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No. IV

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July 11, 1965

TO : For the Record

FROM : Secretary, Advisory Committee on Immunization Practices

SUBJECT: Minutes, Meeting No. 4, Advisory Committee on Immunization Practices - June 11, 1965

I. The Advisory Committee on Immunization Practices met at the Communicable Disease Center on June 11, 1965. Those in attendance were:

a. Committee

Dr. James L. Goddard, Chairman
Dr. Donald A. Henderson, Secretary
Dr. Ernest A. Ager
Dr. Gordon C. Brown
Dr. Alice Chenoweth (for Dr. Lesser)
Dr. Geoffrey Edsall
Dr. David T. Karzon
Dr. Theodore A. Montgomery
Dr. Roderick Murray
Dr. Paul F. Wehrle

b. Invited Participants

Dr. David Stoddard, National Aeronautics & Space Administration

Dr. Harold Glassman, U. S. Army Biological Laboratories, Fort Detrick

Dr. Benjamin Blood, Office of International Health, and

Dr. Louis Jacobs, Division of Foreign Quarantine, were unable to attend.

c. CDC Staff

Immunization Activities - Dr. F. R. Freckleton

Laboratory Branch - Dr. U. P. Kokko, Dr. Roslyn Robinson

Epidemiology Branch - Dr. A. D. Langmuir
Dr. John J. Witte
Dr. Bruce Dull
Dr. William Stuart

II. Influenza Vaccine Use

Information pertaining to the occurrence of influenza during 1964-65 and in recent years was presented as well as data pertaining to the laboratory characterization of recently isolated strains (summarized in Appendix I).

A preliminary report was presented of the results of a collaborative study conducted by CDC and the American Telephone and Telegraph Company dealing with serological responses in adults given these commercially available influenza vaccines in 1964. With one subcutaneous dose, between 17 and 30 percent exhibited four-fold or greater increases in titer to A2/Jap/170/62; between 12 and 29 percent exhibited four-fold or greater increases in titer to B/Maryland/1/59. Postvaccination geometric mean titers were uniformly lower than might have been expected from preliminary studies of these strains in their monovalent form. Two explanations to explain these findings were postulated: (1) That the group of persons tested were in some manner atypical; (2) That the vaccine potency may have been less than optimal in 1964-65, perhaps as a result of the necessity to abandon the mouse protection test for potency evaluation because of the lack of a fully virulent mouse adapted strain. Although of interest, the Committee felt that further documentation was important and recommended monitoring of commercially available vaccines for seroconversions (see recommendations below).

The possibility of replacing the present polyvalent vaccine with a bivalent vaccine containing only the "most recent" A and B strains was raised. Dr. Murray stated that the Division of Biologics Standards would be seeking advice about this from a specially convened group in the immediate future.

A draft recommendation regarding influenza vaccine use during 1965-66 was discussed and revised. Whether or not intradermal vaccine administration should be recommended was considered. Studies conducted during 1957 generally demonstrated a superior antibody response among those given the larger quantity of vaccine subcutaneously. Some studies conducted since this time have shown comparable serological responses among those given 1.0 ml. subcutaneously and those given 0.1 ml. intradermally. It was noted, however, that intradermal administration is difficult and that, in the hands of the relatively less skilled, "intradermal" injections are too frequently subcutaneous. It was felt that unless the individual in question had previously experienced an unusually severe vaccine reaction or unless vaccine was in short supply, the subcutaneous route

should be recommended.

Recommendations:

1. A statement regarding influenza vaccine application for 1965-66 was approved for immediate transmission to the Surgeon General (Appendix I).
2. Monitoring of current, commercially available influenza vaccines from several manufacturers to assess the frequency of serological conversions should be carried out particularly when there is a change in the composition of influenza vaccines. The studies should be in both adults and children.

III. Measles Vaccine Programs

General publicity given to the desirability of widespread use of measles vaccines coupled with the indication that such vaccines may be provided in the near future through the Vaccination Assistance Act have recently led several communities to consider the possibility of mass campaigns. The Advisory Committee, however, had stated previously "rarely would there appear to be a need in the United States for mass community immunization programs." This position was reconsidered and extended in light of accumulating experience with measles vaccines (Appendix II).

Recommendation:

A statement for general distribution was prepared which discusses the need and means for achieving high levels of measles immunization in communities (Appendix II). This statement, in draft form, will be sent for comment to Dr. Coriell, Chairman, Committee on Infectious Diseases, American Academy of Pediatrics.

IV. Provision of Infrequently Used Immunizing Agents

At the request of Dr. Harold Glassman, the problem at Fort Detrick in continuing to provide infrequently used, commercially non-licensed immunizing agents to the civilian community under the present rules applicable to their operations was presented for discussion. Specific antigens immediately of concern include pentavalent botulinal toxoid and vaccines for anthrax and tularemia.

These vaccines have been prepared and/or developed and tested over a number of years by Fort Detrick; none have been licensed nor have claims for exemption as investigational new drugs been filed. They have been provided to the civilian community on request, primarily to laboratory workers and, in the case of anthrax and tularemia vaccines, to a limited "high risk" industrial component.

Responsibility for approval of the vaccines prepared by Fort Detrick for clinical investigative purposes resides with the Department of Defense which acts after these vaccines are reviewed by the Investigational Drug Review Board. Under this authority, it is felt that Fort Detrick may provide these antigens only to Army personnel, civilians hired by the Army and Army contractees. There is presently no provision for supplying the vaccines noted to other Government laboratories or the civilian community.

Although the need for these antigens was clear, it was pointed out that repeated efforts to encourage commercial production had been unsuccessful.

Proposed steps to resolve the problem were presented to the Committee and subsequently endorsed:

1. Provision of Anthrax Vaccine - A contract has been negotiated by Fort Detrick-CDC with the Michigan State Health Department Laboratories to obtain anthrax vaccine. This contract includes costs for establishing production and for a licensure submission. Vaccine so obtained would be made available on request by the CDC to those at particular risk in the civilian community. Pending licensure, the vaccine would be cleared for investigational new drug use and distributed on request with provision for the collection of information on individual responses to the vaccine.
2. Provision of Botulinal Toxoid and Tularemia Vaccine - The CDC, Laboratory Branch, would plan to produce and distribute the requisite small quantities of these vaccines commencing in July 1966. As indicated by Dr. Murray, so much information is available about these products that their use on an investigational new drug status would be relatively simple. Records of individual responses to these drugs would be collected and collated in the

usual manner by CDC, Epidemiology Branch.

3. In the interim period, until July 1966, when more sufficient space and personnel become available for CDC to discharge fully these responsibilities, CDC and Fort Detrick would jointly evolve mechanisms to insure that these antigens could be available on request to the civilian community.

V. Expert Testimony

The status of Committee members in providing expert testimony in legal actions was raised by Dr. Wehrle. The question related specifically to testifying in the capacity of an Advisory Committee member.

It was pointed out that, in no instance, should a member testify as a voluntary witness concerning the internal proceedings of the Committee. As to what the posture of the individual should be if subpoened has not yet been clarified by the general counsel in the Surgeon General's office. If an individual should be subpoened, CDC should promptly be notified.

VI. Pneumococcal Typing Serum and Vaccine

The Committee considered a request by the Council Policy Committee of the American Society for Microbiology for the Public Health Service to exert leadership in implementing recommendations made by Dr. Robert Austrian, Professor of Research Medicine, University of Pennsylvania: (1) To assure the general availability of pneumococcal typing serums and (2) to make generally available a vaccine containing six pneumococcal capsular polysaccharides for administration to populations at greatest risk of dying of pneumonia.

The Committee took cognizance of Dr. Austrian's paper on this subject (Austrian, R. and Gold, J.: Pneumococcal Bacteremia with Special Reference to Bacteremic Pneumococcal Pneumonia, Annals of Internal Medicine 60:759-776, 1964) and the clear demonstration that a purified capsular polysaccharide vaccine prepared against Types I, II, V and VII has been shown to be efficacious in the prevention of pneumonia (MacLeod, C.M., Hodges, R.G., Heidelberger, M., and Bernhard, W.G.: Prevention of Pneumococcal Pneumonia by Immunization with Specific Capsular Polysaccharides, J. Exp. Med. 82:445-465, 1945.)

Noted, however, were two significant problem areas pertinent to considering possible widespread application of pneumococcal vaccines:

1. The Type III pneumococcus, accounting for 21 percent of all deaths in Dr. Austrian's series, is somewhat different than the other types in its biological characteristics. Production of an effective purified capsular polysaccharide vaccine against this type is problematical. Assuming that a 100 percent effective vaccine of the formulation suggested by Dr. Austrian could be produced, incorporating Types I, IV, VII, VIII and XII (omitting Type III), only 46 of the 131 pneumococcal deaths occurring over a 10 year period at the King County Hospital, could have been prevented. Further, recognizing that the pattern of occurrence of the many different types of pneumococci is a fluctuating one, difficult to predict, and recognizing that the vaccines have not approached 100 percent effectiveness, it is reasonable to suppose that, in fact, a prepared vaccine, even widely applied, might have limited impact on pneumonia mortality.
2. It was the impression of the group that many, perhaps most of the pneumococcal deaths occurred among "skid row" type individuals. If this were so, even a highly potent, broad spectrum vaccine would be of limited value because of the demonstrated intrinsic difficulties in vaccinating such a group on a continuing basis.

Recommendations:

Before a pneumococcal polysaccharide antigen can be considered, careful epidemiological studies of total community populations must be conducted to define the extent of the problem and the characteristics of individuals succumbing to the disease to ascertain whether, in fact, such a population potentially might be reached by vaccination. Typing sera are available for some types from the Michigan State Health Department Laboratories and from the State Serum Institute in Denmark in adequate quantity for those interested in pursuing these studies.

VII. Oral Polio Vaccine Recommendations

A letter from the American Medical Association requested that the Committee reconsider its recommendation that adults not receive oral polio vaccine unless at unusual risk of acquiring the disease.

Data pertaining to poliomyelitis occurrence to date and the immunization status of the population were considered. In 1964, 91 cases of paralytic poliomyelitis were recorded of which 30 cases occurred among those 15 years of age and over. Fifteen of the 30 cases in adults occurred less than 30 days after receipt of oral polio vaccine. In 1965 to date, the incidence of polio has continued to decline with less than half the number of cases reported through mid-June as were reported during the comparable period in 1964. Based on Bureau of the Census surveys of the country at large, immunization levels are continuing to rise.

The Committee concluded that the principal concern at present should be directed at the infant not the adult population. With an apparent decrease in circulating wild polioviruses, little natural immunity is being provided; thus the newborn population is now almost completely dependent upon artificial immunization. Immunization levels in preschool children are still far from adequate. Greater efforts must be made in the establishment of continuing, maintenance programs of immunization. Through interruption of wild poliovirus transmission, adequate infant immunization will serve to protect the adult population.

VIII. Rabies Vaccine for Severely Exposed Individuals

It was pointed out in communications from Dr. Edsall that the established routine of administering 21 doses of rabies vaccine to severely bitten individuals has not been noted in the American Academy of Pediatrics "Red Book" and WHO Expert Committee reports. Dr. Edsall and Dr. Habel with whom he had been in communication felt that this long established procedure should be more carefully spelled out.

The Committee agreed and suggested that this be called to the attention of the American Academy of Pediatrics Committee on Infectious Diseases, the

American Public Health Association's Subcommittee on Communicable Disease Control and the World Health Organization.

IX. Compensation for Vaccine Associated Cases

Dr. Wehrle raised for discussion the possibility of providing compensation to individuals developing vaccine associated illness following receipt of vaccine (diphtheria, pertussis, poliomyelitis, smallpox) given as much for community protection as for individual protection. It was pointed out that the net cost of litigation and settlements resulting from the oral polio vaccine associated illnesses must necessarily be reflected in increased vaccine costs. Further, it would seem but a matter of time until lawsuits under the "implied warranty" principle would be applied to other immunizing agents and in many additional states. It seemed conceivable that increasing costs of settlement would be reflected in increasing costs of vaccine and less effective community coverage and protection. It was noted that in West Germany, treatment for vaccine associated complications was provided free of charge and provision was made for suing the government. France has recently adopted a law which provides compensation for those who suffer ill effects following polio vaccination when this is carried out as a state requirement. The possibility was raised of providing relief to afflicted individuals in this country through some compensation mechanism.

It was recognized that administration and application of such a provision would be difficult with many "gray" areas. The question, for example, as to whether such compensation should be extended to individuals experiencing penicillin reactions following syphilis treatment evoked a divided response from the Committee.

It was felt that the question needed to be explored further. Dr. Goddard proposed submitting the problem to the Boston Law and Medicine Institute for their reaction. This was agreed.

X. The next meeting of the Committee was proposed for mid to late November. Pending topics for the agenda include: (1) Typhoid vaccines and schedules, (2) Policies pertaining to smallpox control, (3) Immunization schedules in infancy, and (4) Adult immunization schedules.

With the thanks of the Chairman, the Committee adjourned at 4:00 p.m.

Donald A. Henderson, M.D.

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Appendix I

1965-66 Recommendations for Influenza Immunization and Control in the Civilian Population

Advisory Committee on Immunization Practices

1. Influenza Prospectus - 1965-66 - United States

Influenza was confirmed in a majority of States in the eastern two-thirds of the country during the 1964-65 season. Although widespread in some areas, the level of involvement was generally low and excess pneumonia-influenza mortality was only modestly elevated. Most States in the Far West were unaffected.

Numerous strains of type A2 virus were isolated and subsequently characterized as showing a drift in antigenic constitution from previous A2 viruses. There was, however, no major antigenic change. A few strains of type B influenza virus were recovered from discrete outbreaks recognized in the West.

Based on available morbidity and mortality data the 1964-65 influenza experience in the United States was limited. The last major epidemic of type A illness occurred in 1962-63 and on the West Coast in 1963-64. In view of influenza's two to three year periodicity, increased amounts of influenza may be expected in the coming season. Areas that were most involved in 1964-65 might expect a lesser amount of disease in 1965-66.

Although type A viruses may predominate in 1965-66, the presence of type B influenza in the U.S. and its prevalence in Europe in 1964-65, increases the expectation of type B outbreaks in 1965-66 in the U.S.

2. Vaccine Efficacy

Influenza vaccine has consistently shown a substantial protective value when the viruses incorporated in the vaccine were antigenically similar to those causing the epidemic disease. Exceptions to the vaccines' apparent effectiveness have occurred in instances when the prevalent virus underwent a major antigenic shift after vaccines had been formulated. Careful study goes into the annual design and updating of the composition of influenza vaccines. The final selection of components reflects the best judgment regarding a potent, contemporary vaccine.

That influenza vaccine prevents mortality from influenza, particularly among the aged and chronically ill, is based upon inference. It is presumed that vaccine protection demonstrated in studies among younger persons is similar among the aged and chronically ill, the group at particular risk of death should they acquire the disease. It is further assumed that such protection against clinical disease serves to protect them also against mortality associated with epidemic influenza.

3. High Risk Groups

Annual immunization is generally recommended for persons in groups who experience high mortality from epidemic influenza. Such groups include:

(a) Persons at all ages who suffer from chronic debilitating disease, e.g., chronic and cardiovascular, pulmonary, renal or metabolic disorders; in particular:

1. Patients with rheumatic heart disease, especially those with mitral stenosis.

2. Patients with other cardiovascular disorders such as arteriosclerotic heart disease and hypertension, especially those with evidence of frank or incipient cardiac insufficiency.

3. Patients with chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, pulmonary tuberculosis.

4. Patients with diabetes mellitus and Addison's disease.

(b) Persons in older age groups. During three successive recent epidemics a moderate increase in mortality has been demonstrated among persons over 45 years and a marked increase among those over 65 years of age.

(c) Pregnant women - It is to be noted that some increased mortality was observed among pregnant women during the 1957-58 influenza A2 epidemic both in this country and abroad. It has not, however, been demonstrated in subsequent years.

(d) Patients residing in Nursing Homes, Chronic Disease Hospitals, and other such environments should be considered at particular risk since their more crowded living arrangements may allow for greater spread of disease once an outbreak has been established.

4. Time of Vaccination

Vaccination should begin as soon as practicable after September 1 and ideally should be completed by mid-December. It is important that immunization be carried out before influenza occurs in the immediate area since there is a two week interval before the development of antibodies.

5. Vaccine Composition

Recent isolates of the type A viruses demonstrate a continued alteration in antigenic structure. Accordingly, it will be noted that a more recent strain of influenza A2 has been added. The antigenic composition of the vaccine for the 1965-66 season is as follows:

Type	Strain	CCA Units per ml.
A	PR8	100
A1	Ann Arbor/1/57	100
A2	Japan/170/62	100
A2	Taiwan/1/64	100
B	Maryland/1/59	200
		600

6. Dose and Schedule of Vaccination

(a) Primary Series - Individuals not vaccinated since July 1963 when the last major change in vaccine formulation was made should receive an initial subcutaneous dose of polyvalent vaccine followed by a second dose two months later. It is to be pointed out, however, that even a single dose can afford

significant protection. A second dose given as early as two weeks following the first will enhance the protection.

Summary:

Adults and children over 12 years
1.0 ml. dose subcutaneously on two occasions as specified above

Children 6 to 12 years*
0.5 ml. dose subcutaneously on two occasions as specified above

Children 3 months to 5 years*
0.1 - 0.2 ml. of vaccine given subcutaneously on two occasions separated by one to two weeks followed by a third dose of 0.1 - 0.2 ml. about two months later.

*Since febrile reactions in this age group are common following influenza vaccination, an antipyretic may be indicated.

(b) Revaccination - Individuals vaccinated since July 1963 need receive but a single booster of vaccine at the dose level specified for the primary series. For those in the older age groups who have previously experienced undue reactions to influenza vaccine, a revaccination dose of 0.1 ml. given by careful intracutaneous injection can be expected to give an antibody response which is somewhat comparable to that induced by the 1.0 ml. subcutaneous dose. The intracutaneous route is not recommended, however, for use in other than these special cases.

(c) Contraindication - Since the vaccine viruses are produced in eggs, the vaccine should not be administered to those who are hypersensitive to eggs or egg products.

Appendix II

The Importance of Measles and Methods for Achieving High Levels of Measles Immunization in the Community

Recognizing the significance of measles as one of the most important causes of serious morbidity in childhood, the Committee recommends that, with highly effective vaccines available, every effort should be applied to eradicating the disease in the United States. All children presumed susceptible should be immunized.

Continuing "maintenance" programs aimed at vaccinating children about one year of age should be established in all communities. Additionally, consideration should be given to the concept of full immunization of all children entering schools, nursery schools, etc. since measles transmission in the community occurs principally among children in such settings.

Widespread immunization may be achieved through routine and intensive programs conducted in physicians' offices and immunization clinics in both public health and private medical practice. In some instances, mass community-wide vaccination programs may prove practicable in communities or segments of communities in which immunization levels achieved through routine practice are known to be low.

Community-wide, mass programs - special comments:

If community-wide programs are conducted, cognizance must be taken of the fact that such programs are necessarily more complex than those involving oral polio vaccine, for example, since measles vaccines must be parenterally administered. Further, a febrile illness is expected to occur in a proportion of those vaccinated between 6 and 8 days after vaccination.

The following points should be considered in a community-wide program:

1. The active participation of essentially all physicians who normally provide care for children is requisite. Since febrile responses of varying severity often accompanied by a rash are observed approximately a week following live vaccine administration in a proportion of those vaccinated, the practicing physicians must be available to respond to calls concerning these symptoms.

If a program were to be conducted on a weekend, for example, a substantial number of calls might be anticipated during the following weekend.

2. Since measles vaccine must be administered parenterally, more medical personnel are required for the conduct of the program than has been required for oral polio vaccine programs.

3. For programs to be successful, a substantial effort will be required to motivate a high degree of interest among parents in the community. Despite the high incidence of measles and the frequent occurrence of complications, measles as a disease generally engenders less concern than does poliomyelitis.

4. The selection of the vaccine must be carefully considered. Recommended schedules have previously been described by the Committee (Morbidity and Mortality Weekly Report, Vol. 14, No. 7).

It should be noted parenthetically that although a number of children may exhibit notable febrile responses following live vaccine administration, the present experience of private practitioners indicates that for only a fraction of such febrile responses is medical attention requested.

5. Since, in general, 90 percent of persons beyond 15 years of age will have experienced measles, the program should be directed to those with no history of measles, between the ages of 12 months and 15 years with particular emphasis on the most susceptible group, the preschool children.