean fold increase of 2.00 or more was recorded 3 to 4 weeks after immunization for six of the eight types of pneumococci represented in the vaccine. A mean fold increase of 2.00 or more for six of the eight types also was recorded among both groups of patients 1 year after immunization.

The only adverse reactions Ammann found were local pain at the injection site and one case of brief fever (38 °C). During a 2-year postimmunization period, he found no cases of pneumococcal infection among the 77 vaccinated sickle-cell patients and eight cases among the 106 unvaccinated sickle-cell patients who served as controls.

Based on his results, Ammann's conclusions were that 1) the 8-valent pneumococcal polysaccharide vaccine stimulates type-specific antibody formation in patients with inadequate spleen function, 2) the vaccine may help reduce the incidence of pneumococcal infection in sickle-cell patients and 3) the vaccine produces very few adverse reactions.

⁷See tables 7 and 8 in ch. 3.

Appendix 3.7

CDC'S PASSIVE, VOLUNTARY CASE REPORTING SYSTEM FOR MONITORING ADVERSE REACTIONS TO LICENSED VACCINES¹

Introduction

Vaccinations are recommended and administered to millions of children and other individuals each year on the presumption that the benefits far outweigh the risks. The benefit side of the equation is

straightforward: vaccinations can prevent serious disease. The risk side is not as straightforward, since it includes factors that are known and others that

¹This appendix (apart from the title) is a verbatim reproduction of CDC's official written description of its system for monitoring and reporting adverse reactions to licensed vaccines.

may exist but have not yet been discovered. It is necessary, therefore, to maintain surveillance of potential risks of vaccination to continually reevaluate whether individual vaccinations are, on balance, good for people. Such surveillance is important, not only to provide potential vaccinees with accurate information about the consequences of vaccination, but also to stimulate improvements in the vaccination process or recommendations that will minimize or eliminate the risks.

The surveillance of these risks, or adverse reactions to vaccination, can be carried out actively or passively. In the active approach, systematic and intensive efforts are made to obtain reports of all adverse effects following vaccination. An example of this is a clinical field trial, required for licensure of a new vaccine. In the passive approach, a mechanism is established by which individuals may voluntarily report vaccine reactions. The active approach is comprehensive, but costly in terms of personnel time and other resources. The passive approach is not comprehensive, but it can be reasonably efficient at detecting severe and uncommon reactions without substantial expenditures of time and resources since it makes maximum use of existing reporting mechanisms and procedures.

The following discussion describes a passive system for monitoring adverse reactions to vaccination that should be used by all immunization projects. Included will be a form for reporting adverse reactions to the Center for Disease Control where a National Adverse Reactions Monitoring System will be maintained.

System Description

The system description will center around these topics:

- designation of adverse reaction coordinators,
- establishment of a reporting mechanisms,
- stimulation of reporting,
- criterion for reporting, and
- submission of reaction reports to CDC.

Designation of Adverse Reaction Coordinators

The responsibility for establishing an Adverse Reaction Monitoring System is that of each Immunization Project Office. The first step is to designate an individual on the Immunization Project staff to serve as System Coordinator. This individual will then be responsible for establishing the system in the Project area and for coordinating its operation.

In establishing the system, the first task of the System Coordinator should be to have Adverse Reaction

Coordinators designated in each local health jurisdiction within the Project area. These could be individuals in county health departments or large public clinics. In addition, Adverse Reaction Coordinators should be designated in hospital emergency rooms wherever possible and representatives of the State and local medical societies and pediatric organizations should be invited to serve as liaison people to the system to promote the reporting of reactions from the private sector. (The establishment of these contacts can be delegated to the local coordinators.)

The designation of Adverse Reaction Coordinators will create a surveillance network which can be used to collect information about vaccine reactions and channel the reports to the points at which analysis can be carried out. These local Coordinators will have the specific responsibilities of implementing a reporting mechanism in their areas, of stimulating reporting by the public and local immunization providers, and of making sure that reports are submitted promptly and correctly to the Immunization Project Office. The System Coordinator in the Central Office may be the logical person to be responsible for monitoring all phases of the operation and for submitting reaction reports to the Center for Disease Control. Copies of the reports should be forwarded to the Regional Offices.

Establishment of a Reporting Mechanism

The next task of the System Coordinator is the establishment of a mechanism through which the public and immunization providers can easily report vaccine reactions. One possibility is the installation of a toll-free telephone which can be called without charge from anywhere within the Project area. Another possibility is the designation of local telephones in each health jurisdiction for receiving reaction reports. Both methods may be used conjointly.

The telephones should be attended during regular business hours by the designated Coordinator or other health professional. A supply of the form, "Report of Illness Following Vaccination" (Exhibit One),² should be kept near the telephone(s) so that reports can be documented on it directly. Consideration should be given to the use of tape recording units to handle calls made after hours.

Telephone communication should be the primary mechanism for receiving reaction reports in a Project Area. It may be supplemented, however, by a mechanism for receiving reports through the mail, primarily from immunization providers. This can be effected by supplying providers with the report form

²CDC's "Report of Illness Following Vaccination" form (Exhibit One) appears in this appendix as figure 3.7A.

(Exhibit One) and business reply envelopes. Another possibility is the inclusion of a line for reporting vaccine reactions on the morbidity report form used in the Project area. Such reports would be followed up to obtain the more detailed information required.

Stimulation of Reporting

To be effective, the mechanism for reporting vaccine reactions must be made known to the public and to the public and private immunization providers. The stimulation of reporting, therefore, is an important responsibility of each Adverse Reaction Coordinator.

Where it is used, the "Important Immunization Information" statement provides a basic means of stimulating reporting since it must contain a name or telephone number for reporting adverse events following vaccination. In addition, when the "Important Immunization Information" statement is explained to parents, the importance of being alert to possible reactions and using the telephone number to report any that occur should be emphasized specifically.

Ongoing efforts should be made to encourage reporting by the immunization providers themselves, especially in the private sector. This may be done by advertising the toll-free, or other, telephone number in the periodic newsletters that go from the State Health Department to physicians. Also, the "Report of Illness Following Vaccination" form may be reprinted in such a newsletter or in newsletters published by the respective medical organizations.

An important aspect of stimulating reporting by providers is feedback from the system. Providers should always be consulted when reaction reports are received from their patients. Also, any interesting analyses of reports should be shared with providers (through mechanisms like communicable disease newsletters) to show what happens to the information that they provide to the system.

Some use of the news media may be considered to promote reporting, but care should be taken not to overplay the negative aspects of the immunization process. In this context, the Adverse Reaction Monitoring System can be cast in a positive light as cooperative effort between parents and providers to maintain "quality control" in the immunization process. In general, the best use of the media will be low-key, but ongoing.

Criterion for Reporting

The types of reaction reports to be expected will include those that are obviously unrelated to vaccination, those that are known to be vaccine-related, and those that may or may not be currently recognized as

vaccine-related. One important purpose of the Adverse Reaction Monitoring System is to detect previously unrecognized vaccine reactions. It is desirable to screen from the system reactions that are known to be insignificant. For this purpose, the following criterion for documenting reported reactions on the "Report of Illness Following Vaccination" form has been established: Only those reactions that are serious enough to require hospitalization or a visit to a physician or public health facility are to be reported. One qualification to this rule should be observed: Any reaction involving only soreness, redness or swelling at the point of injection should not be reported even if a physician was visited.

Submission of Reaction Reports to CDC

All reaction reports, meeting the above criterion, that are generated at any point in the surveillance network should be collected centrally in the Immunization Project Office and submitted to the Center for Disease Control at the beginning of each month. The reports should be sent to:

The Center for Disease Control
Attn: Surveillance & Assessment Branch
Immunization Division, BSS
1600 Clifton Road
Atlanta, GA 30333

The reports that are sent to the Center for Disease Control must not contain any information that would identify the individual involved. The "Report of Illness Following Vaccination" form is designed as a two-part carbonized record in which the CDC copy does not contain any individual identification fields. If the form is not available in this format, the draft form shown in Exhibit One may be used, provided that the fields identifying the individual are removed. This may be done by photocopying the original report and cutting off, or masking, the top two lines. The original report should be kept on file in the Immunization Project Office. The System Coordinator may be the logical person to be responsible for seeing that all reports are submitted promptly and properly, according to the instructions shown in Exhibit One. Any reports alleging death as a result of vaccination should be telephoned immediately to the Immunization Division of the Center for Disease Control at (404) 329-3071. After hours, call (404) 923-4226.

The Immunization Division will maintain a computerized file of all reports. Crude adverse reaction rates will be determined and special analyses will be made of unusual reactions and clusters. Quarterly, the Immunization Division will send to each Immunization Project a report, showing a line listing and tabulation of all reports submitted by the Project and a national summary of reactions reported from all

Projects. This will assist projects in the analysis of accumulated reports.

At the national level, the Center for Disease Control will collaborate with the American Medical Association and the American Academy of Pediatrics to promote the reporting of vaccine reactions by private physicians. Also, cooperative arrangements

with vaccine manufacturers and other Government agencies, like the Food and Drug Administration, will be sought to obtain vaccine reaction reports received by them. In this way, it is hoped that the Adverse Reactions Monitoring System will become a definitive source of information about the risks of vaccination.

Figure 3.7A-CDC'S "Report of Illness Following Vaccination" Form and Guidelines for Completion (Exhibit One)

Guidelines for Completing the "Report of illness Following Vaccination"

1. The "Report of Illness Following Vaccination" form should be completed if and only if the reaction was severe enough to require hospitalization or a visit to a physician or public health facility.
2. Reactions involving only soreness, redness or swelling in the immediate vicinity of the injection should not be reported even if a physician was visited.
3. Most of the items on the form are self-explanatory. The following ones may need some explanation:

PATIENT Section

State: A two-digit code (see attachment).

Report Number; Each report should be assigned a number, serially, from 0001 through 9999.

VACCINES Section

Enter the date the vaccinations were given. Check the type of provider and enter the name on the line underneath. Then record, in the spaces below, all the vaccines given on that date.

Type: Type of vaccine, e.g., DTP, Td, polio, influenza, measles-mumps-rubella, etc.

Manufacturer; Vaccine manufacturer, e.g., Merck, Sharp & Dohme, Merrell-National, Wyeth, Parke-Davis, Lederle, Connaught, etc.

Lot Number: Vaccine lot number, recorded on vaccine vial or important Immunization information Statement.

Route: Subcutaneous (SC), intramuscular (IM), intradermal (ID), Oral (O) or Unknown (U).

Method: Needle & Syringe, Oral, Jet Gun, Unknown.

Site: Left arm, right thigh, buttocks, etc.

Note: For orally administered vaccines, enter "O" on the "Route" line and leave the "Method" and "Site" lines blank.

PREVIOUS HISTORY Section

In each box, enter "Y", "N" or "U" for "Yes", "No" or "Unknown," respectively.

4. After 7 days, a follow-up enquiry should be made to determine the condition of the patient. Enter the date and the results of the enquiry in the "7-Day Follow-Up" Section. Additional comments should be recorded on a separate sheet and attached to the report form.
5. Accumulated reports should be submitted at the end of each month. The top copy should be retained by the Reporting Agency. The bottom copy should be sent to:

Center for Disease Control
Attn: Immunization Division
Surveillance & Assessment Branch
1600 Clifton Road
Atlanta, GA 30333

Forms should not be sent until the follow-up is complete. However, if follow-up has not been completed within 30 days after the initial report, forms should be submitted without completing the "7-Day Follow-Up" Section.

6. In the case of a death allegedly resulting from a vaccination, call the Center for Disease Control immediately at (404) 329-3071.
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(Suggested Prototype)
 REPORT OF ILLNESS FOLLOWING VACCINATION

PATIENT	Date of Birth: <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> mo dy yr Sex: M F State: <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> Report Number: <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> County of Residence: _____ Date of Report: <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> <input style="width: 20px; height: 15px;" type="text"/> mo dy yr																																			
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Record additional comments on a separate page and attach to this form.

(Suggested Prototype)
REPORT OF ILLNESS FOLLOWING VACCINATION

PATIENT	Patient Name: _____ Phone: [][]-[][]-[][][][] Patient Address: _____ Date of Birth: [][][][] Sex: M F State: [][] Report Number: [][][][] <small style="margin-left: 40px;">mo dy yr</small> County of Residence: _____ Date of Report: [][][][] <small style="margin-left: 100px;">mo dy yr</small>																																			
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Record additional comments on a separate page and attach to this form.

REPORTING AGENCY COPY