MINUTES, MEETING NO. 14, ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES, FEBRUARY 4-6, 1969

The Advisory Committee on Immunization Practices met at the National Communicable Disease Center on February 4-6, 1969. Those in attendance were:

Committee

Dr. David J. Sencer, Chairman
Dr. H. Bruce Dull, Secretary
Dr. Alice D. Chenoweth
Dr. Geoffrey Edsall
Dr. Johannes Ipsen, Jr.
Dr. David T. Karzon
Dr. Roderick Murray
Dr. Ira L. Myers
Dr. Donald R. Peterson
Dr. Jay P. Sanford
Dr. Gene H. Stollerman

Representing the American Academy of Pediatrics

Dr. Margaret H.D. Smith

Invited Participants

Dr. Earl S. Beck, Assistant to the Chief, Vaccine Development Branch, National Institute of Allergy and Infectious Disease, Bethesda, Maryland
Dr. Philip A. Brunell, Assistant Professor of Pediatrics, New York University, New York, New York
Dr. Saul Krugman, Professor and Chairman, Department of Pediatrics, New York University, New York, New York
Dr. Harry M. Meyer, Jr., Chief, Laboratory of Immunology, Division of Biologics Standards, National Institutes of Health, Bethesda, Maryland
Dr. Daniel I. Mullally, Chief, Vaccine Development Branch, National Institute of Allergy and Infectious Disease, Bethesda, Maryland
Dr. Nicola Tauraso, Division of Biologics Standards, National Institutes of Health, Bethesda, Maryland
Dr. Paul F. Wehrle, Chief Physician, Pediatric and Communicable Disease Services, County of Los Angeles General Hospital, Los Angeles, California

CDC Staff--Participants and Discussants

Epidemiology Program:
Dr. Alexander D. Langmuir
Dr. A. W. Karchmer

Foreign Quarantine Program:
Dr. H. Brandeis Marsh
Dr. James W. Mosley
Dr. John R. Richardson

The meeting was devoted in part to completing review of a statement dealing with the live attenuated rubella virus vaccine. An essentially final version was prepared for release prior to product licensing. (Copy of published recommendation attached.)

The Smallpox Eradication Program, NCDC reviewed data on the current world distribution of smallpox and developed projections on its future occurrence. The current rate of reactions from smallpox vaccination in the United States and the risk of importing disease stimulated the Committee to request a continuing review of the country's "traditional" policy on vaccination. It was suggested that studies be undertaken to characterize fully the alternative vaccines, leading perhaps to development of a suitable "conditioning" product for childhood use prior to using "full-strength" vaccination. (Copy of position paper attached.)

Yellow fever vaccine was discussed in the context of worldwide surveillance of disease and the International Sanitary Regulations governing utilization of the available and excellent live virus (17D) vaccine. A draft recommendation was prepared by a working subgroup of the Committee for discussion and publication prior to the 1969 tourist season when demand for yellow fever vaccine would be at a peak. (Copy of published recommendation attached.)

Agenda for the spring meeting (May 14-15, 1969) was suggested to include influenza and a review of the full series of ACIP statements.

With thanks to the participants, the meeting was adjourned by the Chairman.

DRAFT -- 4/17/69

Statement From the Public Health Service Advisory Committee on Immunization Practices for Administrative Use

SMALLPOX VACCINE AND VACCINIA IMMUNE GLOBULIN

1) The ACIP recognizes a need for research efforts directed toward developing attenuated strains of vaccinia and for testing existing strains reported to be attenuated. This recommendation is made because:

   a) The rate of vaccination complications with the current vaccinia strain is substantial. During the past 18 years, no cases of smallpox have occurred in the United States but each year, several deaths are attributable to smallpox vaccination.

   b) Primary vaccination of adults is known to carry a higher risk than either primary vaccination of children or revaccination of adults. One of the main benefits of childhood vaccination in areas where no smallpox exists is a reduction of the risks accompanying primary vaccination of adults.

   c) There is a growing population of individuals at high risk of adverse reactions to smallpox vaccination by virtue of receiving immunosuppressive agents or suffering from malignancy or diseases of the immunological system. Therefore, the National Communicable Disease Center should undertake and encourage investigative trials with attenuated strains of vaccinia to determine their immunogenicity and rates of complications.

2) There should be continued surveillance of the risk of importation of smallpox accompanying a more precise definition of its worldwide geographic distribution. Surveillance of smallpox should include careful interpretation of the morbidity and mortality from smallpox vaccination.

3) The ACIP recommends a Federally sponsored program to obtain ample supplies of Vaccinia Immune Globulin (Human) of defined potency. (This recommendation is made because past evaluation of VIG has been hampered by the small size of previously available lots.)

Three uses for VIG which require further evaluation are its ability:

a) To modify certain complications of vaccination, especially vaccinia necrosum, eczema vaccinatum and generalized vaccinia. VIG has not been effective treatment for postvaccinal encephalitis.

b) To reduce complications of primary vaccination in high risk individuals by its concurrent administration with vaccine.

c) To avoid passive protection for individuals with immunological deficits if accidentally exposed to smallpox or vaccinia.

4) The Committee recommends that the Foreign Quarantine Program, NCDC, increase the number of countries for which travelers would be exempted from the requirement for a valid International

Certificate of Vaccination Against Smallpox. This action is warranted in view of: (1) the success of eradication efforts in many areas of the world; (2) the lack of evident risk from travelers who enter the United States from many areas not now included on the quarantine-exempt list; (3) recent evidence that transmission of smallpox may require closer contact than was previously believed.

RECOMMENDATION OF THE PUBLIC HEALTH SERVICE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

The Public Health Service Advisory Committee on Immunization Practices developed the following recommendation in close collaboration with the Committee on the Control of Infectious Diseases, American Academy of Pediatrics, which endorses the recommendation. (Reprinted from the Morbidity and Mortality Weekly Report, Vol. 18, No. 15, Week Ending April 12, 1969.)

PRELICENSING STATEMENT ON RUBELLA VIRUS VACCINE

INTRODUCTION

The live, attenuated rubella virus vaccine* soon to become available appears to be a highly effective immunizing agent and the first suitable method of controlling rubella.

Rubella is generally a mild illness, but if the infection is acquired by a woman in the early months of pregnancy, it poses a direct hazard to the fetus. Preventing infection of the fetus is the principal objective of rubella control. This can best be achieved by eliminating the transmission of virus among children, who are the major source of infection for susceptible pregnant women. Furthermore, the live, attenuated rubella virus vaccine is safe and protective for children, but not for pregnant women because of an undetermined risk of the vaccine virus for the fetus.

RUBELLA

Rubella is one of the common childhood exanthems. Most cases occur in school-age children particularly during the winter and spring. By early adulthood, approximately 80 to 90 percent of individuals in the United States have serological evidence of immunity.

Rubella is clinically variable, and its common features, such as post-auricular and sub-occipital lymphadenopathy and transient erythematous rash, are often overlooked or misdiagnosed. A mild febrile illness may not be recognizable as rubella, and moreover, subclinical infection occurs, which further decreases the reliability of clinical history.

Complications of rubella are rare in children, but in adults, particularly women, the illness is commonly accompained by transient polyarthritis. Far more important is the frequent occurrence of fetal abnormalities when a woman acquires rubella in the first trimester of pregnancy.

RUBELLA IMMUNITY

Immunity following rubella appears to be long lasting, even after mild illness or clinically inapparent infection. The only reliable evidence of immunity is a positive serological test. However, because of the variation among reagents and technical procedures, results of serological tests should be accepted only from laboratories of recognized competency that regularly perform these tests.

At the present time, the hemagglutination-inhibition (HI) antibody determination is particularly useful for evaluating immunity. It is a rapid and sensitive procedure. The complement fixation (CF) and other serological tests are less useful.

LIVE RUBELLA VIRUS VACCINE

Live rubella virus vaccine is prepared in cell culture of avian or mammalian tissues. It is administered as a single subcutaneous injection. Although vaccinees shed virus from the pharynx at times for 2 or more weeks after vaccination, there is no clear evidence of communicability. Approximately 95 percent of susceptible vaccinees develop antibodies, but titers are lower than those observed following natural rubella infection. Recent investigations have shown that vaccination affords protection against illness following either natural exposure or artificial challenge.

Antibody levels have declined very little during the 3-year period of observation of children who were among the first to be immunized with rubella vaccine. Long-term protection is likely, but its exact duration can be established only by continued observation.

More than 30,000 susceptible children have received live rubella virus vaccine in field investigations, with almost no untoward reactions. Only rarely has transient arthralgia or evanescent rash been reported in children.

Many susceptible women have had lymphadenopathy, arthralgia, and transient arthritis beginning 2 to 4 weeks after vaccination; however, fever, rash, and other features of naturally acquired rubella have occurred less commonly. Not enough susceptible men have been vaccinated to show whether they experience comparable reactions as frequently as women.

*Its official name is Rubella Virus Vaccine, Live.

RECOMMENDATIONS FOR VACCINE USE

Live rubella virus vaccine is recommended for boys and girls between the age of 1 year and puberty. Vaccine should not be administered to infants less than 1 year old because of possible interference from persisting maternal rubella antibody.

Children in kindergarten and the early grades of elementary school deserve initial priority for vaccination because they are commonly the major source of virus dissemination in the community. A history of rubella illness is usually not reliable enough to exclude children from immunization.

Vaccination of adolescent or adult males is of much lower priority because so few are susceptible. However, the vaccine may be useful in preventing or controlling outbreaks of rubella in circumscribed population groups.

Pregnant women should not be given live rubella virus vaccine. It is not known to what extent infection of the fetus with attenuated virus might take place following vaccination, or whether damage to the fetus could result. Therefore, ***routine*** immunization of adolescent girls and adult women should ***not*** be undertaken because of the danger of inadvertently administering vaccine before pregnancy becomes evident.

Women of child-bearing age may be considered for vaccination only when the possibility of pregnancy in the following 2 months is essentially nil; each case must be considered individually. This cautious approach to vaccinating post-pubertal females is indicated for two reasons: First, because of the theoretical risk of vaccination in pregnancy; and second, because significant congenital anomalies occur regularly in approximately 3 percent of all births, and their fortuitous appearance after vaccine had been given during pregnancy could lead to serious misinterpretation.

If vaccination of a woman of child-bearing age is contemplated, the following steps are indicated:

Optimally, the woman should be tested for susceptibility to rubella by the HI test (See *Rubella Immunity*).

If immune, she should be assured that vaccination is unnecessary.

If susceptible, she may be vaccinated only if she understands that it is imperative for her to avoid becoming pregnant for the following 2 months. (To ensure this, a medically acceptable method for pregnancy prevention should be followed. This precaution also applies to women in the immediate post-partum period.) Additionally, she should be informed of the frequent occurrence of self-limited arthralgia and possible arthritis beginning 2 to 4 weeks after vaccination.

Use of Vaccine after Exposure to Natural Infection

There is no evidence that live rubella virus vaccine given after exposure will prevent illness. There is, however, no contraindication to vaccinating children already exposed to natural rubella. For women exposed to rubella, the concepts listed previously apply.

Precautions in Using Live Rubella Virus Vaccine

Pregnancy: ***Live rubella virus vaccine is contraindicated.*** (See *Recommendations for Vaccine Use.*)

Altered Immune State: Attenuated rubella virus infection might be potentiated by severe underlying diseases, such as leukemia, lymphoma, or generalized malignancy, and when resistance has been lowered by therapy with steroids, alkylating drugs, antimetabolites, or radiation. Vaccination of such patients should be avoided.

Severe Febrile Illness: Vaccination should be postponed until the patient has recovered.

Hypersensitivity of Vaccine Components: Rubella vaccine is produced in cell culture. Care should be exercised in administering vaccine to persons with known hypersensitivity to the species from which the cells were derived (indicated in the labeling). The vaccine contains a small amount of neomycin and should not be given to individuals known to be sensitive to this antibiotic.

Simultaneous Administration of Live Rubella Virus Vaccine and Other Live Virus Vaccines

Simultaneous administration of live rubella virus vaccine and other live virus vaccines should be deferred until results of controlled clinical investigations are available. Until then, it is recommended that rubella vaccination be separated by at least 1 month from administration of other live virus vaccines.

SURVEILLANCE

Careful surveillance of rubella infection is particularly important with an effective vaccine in use. Emphasis should be placed upon improved diagnosis and reporting of rubella, of the congenital rubella syndrome, and of complications of the disease. Competent laboratory investigation of all infants with birth defects suspected of being due to rubella is essential. It will likewise be important to observe patterns of vaccine use and determine their effectiveness.

RECOMMENDATION OF THE PUBLIC HEALTH SERVICE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Reprinted from the Morbidity and Mortality Weekly Report, *Vol. 18, No. 21, for Week Ending May 31, 1969.*

YELLOW FEVER VACCINE

INTRODUCTION

At present, cases of yellow fever are reported from only Africa and South America. Two forms of yellow fever – urban and jungle – are distinguishable epidemiologically. Clinically and etiologically, they are identical.

Urban yellow fever is an epidemic viral disease of man transmitted from infected to susceptible persons by a vector, the *Aedes aegypti* mosquito. With the elimination of *A. aegypti,* urban yellow fever has disappeared from previously epidemic foci.

Jungle yellow fever is an enzootic viral disease transmitted among non-human hosts by a variety of mosquito vectors. It is currently observed only in the jungles of South America and Africa, but in the past has extended into parts of Central America as well. Human cases occur by chance. The disease can ostensibly disappear from an area for years and then reappear. Delineation of areas affected depends upon accurate diagnosis and prompt reporting of all cases.

Urban yellow fever can be prevented by eradicating *A. aegypti* mosquitoes. Jungle yellow fever can be prevented in humans only by immunization. Because infection is from a non-human reservoir, prevention of human cases requires vaccination of all persons at risk.

YELLOW FEVER VACCINE

Yellow fever vaccine is a live, attenuated virus preparation made from one of two strains of virus: 17D and Dakar (French neurotropic). The Dakar strain has been associated with a significant (0.5 percent) incidence of meningoencephalitic reactions and is not recommended. The 17D strain has caused no significant complications.

Licensed vaccine available in the United States is prepared from the 17D strain, which is grown in chick embryo inoculated with a fixed passage level seed virus. The vaccine is freeze-dried supernate of centrifuged embryo homogenate.

Vaccine should be stored at the temperature recommended by the manufacturer until it is reconstituted by the addition of sterile physiologic saline. Unused vaccine should be discarded within approximately 1 hour of reconstitution.

RECOMMENDATIONS OF VACCINE USE

Vaccination against yellow fever is recommended for:

1) Persons 6 months of age or older traveling or living in areas where yellow fever infection exists (currently Africa and South America; see *Vaccination for International Travel).*

2) Laboratory personnel who might be exposed to virulent yellow fever virus.

Vaccination for International Travel

To be acceptable for purposes of international travel, yellow fever vaccines must be approved by the World Health Organization and administered at a Yellow Fever Vaccination Center listed with WHO. Vaccinees should have an International Certificate of Vaccination filled in, signed, and validated with the stamp of the Center where the vaccination is administered. (Yellow Fever Vaccination Centers in the United States are designated by the Foreign Quarantine Program of the Public Health Service*).

Vaccination for international travel may be required under circumstances other than those included in these recommendations. A number of countries in Africa and South America require evidence of vaccination from all entering travelers; some may waive the requirement for travelers coming from non-infected areas and staying less than 2 weeks. These requirements may change, so that travelers should seek current information from health departments and travel agencies.

Some countries require an individual, even if only in transit, to have a valid International Certificate of Vaccination if he has been in countries either known or thought to harbor yellow fever virus. This applies particularly to travelers to South and Southeast Asia by way of the Atlantic.

Vaccination Schedule

Primary Vaccination: A single subcutaneous injection of 0.5 ml. of reconstituted vaccine for both adults and children.

Revaccination: Yellow fever immunity following vaccination with 17D strain virus has been shown to persist for more than 10 years; the International Sanitary Regulations do not require revaccination more frequently than every 10 years.

Reactions

The few reactions to 17D yellow fever vaccine that occur are generally mild. Five to ten percent of vaccinees have mild headache, myalgia, low-grade fever, or other minor symptoms 5-10 days after vaccination. Symptoms cause less than 0.2 percent to curtail regular activities. Only two cases of encephalitis have been reported in the United States, for more than 34 million doses of vaccine distributed.

Because yellow fever vaccine is prepared from chick embryos, it may induce reactions of varying degrees of severity in individuals hypersensitive to eggs. Experience

*For a list of such centers, see *Immunization Information for International Travel,* PHS Publication No. 384, available from the Supt. of Documents, U.S. Government Printing Office, Washington, D.C. 20402 at 40 cents.

in the Armed Forces suggests that allergy severe enough to preclude vaccination is very uncommon and occurs only in those who are actually unable to eat eggs.

Precautions and Contraindications

Pregnancy: Although specific information is not available concerning adverse effects of yellow fever vaccine on the developing fetus, it is prudent on theoretical grounds to avoid vaccinating pregnant women.

Altered Immune States: Yellow fever vaccine virus infection might be potentiated by severe underlying diseases, such as leukemia, lymphoma, or generalized malignancy, and by lowered resistance, such as from therapy with steroids, alkylating drugs, antimetabolites, or radiation; therefore, vaccination of such patients should be avoided.

Allergy: Documented hypersensitivity to eggs can be contraindication to vaccination. In making the decision to vaccinate despite a history of egg allergy, a physician must weigh three factors: (1) the nature of the history and of the reported hypersensitivity, (2) the relative risk of exposure to yellow fever, and (3), in the case of international travel, the possible inconvenience from disrupted travel plans.

If international quarantine regulations are the only reason to vaccinate a patient hypersensitive to eggs, efforts should first be made to obtain a waiver. A physician's letter which clearly states the contraindication to vaccination has been acceptable to some governments. (Ideally, it should be written under his letterhead and bear the authenicating stamp used by health departments and official immunization centers to validate International Certificates of Vaccination.) Because this is not uniformly true, however, it is prudent for the traveler to obtain specific and authoritative advice from the country or countries he plans to visit. Their embassies or consulates may be contacted. Subsequent waiver of requirements should be documented by appropriate letters.

Simultaneous Administration of Live Virus Vaccines

There are obvious practical advantages to administering two or more live virus vaccines simultaneously. Data from specific investigations are not yet sufficient to develop comprehensive recommendations on simultaneous use, but a summary of current experience, attitudes, and practices provide useful guidance.

It has been generally recommended that live virus vaccines be given at least 1 month apart whenever possible – the rationale for this being that more frequent and severe adverse reactions as well as diminished antibody responses otherwise might result. Field observations indicate, however, that with simultaneous administration of certain live virus vaccines, results of this type have been minimal or absent. (For example, the third dose of trivalent oral poliovirus vaccine, which is recommended during the second year of life, is commonly given at the same time as smallpox vaccination without evident disadvantage.)

If the theoretically desirable 1-month interval is not feasible, as with the threat of concurrent exposures or disruption of immunization programs, the vaccines should preferably be given on the same day – at different sites for parenteral products. An interval of about 2 days to 2 weeks should be avoided because interference between the vaccine viruses is most likely then.

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