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July 6, 1964

TO : For the Record

FROM : Secretary, Advisory Committee on Immunization Practice

SUBJECT: Minutes, Meeting No. 1, Advisory Committee on Immunization Practice - May 25-26, 1964

I. The Advisory Committee on Immunization Practice met at the Communicable Disease Center in Atlanta on May 25-26. Those in attendance were as follows:

a. Committee*

Dr. James L. Goddard, Chairman
Dr. Donald A. Henderson, Secretary
Dr. Ernest A. Ager
Dr. Gordon C. Brown
Dr. Alice D. Chenoweth
Dr. Geoffrey Edsall
Dr. Theodore A. Montgomery
Dr. Roderick Murray (May 26 only)
Dr. Paul F. Wehrle

*Because of illness, Dr. David Karzon could not attend.

b. Invited Participants

Dr. Joseph A. Bell, National Institute of Allergy and Infectious Diseases, NIH
Dr. Benjamin D. Blood, Office of International Health
Dr. Joe L. Stockard, Division of Foreign Quarantine

c. CDC Staff (Most attended intermittently dependent upon pertinence of subject matter.)

Dr. Philip R. Edwards
Dr. F. R. Freckleton
Dr. Vincent F. Guinee
Dr. U. P. Kokko
Dr. Alexander D. Langmuir
Dr. J. D. Millar
Dr. Roslyn Q. Robinson
Dr. Carl G. Silverman
Dr. Telford H. Work
Dr. Stanley B. Lyss

## II. Committee Responsibility

The Committee's scope, purpose and function were discussed at length. A draft statement defining the Committee's responsibilities was considered and minor modifications proposed. (Appendix I) It was felt that consideration should be given as to whether the Committee should deal with recommendations regarding immunization for international travel. Although it was agreed that immunization in international travel bore an intrinsic relationship to the problem of immunization in public health practice, it was clear that a decision as to whether the Committee should assume this function would be contingent upon the wishes of the Surgeon General.

In the commentary portion of the draft statement, relating the Committee's activities to those of other groups concerned with immunization practice, it was felt that it would be useful to incorporate a statement dealing with the responsibilities of the Division of Biologics Standards.

A final draft of this document will be considered for final approval at the next regular meeting of the Committee.

Since the number and scope of questions and problems intrinsic in public health immunization practice is extensive, the Committee agreed that it would be important to focus initially upon problems pertaining to application of the more frequently used immunizing agents. It was felt that less common antigens, the problems of chemoprophylaxis, etc. should be dealt with when the more central problems were better in hand.

It was felt by the Committee that as part of the modus operandi of its functioning that it would be desirable from time to time to call upon appropriate technical consultants or, as need be, to convene special subcommittees or panels to consider specific, complex problems regarding immunization practice.

## III. Simplification of Vaccination Schedules

Dr. Joseph Bell discussed the desirability of an immunization schedule for public health practice simpler than that propounded by the Academy of Pediatrics "Red Book" Committee which presently recommends 14 separate visits in 16 years. It was agreed that simplification was of practical importance. Principal discussions focused on DPT vaccination, the relative advantages and disadvantages of administration of these antigens at various intervals after birth, the spacing of doses and the scientific and administrative decisions inherent in establishing practicable schedules.

The Committee agreed that the problem was complex and that a first step would be that of a definitive review of the DPT problem. Dr. Edsall agreed to assume this responsibility with staff support from CDC.

IV. Influenza

Assuming the role previously borne by the Surgeon General's Advisory Committee on Influenza, the Committee reviewed recent data regarding the occurrence of influenza, the antigenic characteristics of recent isolates, the extent of vaccine use during the previous year, and cyclical patterns of influenza. Recommendations were developed for the 1964-65 season. (Appendix II)

V. Rubella

In the context of a current extensive outbreak of rubella, the question of the status of vaccine development and questions regarding the present use of gamma globulin in prophylaxis were discussed.

From the status of studies reported recently at a meeting on rubella at the Division of Biologics Standards, it would appear that the development of practicable rubella vaccines may not be anticipated for some years.

A serious shortage of gamma globulin has been reported this year by many health departments as a result of its extensive use in prophylaxis of presumed exposed pregnant women. A question regarding the scientific advisability of continued globulin use for this purpose has recently been raised by Drs. Krugman and Greene. These investigators demonstrated, in carefully conducted trials among children, that use of gamma globulin did not serve to protect contacts of cases against viremia. Although not directly answering the question as to whether the globulin would or would not prevent congenital malformations among children of exposed mothers, the study suggests the possibility that it might not.

A review of the literature pertaining to trials of gamma globulin in rubella prophylaxis reveals that there have been several well conducted, control trials which demonstrate that gamma globulin serves at least to suppress the clinical illness among exposed persons. Evidence is lacking as to whether gamma globulin serves to prevent congenital malformations among children born to mothers exposed during the first trimester. The problems inherent in endeavoring to answer this latter, crucial point are portrayed in a recent article by McDonald who adduced that, in recent years in the United Kingdom, globulin given to 13,000 household contacts of cases would have served to prevent, at best, 20 severe malformations and 30 minor hearing deficits or .05 percent of all malformations during this same period.

Based on the Committee discussions, a summary statement of the problem of gamma globulin use in rubella prophylaxis was prepared. (Appendix III) This will be circulated for comment and, if necessary, discussed at a subsequent meeting.

## Appendix I. Draft Statement Pertaining to Responsibilities of the Advisory Committee on Immunization Practice

(For subsequent discussion at next regular meeting)

### Responsibility

The Advisory Committee on Immunization Practice was appointed in May, 1964. The Committee is charged with the responsibility of advising the Surgeon General regarding the most effective application in public health practice of specific preventive agents which may be applied in communicable disease control. Included among the agents to be considered by the Committee are inactivated and live-attenuated bacterial, rickettsial and viral agents, toxoids, antitoxins, chemoprophylactic agents and immune globulin. The Committee shall concern itself with immunization schedules, dosages and routes of administration and indications and contraindications for the use of these agents. The Committee shall also provide advice as to the relative priority of various population groups to whom the agents should be made available and shall advise regarding the relative merits and methods for conducting mass immunization programs. It shall also advise appropriately regarding needed programs in research.

### Commentary

Since the primary responsibility for public health immunization activities rests with the individual States and their State Health Officers, the Committee will assess the problems of effective application of the preventive agents particularly from this point of view. A continuing reappraisal of all facets of immunization practice is, of course, requisite if recommendations are to be consonant with the most recent developments in this field.

It is recognized that there are presently several groups which issue formal recommendations regarding immunization practices. The principal groups so involved are 1) the Armed Forces Epidemiological Board, 2) the American Academy of Pediatrics Committee on the Control of Infectious Diseases, and 3) the American Public Health Association Subcommittee on Communicable Disease Control.

The Armed Forces Epidemiological Board is concerned solely with the armed services and their dependents. This population is provided medical care through government or government-contract facilities. By virtue of their responsibilities in many parts of the world, those in the armed services are frequently placed in situations of unusually high risk for both the usual and unusual infectious diseases. Recommendations for immunization of both those in the armed services and their dependents must take these problems into account; the recommendations in many instances are not applicable in civilian public health practice.

The American Academy of Pediatrics Committee recommends regarding immunization practice, principally for those concerned with private pediatric patient care. Desirable immunization schedules and preventive procedures are proposed which provide an ideal or maximum level of protection from the vantage point of the private practitioner.

The last of the groups providing recommendations, the American Public Health Association Subcommittee, provides advice broadly regarding all aspects of communicable disease control for public health authorities in the United States and elsewhere throughout the world. Its scope is comprehensive; immunization practice is but one small part of its function. Its recommendations, revised at five year intervals, do not permit the necessary flexibility necessary in this rapidly changing field.

None of these committees is directly concerned with providing advice on a concurrent basis regarding the effective application in public health practice of agents for communicable disease control purposes. It is hoped that the Advisory Committee on Immunization Practice may fulfill this function. It is recognized that recommendations made by this Committee may differ significantly from those provided by other groups. This is implicit in the divergent responsibility of the Committee. However, in order to minimize unnecessary differences in the recommendations and to insure a full understanding of the reasons for necessary differences a close liaison will be maintained with the other principal groups providing recommendations in immunization practice.

Appendix II. Recommendations for Influenza Immunization and Control in the Civilian Population

Advisory Committee on Immunization Practice

1. Expected Occurrence of Influenza During 1964-65

a. Influenza $A_2$

Widespread outbreaks of influenza $A_2$ occurred in 1962-63 in most areas of the United States except for the West Coast. During 1963-64, influenza $A_2$ was widely prevalent along the West Coast; limited outbreaks occurred also in Southern Minnesota. Although influenza A commonly occurs in two to three year cycles, it would seem, in the face of the extensive 1962-1963 outbreak and the West Coast involvement in 1963-64, that a major outbreak would be unlikely this year. As in other inter-epidemic years, however, focal outbreaks might be anticipated.

b. Influenza B

A nation-wide epidemic of influenza B was last observed in the United States during 1961-62. During 1963-64, influenza B in epidemic proportions was observed in Japan. The strain involved was related to previous strains isolated in the United States and was unrelated to the sharply modified B strain recovered in Taiwan in 1962 during an institutional outbreak. This strain has not since been isolated. Possibilities that the Japanese influenza B epidemics might herald outbreaks on the West Coast during the coming year or that the Taiwan B strain might reappear cannot be completely dismissed. It seems

unlikely, however, in view of the relatively rare occurrence of major epidemics of influenza B, that the United States would experience more than scattered, limited outbreaks of influenza B during 1964-65.

2. Vaccine Efficacy

Since its introduction, influenza vaccine has been shown, in repeated control trials, to confer substantial protection (60 to 80 percent) against the epidemic disease. Notable exceptions were observed when major shifts occurred in the antigenic composition of the virus (1947 and 1957) and more recently, when more gradual antigenic changes within the $A_2$ family of viruses have evolved, as occurred between 1957 and 1962. It would appear that, in general, the greater the similarity between viruses incorporated in the vaccine and naturally occurring strains, the better the degree of protection. Since influenza viruses are constantly undergoing antigenic change, the incorporation of recent isolates into the vaccine has merit. The incorporation of recent $A_2$ and B isolates in the 1963-64 vaccine and the increase in their concentration during 1964-65 should result in a vaccine capable of confering substantial protection in 1964-65. There has yet, however, been no opportunity to evaluate the newly constituted vaccine under conditions of a natural challenge.

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. No studies, however, have yet been reported which measure the efficacy of the vaccine in prevention of influenza-associated mortality.

3. High Risk Groups

Immunization should be considered and 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 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 $A_2$ epidemic both in this country and abroad. It has not, however, been demonstrated in subsequent years.

4. Time of Vaccination

Vaccination should begin as soon as practicable after September 1 and ideally should be completed by mid-December. In any case a two week delay in the development of antibodies may be expected and it is important, therefore, that immunization be carried out before influenza occurs in the immediate area.

5. Vaccine Composition

Recent isolates of both the A and B strains demonstrate a continuing alteration in antigenic structure. Accordingly, it is noted that more recent strains of both the influenza $A_2$ and B strains have been added in increased amounts. The antigenic composition of the vaccine for the 1964-65 season is as follows:

| Type | Strain | CCA Units per cc. |
|---|---|---|
| A | PR8 | 100 |
| $A_1$ | Ann Arbor 1/57 | 100 |
| $A_2$ | Japan 170/62 | 200 |
| B | Maryland 1/59 | 200 |
| | | 600 |

6. Dose and Schedule of Vaccination by Age (for those for whom immunization is recommended).

a) Primary Series - Those not vaccinated since July 1963 should receive a subcutaneous dose of polyvalent vaccine followed by a second dose about 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.

b) Revaccination - Those revaccinated since July 1963 need receive but a single dose of the vaccine.

c) Dosage

1. Adults and children over 12 - 1.0 ml. (600 CCA units)
2. Children 6 to 12 years* - 0.5 ml. (300 CCA units)
3. Children 3 months to 5 years*

   Primary series should consist of 0.1-0.2 ml. (60-120 CCA units) 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. For those previously vaccinated, a single booster of 0.1-0.2 ml. is recommended.

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

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

7. Future Studies

Constant vigilance, nationally and internationally, is important if early detection of strains showing a marked antigenc shift is to be accomplished. Should such strains be detected, it is important that some isolations be made in systems compatible with subsequent vaccine production. Such systems would include cercopithecus monkey kidney tissue culture or eggs.

Controlled field studies of vaccine efficacy among elderly persons and other high risk groups are of vital importance. As previously noted, evidence that influenza-associated mortality is prevented among such groups by vaccination has not been directly documented. Since use of the vaccine is not without costs, the protective value of the procedure demands further documentation.

DRAFT STATEMENT

Appendix III. Summary Statement - Status of Gamma Globulin Prophylaxis for Pregnant Women Exposed to Rubella

Advisory Committee on Immunization Practice

(For subsequent discussion at next regular meeting)

Although gamma globulin in adequate dosage has often been shown to suppress the clinical manifestations of rubella, evidence that it will or will not prevent congenital malformations among children of exposed mothers is lacking. Recent studies suggest that gamma globulin may, in fact, only prevent the clinical manifestations of rubella without affecting the occurrence of infection or viremia. In light of this evidence and with gamma globulin in limited supply, health officers might properly elect to conserve available globulin for prophylaxis of hepatitis, modification of measles or for other applications of demonstrated efficacy.

Appendix IV. Statement on the Status of Measles Vaccine
by the
Ad Hoc Advisory Committee on Measles Control
(March 21, 1963)
as revised by the
Advisory Committee on Immunization Practice
May 25, 1964

A. Live Attenuated Measles Virus Vaccine (Edmonston Strain)

Developed in the laboratory of Dr. John Enders, this vaccine, prepared in chick embryo tissue culture, was first tested in 1958 and since has been given to several million persons in the United States, either alone or in combination with gamma globulin. The vaccine produces in the recipient a mild or inapparent, non-communicable infection which induces active immunity. Although in the majority the symptoms are minimal, approximately 30-40 percent experience fever of 103°F (rectal) or greater, beginning about the sixth day and lasting two to five days. However, even those with high fever may experience relatively little disability and minimal toxicity. In 30 to 60 percent a modified measles rash is seen which begins with or after the subsidence of fever. A few develop mild cough, coryza and Koplik spots.

An antibody response equivalent to that seen in regular measles develops in over 95 percent of susceptible children. Measured as late as four years later, antibody levels induced by the vaccine have demonstrated a stability equivalent to that following the natural disease. Protection upon exposure to measles has been noted for at least four years after vaccination.

If standardized Measles Immune Globulin is given in the recommended dose at the same time as the live attenuated vaccine, but at a different site and with a separate syringe, clinical reactions to the vaccine are sharply reduced. About 15 percent demonstrate fever over 103°F (rectal); the duration of fever is shortened and the incidence of rash is markedly reduced. Although the frequency of serological conversion is the same as that following live attenuated vaccine alone, the level of induced antibody attained appears to be slightly decreased. Antibody titers have been shown to persist for at least three years and protection against the naturally occurring disease has been noted for at least two years.

To date, there have been no reports of encephalitis or other serious reactions following administration of the live attenuated vaccine to normal children. A few instances of convulsions, apparently of the febrile type and without known sequelae, have been recorded.

103°F (rectal); rash, cough and coryza are rarely observed. Serological conversion following the live vaccine occurs in over 95 percent. The duration of immunity, as measured by natural challenge or persistence of antibodies, has not yet been assessed in the infant group.

D. Recommendations for Vaccine Use

1) Age

Virtually all children will, at some time, have clinically evident measles. Marked by severe constitutional symptoms and a seven to fourteen day course, the disease is of additional concern because of secondary complications such as bronchopneumonia and encephalitis. The vast majority of cases of measles occur among those under 15 years of age, particularly those aged 2 to 6 years; only occasionally do cases occur among adults.

Vaccine use then is indicated primarily for children. The live virus vaccine should be administered only to those at least nine months of age since residual and maternal antibody may interfere with a response among those younger. The inactivated vaccine may be given at any age. Vaccination of adults is rarely indicated since all but a very small percentage, by history, have experienced the disease. Limited data indicate that in the adult, reactions to the vaccine approximate those seen in children.

2) High Risk Groups

Immunization against measles is recommended particularly for those especially prone to develop serious complications should they acquire natural measles infection. Specifically, these include children in institutions and those with cystic fibrosis, tuberculosis, heart disease, asthma and other chronic pulmonary diseases.

3) Prevention of Natural Measles Following Exposure

Limited studies reported to date indicate that there is no protective effect conferred by either vaccine when given after exposure to the natural disease. However, live attenuated vaccine administered only a few days previous to exposure appears to confer substantial protection.

4) Community Programs

Rarely would there appear to be a need in the United States for mass community immunization programs. Immunization should be carried out as indicated by private practitioners and through well-child conferences of established public health programs.

E. Dosage Schedules

Four different dosage schedules can be considered for use at the present time in the United States. (See table)

F. Contraindications to use of the Vaccines

Parenthetically, it should be noted that neither the live nor the inactivated vaccines contain penicillin.

1) Live Attenuated Vaccine

*a) Pregnancy

*b) Leukemia, lymphomas and other generalized malignancies

*c) Therapy which depresses resistance such as steroids, irradiation, alkylating agents and antimetabolites

*d) Severe febrile illness

* Although there are no reports of unusual complications in any of these conditions excepting leukemia, it is conceivable on theoretical grounds that potentiation of the attenuated disease might occur or, in the case of pregnancy, that damage of the fetus might result. Accordingly, if immunization is indicated, the inactivated vaccine should be used.

e) Recent Gamma Globulin Administration

If more than .01 cc/lb. of gamma globulin has been administered within the preceding 6 weeks, immunization should be deferred since the administered globulin may block the vaccine take.

f) Marked Egg Hypersensitivity

Since the virus is grown in chick embryo tissue culture, the vaccine probably should not be administered to extremely allergic children as indicated by their inability to eat eggs or egg products.

2) Inactivated Vaccine

Either monkey kidney or chick embryo tissue culture may be employed for inactivated vaccine production. (This will vary according to the manufacturer.) If chick embryo tissue culture material has been used precautions (as above) should be taken for possible marked egg sensitivity.

No other contraindications are known.

G. Continued Surveillance

Although several million children in the United States have received the vaccines without serious complications, continuing careful surveillance for significant adverse reactions is of the utmost importance. It is important that any serious reactions be carefully evaluated and reported in detail to local and State health officials. The Communicable Disease Center will maintain a close surveillance of all such cases.

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