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No. III

January 20, 1965

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TO : For the Record

FROM : Secretary, Advisory Committee on Immunization Practice

SUBJECT: Minutes, Meeting No. 3, Advisory Committee on Immunization Practice - November 19-20, 1964

I. The Advisory Committee on Immunization Practice met at the Communicable Disease Center on November 19-20. Those in attendance were:

a. Committee*

Dr. David J. Sencer, Acting Chairman
Dr. Donald A. Henderson, Secretary
Dr. Ernest A. Ager
Dr. Gordon C. Brown
Dr. Geoffrey Edsall
Dr. David T. Karzon
Dr. Theodore A. Montgomery
Dr. Roderick Murray
Dr. Paul F. Wehrle

* As Dr. Goddard was abroad, Dr. Sencer served as Chairman. Dr. Lesser could not attend.

b. Invited Participants

Dr. Benjamin D. Blood, Office of International Health

Dr. Joe L. Stockard, Miss Regina Burns; Division of Foreign Quarantine

c. CDC Staff

Immunization Activities - Dr. F. R. Freckleton

Laboratory Branch - Dr. U. P. Kokko

Epidemiology Branch

Dr. John J. Witte
Dr. Thomas M. Mack
Dr. Michael Lane
Dr. J. D. Millar
Dr. John M. Neff
Dr. George Miller

II. Committee Responsibilities

The draft statement defining the Committee's responsibilities, discussed originally at the first meeting, was presented for final consideration. It was again noted that the defined responsibilities were broad and the problems to be dealt with manifold and complex. Specific major problems and issues would necessarily be dealt with initially; questions and considerations of lesser immediate importance would be taken up successively as time permitted. Since the previous meeting, the Surgeon General's Office has expressed the desire that the Committee provide advice with respect to possible changes in vaccination requirements in international travel. Specific queries with respect to smallpox and yellow fever vaccination were submitted to the Committee for consideration at the present meeting (see below). The statement of Committee responsibility has been appropriately rephrased to reflect this function. Additional changes in wording of the statement for purposes of clarity were also discussed and incorporated. A statement defining the functions of the Division of Biologics Standards was incorporated into the commentary portion of the statement. The revised Committee's Statement of Responsibilities constitutes Appendix I.

Dr. Karzon, a member of the Academy of Pediatrics Committee on the Control of Infectious Diseases, reported that this Committee had recently met in New York and had developed a number of recommendations with respect to the use of oral polio

vaccines and other agents, some of which were at variance with recommendations of the Advisory Committee. He conveyed the request on the part of the Academy Committee that they have the opportunity to review and comment on proposed recommendations of the Advisory Committee on Immunization Practice before they are released. In the active discussion which ensued, three principal points were developed;

1) Recommendations developed by the two groups may be expected occasionally to be at variance since the Advisory Committee specifically deals with the effective application of preventive agents from the standpoint of public health practice while the Academy's concern is with recommended immunization procedures which will provide maximum levels of protection for the individual child in private patient pediatric care.

2) While it is recognized that there may be valid bases for differences in recommendations for immunization by the two Committees, it would be desirable that both Committees be made cognizant of data available to, and the rationale in decisions reached by, the other in order to minimize differences in the recommendations.

3) A mechanism permitting a continuing exchange of information and comment regarding proposed recommendations should be established.

To explore the most effective means to achieve these objectives, it was proposed that Drs. Goddard, Henderson, and Karzon meet with Dr. Lewis Coriell, Chairman of the Committee on the Control of Infectious Diseases.

III. Simplification of Vaccination Schedules

Pursuant to the first Committee meeting in which the desirability for simplification of immunization schedules was expressed, the initial step in consideration of the problem, a review of information pertaining to DPT immunization, has been initiated by Dr. Edsall with the assistance of Dr. Alan Ominsky, Epidemiology Branch, CDC. A first draft of the review has been completed.

IV. Smallpox Vaccination

At the request of the Surgeon General's Office, the Committee considered changes in the requirements for smallpox vaccination certification proposed at the last World Health Assembly but deferred for consideration until the 1965 meeting. Proposed changes pertain only to revaccinees. In the present practice, the certificate becomes valid on the date of revaccination. Under the proposed changes, the certificate would become valid on the date a major reaction is recorded (read not earlier than the sixth day after vaccine insertion) or, in the absence of such a reaction, on the date of the second insertion of vaccine if made within 30 days. For those successfully vaccinated or revaccinated within the preceding 5 years, the certificate would be valid on the date that revaccination is carried out with two insertions of vaccine.

The changes in vaccination certification were proposed with the hope that the introduction of smallpox into non-endemic areas might, with greater certainty, be prevented. Accordingly, available data pertaining to importations into the United States, Western Europe, Australia and New Zealand over the past 17 years was reviewed. A recent study comparing the relative frequency of cutaneous responses following one as opposed to two vaccine insertions was presented. Additional information relating to the relative risks of smallpox importation from abroad, the present status of vaccination in the United States and the frequency of complications was also discussed.

Weighing the technical, administrative and practical considerations involved in the proposed change in vaccination certification, the Committee recommended against changing the certification procedure at this time. A discussion of the problem and the conclusions and recommendations of the Committee are presented in Appendix II.

V. International Certification of Yellow Fever Vaccination

A resolution affirming the desirability of extending the validity of the yellow fever vaccination certificate from 6 to 10 years was passed by the Armed Forces Epidemiological Board and transmitted to Dr. Terry with the request that he consider bringing this to the attention of the World Health Organization for possible action. Dr. Terry referred this to the Committee for consideration.

The resolution is presented in Appendix III.

The reference cited in the AFEB resolution was reviewed along with other studies of a similar character. All support the conclusion that serological immunity following yellow fever vaccination persists over an extended period. Although no data are available pertaining to the long-term efficacy of yellow fever vaccine in the face of clinical challenge, the absence of yellow fever in extensive, previously endemic areas is substantive testimony to the long-term effectiveness of this vaccine. Noted was the fact that approximately a decade ago, the duration of validity of the yellow fever certificate was extended from four to six years on evidence based on the duration of serological immunity.

The Committee concurred with the resolution of the AFEB and advised that the Surgeon General request the World Health Organization to consider this change in the requirements.

VI. Simultaneous Administration of Smallpox and Yellow Fever Vaccine

The Division of Foreign Quarantine requested the advice of the Committee with respect to the desirability of simultaneous administration of yellow fever and smallpox vaccines.

Documented information pertaining to the frequency of possible complications when the two are simultaneously administered is so limited as to preclude judgment regarding the safety of this procedure. When the two vaccines are administered as a mixture

either by scarification (Meers, P.D., Trans. of the Royal Soc. of Trop. Med. and Hyg. 54:493-501, 1960) or by jet injection (Meyer, H.M., et al., Bull. World Health Organization 30:783-794, 1964) there appears to be a decreased frequency in seroconversions for yellow fever; the titer of induced vaccinial antibody also appears to be diminished. Additional studies, however, would be desirable. Simultaneous administration, however, of the two vaccines at separate sites apparently results in serological responses equivalent to those observed when the vaccines are administered singly (Meers, P.D.).

The Committee concluded that since adequate data are not available concerning the safety of simultaneous administration of these two agents and since both agents have an encephalitogenic potential, it would seem prudent, when practicable, to separate the administration of these two agents by an interval of at least 14 days.

VII. Gamma Globulin Prophylaxis for Pregnant Women Exposed to Rubella

The relative desirability of gamma globulin prophylaxis for pregnant women exposed to rubella was discussed at the first meeting. Consensus regarding a statement could not be reached and the subject was scheduled for subsequent discussion.

Unfortunately, the definitive data necessary to provide a direct answer to the question are not yet available. Cognizance was taken of recent experimental studies and observations by Krugman and others which indirectly bear on the question. Specific studies of the problem, initiated by Dr. Corbett MacDonald, Public Health Laboratory Service, United Kingdom

have been in progress for several years. Preliminary data, just becoming available, suggest to him that gamma globulin may have a preventive effect. Definitive information, however, should be available in 6 to 12 months.

A statement summarizing the present status of the problem was prepared (Appendix IV).

VIII. Measles Immunization in 9 to 12 Month Old Children

Data submitted to the Committee by Drs. Maurice Hilleman, Saul Krugman and E. R. Alexander, as well as data submitted by manufacturers to the Division of Biologics Standards, all indicate that seroconversions following administration of Edmonston strain live attenuated measles vaccines and gamma globulin are not optimal when administered to children less than one year of age. Seroconversion was recorded among approximately 70 percent of those 9 months of age; 80 percent among those 10 months of age; and 90 percent among those 11 months of age. Older children demonstrated seroconversions among 95 percent or more of those tested. A definitive explanation for the poorer response in the 9 to 11 month old age groups is not yet available. It is probable, however, that small amounts of residual passive maternal antibody in a few children, although not yet detectable by laboratory methods, may account for the vaccine failures. It should be noted that earlier studies, in which the Edmonston strain vaccine was administered without gamma globulin, had indicated a high frequency of seroconversions among those 9 months of age and older. The addition of immune globulin to the regimen may have served to alter the balance

sufficiently in a few to prevent replication of the attenuated virus.

Since measles is relatively infrequent among 9 to 12 month old children in the United States and, with wider use of the vaccine, may be expected to be even less common, the Committee concluded that it would be generally advisable to withhold immunization with the live, attenuated vaccine until one year of age, recognizing that under epidemic circumstances, some may wish to vaccinate younger children at risk, recognizing that the vaccine may be less efficacious.

The previously prepared recommendations regarding measles vaccine use was revised to reflect these changes. (Appendix V)

IX. Further Attenuated Measles Vaccine

Testing of several "further attenuated" measles vaccine strains has been in progress for several years. Necessary testing of production lots for the Schwarz strain (developed by Dr. Anton Schwarz, Pitman-Moore) has been completed and some information has been submitted to the Division of Biologics Standards as part of the licensure application.

Information regarding the reactogenicity and efficacy of the Schwarz vaccine was reviewed. Presently available data suggests that this further attenuated strain is substantially less reactogenic than the Edmonston strain and may be recommended for use without gamma globulin. Further data regarding its efficacy are needed.

The Committee elected to postpone making any recommendations regarding the relative desirability of this vaccine in immunization practice until such time as licensure was imminent and more information was available. Dr. Murray indicated that he would notify the Chairman immediately prior to this date to permit the Committee to make such recommendations as would be appropriate.

X. Agenda Items to be Considered for the Next Meeting

1. Typhoid vaccines

2. Cholera vaccines

XI. With the thanks of the Chairman, the Committee adjourned at 11:00 a.m. November 20, 1964.

Donald A. Henderson, M.D.

DRAFT STATEMENT

Appendix I. Responsibilities of the Advisory Committee on Immunization Practice

Responsibility

The Advisory Committee on Immunization Practice 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. Among other factors, the Committee shall consider desirable 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 various population groups for whom the agents should be recommended and shall advise regarding the relative merits and methods for conducting community immunization programs. It will provide advice and guidance regarding present and proposed requirements for immunization in international travel. The Committee 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 a small part of its concern.

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 nature of the Committee's responsibilities. 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.

The Committee also wishes to take cognizance of the important role of the Division of Biologics Standards which has the delegated responsibility for assuring compliance with standards for biologic products which insure the safety, purity, and potency of such products. Reflecting the importance of a close liaison between the DBS and the Advisory Committee in the development of recommendations in immunization practice, the Director of the DBS serves as a member of the Advisory Committee.

Appendix II. Recommendations and Comment Regarding the Rationale of Proposed Changes in Smallpox Vaccination Requirements for International Travel

I. Present Requirements and Changes Proposed in Smallpox Vaccination Requirements by the International Quarantine Committee, WHO

a) Present Requirement

"The validity of this certificate shall extend for a period of three years, beginning eight days after the date of a successful primary vaccination or, in the event of a revaccination, on the date of that revaccination."

b) Proposed Requirement

"The validity of this certificate shall extend for a period of three years beginning eight days after the insertion of vaccine resulting in a successful primary vaccination.

In the event of a revaccination, the validity shall extend for a period of three years beginning:

(a) on the date a major reaction is recorded (read not earlier than the sixth day after insertion of vaccine) or, in the absence of such reaction, on the date a second insertion of vaccine if made within thirty days, or

(b) on the date of two insertions at the same time when the vaccinator is satisfied that a re-vaccination or a successful primary vaccination has been performed within the previous five years.

A major reaction after revaccination is one which on examination at least six days later shows a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion which may be a scab or ulcer."

II. Prevention of Smallpox Importations

The premise for changing present international vaccination requirements is predicated upon the belief that, with the changes, fewer importations of smallpox into non-endemic areas would occur. However, since no data pertaining to the circumstances of past introductions have been compiled by the WHO, a definitive appraisal of the causes for failures in the present system of certification is not possible.

Intensive search by CDC through published and unpublished documents reveals that since 1950, there have been 38 identifiable importations into Western Europe, North America, Australia and New Zealand. Of the 38 importations, over half were recorded by the United Kingdom (13) and Germany (7). The area of origin of the smallpox was identified as Southeast Asia for 21 of the 29 for which information was available. Little information, however, is available as to the vaccination status of the imported cases. Of 20 cases for which some information is available, 19 claimed vaccination within the preceding 3 years. However, data are not available as to the probable potency or source of the vaccine used, the charater of the cutaneous response, or, in most instances, whether the vaccination represented primary

vaccination (for which no change in vaccination certification is proposed). In a number of the importation incidents, it was stated by authorities that they believed the ostensibly valid certificates may have been fraudulently issued; in other instances, it was believed that impotent vaccine may have been used. However, almost no confirming evidence can be adduced from available records.

It would appear self-evident that if changes are to be made in smallpox certification requirements to reduce the frequency of importations, the changes should be directed specifically to correct the weaknesses in the present system under which the importations occurred. There is presently no available evidence which would indicate that a change in the present system of vaccination certification would serve to correct these deficiencies.

III. Rationale for Appraisal of Cutaneous Reaction in Revaccinees

It should be noted that, under current regulations, validation of the vaccination certificate for primary vaccinees, requires an assessment of the success of the procedure through appraisal of the cutaneous response. The proposed change in requirements would extend this requirement to include revaccinated individuals. This provision would apply to most U. S. citizens traveling abroad. Recent surveys indicate that approximately 90 percent of Americans 5 years and older have, at some time, been vaccinated.

The cutaneous response following revaccination may range from a minimal to nil reaction among highly immune individuals, to one which resembles a primary response in individuals whose immunity has waned. It has been demonstrated, however, that insertion of virus, inactivated by heat, can invoke a response characterized by erythema and occasionally papular formation which may persist for several days. During the first few days after vaccination, the response invoked by inactivated vaccine and by live, potent vaccine may be identical. Persistence of erythema at the sixth day, however, is reasonably definitive evidence of active infection, i.e. virus replication. Provision in the regulations for a reading at the sixth day and for revaccination of those not exhibiting a "major response" is believed to be an added guarantee that a high level of immunity has been induced in the recipient.

There is little question that appraisal of the response to vaccination at day 6 to 8 is a sound procedure as a "quality control" measure in medical practice. Undoubtedly, this should be encouraged as good medical practice. To make this mandatory as part of the quarantine regulations with the necessarily imposed time barriers to travel, etc. is, however, questionable. It is doubtful that it would provide solutions to what are believed by many to be the principal causes for past failures to prevent importations, specifically, usage of low potency vaccine and the issuance of fraudulent certificates. It may be anticipated that,

in the former instance, the same physician who employed impotent vaccine in vaccination would evaluate the response; observing the absence of a major reaction, he would, unless particularly conscientious, reapply the same impotent vaccine, at the same time validating the certificate.

In summary, the proposed change clearly errs on the side of caution at the cost of imposing an additional barrier to international travel. It would affect most U. S. travelers. It could be expected to do little or nothing to correct the problem of fraudulent certificates and the use of impotent vaccines.

IV. Relative Efficacy of One as Opposed to Two Insertions of Vaccine

For those vaccinated during the preceding five years, it has been proposed that the certificate become valid on the date that two vaccine insertions are made. Under the revised schema, this alternative plan would permit prompt validation of the certificate and would not require the frequent international traveler to visit his physician on two occasions each time that he wished to renew his certificate.

Two insertions presumably would more certainly guarantee the success of the procedure. The five year limitation was proposed on the grounds that reactions to a double insertion of vaccine among those vaccinated more than five years before, would be unduly frequent and severe.

Double insertion results in the implantation of twice as many virus particles at two sites. With vaccine of low potency, such an increase might be of some significance in a few individuals.

However, vaccines failing to meet international standards often contain several logs less of virus than the standard preparations, in other words 1/100 to 1/10,000 the number of virus particles found in properly constituted vaccines. To focus attention on the procedure of double insertion as a significant element in vaccination success seems to be a misplacement of emphasis.

In a study of 300 volunteers conducted by the CDC which was designed to measure the relative frequency of "major reactions" among those given a single as opposed to a double insertion of commercially available, lyophilized vaccine, over 90 percent developed "major reactions" by the WHO criteria. The frequency of "major reactions" was not different among those given a single as opposed to a double insertion of vaccine; there was no difference in the frequency among those vaccinated less than 10 years before as opposed to those vaccinated more than 10 years previously. Antibody studies representing an additional measure in assessment have yet to be completed. In brief, it would appear that when a potent vaccine is used, there is no significant advantage to two insertions.

Data to support the contention that double insertion might result in more complications among those vaccinated more than five years previously could not be found in the available literature.

V. Recommendations of the Committee

1. A change in the procedure for vaccination certification at this time is not warranted.

2. As a matter of good medical practice, appraisal of the vaccination response at day 6 to 8 after revaccination should be encouraged with revaccination of those not evidencing a major reaction. This should not, however, be a requirement in certification.

3. The United States government and the World Health Organization should take more aggressive action in a coordinated global program for smallpox eradication. The development of the jet injector as a technique in mass smallpox immunization should serve as a useful adjunct to accelerate an international eradication scheme. However, so long as endemic foci exist, the threat of importations will persist.

4. Since vaccine potency is of key importance both to the eradication program and to the vaccination certification procedure, the World Health Organization should be urged to devote particular attention to this facet of the program. The importance of the international standardization and testing of vaccines and the particular desirability of the more stable lyophilized vaccine preparations for general use should be emphasized.

5. Since the occurrence of smallpox importations are <u>prima facie</u> evidence of failure in the international vaccination requirements, the World Health Organization should be requested to investigate in detail each importation into

a non-endemic area to determine the specific pertinent factors contributing to the event.

Appendix III. Extension of Validity of Yellow Fever Vaccination Certificates

Resolution adopted by the Armed Forces Epidemiological Board and concurred in by the Advisory Committee on Immunization Practice:

Resolution

Based on definitive studies of long-term immunity following yellow fever vaccination, it is recommended that the period of validity of the international certificate of vaccination or revaccination against yellow fever be extended from 6 years to 10 years.

Support of the Resolution

In view of data demonstrating persisting immunity to yellow fever more than 19 years after vaccination with the 17D strain (Am. J. Trop. Med. and Hyg., 12:230-235, 1963),* extension of the recommended booster interval from 6 years to 10 years would be soundly based and well justified. Such a recommendation cannot be implemented by the Armed Forces unless and until it is adopted by the World Health Organization and the period of validity of the international certificate of vaccination or revaccination against yellow fever is extended.

*Supported by similar studies, e.g., Groot, H., Bahia Ribeiro, R. Bull. World Health Organ. 27:699-707, 1962 and Dick, G.W.A., Gee, F.L., Tr. Royal Soc. Tropical Med. and Hyg. 46:449-458, 1952.

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

Although gamma globulin in adequate dosage has been shown in several studies to suppress the clinical manifestations of rubella, evidence that it will or will not prevent congenital malformations among children of exposed mothers is lacking. Recently reported experimental studies suggest that gamma globulin may prevent the clinical manifestations of the disease with limited or no effect on the occurrence of infection and viremia. A few instances have been reported in which congenital malformations of the type associated with rubella infections were observed in infants born of asymptomatic mothers to whom gamma globulin was administered.

However, neither the experimental studies nor the isolated individual case observations serve directly to answer the question as to whether gamma globulin may exhibit a relative efficacy in protection against congenital malformations in the infant. Extensive studies dealing specifically with this question are in progress in the United Kingdom. Definitive results may be anticipated within the next year. Until such time as this information becomes available, it is not possible to formulate concrete recommendations regarding the relative desirability of gamma globulin administration to pregnant women exposed to rubella infections.

Appendix V. 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
November 19, 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.

B. Inactivated Measles Virus Vaccine

The inactivated vaccine is composed of attenuated Edmonston strain measles virus propagated on monkey kidney or chick embryo tissue culture, and subsequently inactivated, concentrated and precipitated. The vaccine has been customarily administered, in field trials, in a three dose schedule at monthly intervals. Reactions to the vaccine are no more frequent than those seen after administration of alum precipitated products, such as diphtheria and tetanus toxoids.

Serological conversion after three monthly doses of inactivated vaccine is induced in 90 percent or more of susceptible children. Antibody titers, however, are distinctly lower than those following the live vaccine and in most cases decline to undetectable levels over the following year. These children, although without detectable antibody, demonstrate a booster response when given a fourth dose of vaccine.

Under the conditions of natural challenge, the vaccine has demonstrated an efficacy of between 80 and 95 percent during the immediate six months following administration. A year after administration, the level of efficacy in control trials has been shown to decline to between 65 and 75 percent. Field trials employing a fourth or booster dose have not been reported.

C. Combination Schedules Employing Inactivated and Live Attenuated Virus Vaccines

If live attenuated vaccine is administered one to three months after one or two doses of inactivated vaccine, clinical reactions caused by the live vaccine are sharply reduced; resultant antibody titers are boosted over those produced by the inactivated vaccine alone and appear to be equivalent to those observed following the administration of live vaccine. About 10 percent demonstrate fevers over 103°F (rectal); rash, cough and coryza are rarely observed. Serological conversion occurs in 95 percent given this combination; antibody has been shown to persist for at least 14 months in 90 percent of this group.

Under natural challenge, this combination has demonstrated an efficacy of over 97 percent during a period of 14 months following administration. Although the protective effect of this vaccine combination probably persists beyond this time, substantiating data are not yet available.

Infants given inactivated vaccine in three monthly doses beginning as early as one month of age followed by live vaccine at 12 months of age also demonstrate sharply reduced clinical reactions following the live vaccine. About 5 percent demonstrate fever over

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 twelve 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

established public health programs. Particular attention must be given to programs directed at children in lower socioeconomic areas, since attendance of this group at the usual well child conferences beyond 6 months of age is particularly poor.

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.

Schedule	Type of Vaccine	Age	Doses* and Administration	Comment
1	Live, Attenuated Vaccine	12 months and older	1	Although the live, attenuated vaccine may be administered safely with or without the simultaneous administration of Measles Immune Globulin, most physicians will wish to use the two combined because of the lessened frequency of clinical reactions.
2	Live, Attenuated Vaccine plus Measles Immune Globulin	12 months and older	1 plus Measles Immune Globulin (.01 cc per pound at different site with different syringe)	The live attenuated vaccine should be administered only to those 12 months of age or older since residual maternal antibody may interfere with a satisfactory response among younger children.
3	Inactivated Vaccine	Any Age	3** (monthly intervals) plus a booster dose after one year	In view of the rapid fall-off in antibody and evidence of decreasing immunity following a primary immunization series, use of this vaccine is not preferred except for special groups in which live attenuated vaccine is contraindicated. The degree and duration of protection which might be afforded to those given a booster has not yet been determined.
4	Inactivated Vaccine followed by Live, Attenuated Vaccine	12 months and older	1 dose inactivated vaccine followed in 1 to 3 months by 1 dose live attenuated vaccine	The preceding administration of inactivated vaccine serves to reduce the frequency and severity of clinical reactions following live attenuated vaccine administration.
		Under 12 months	3 doses inactivated vaccine at monthly intervals followed by 1 dose live attenuated vaccine at 12 months of age or older.	The live attenuated vaccine should be administered only to those 12 months of age or older since residual maternal antibody may interfere with a satisfactory response among younger children.

* Manufacturers directions regarding volume of dose should be followed.

** In view of rapidly declining antibody levels and protection, at least one booster dose about a year later is necessary. Data are not yet available to indicate when or with what frequency additional booster doses might be required.

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.

Members: Ad Hoc Committee on Measles Control

Dr. James L. Goddard, Chairman
Dr. Donald A. Henderson, Secretary
Dr. John F. Enders
Dr. Harry A. Feldman
Dr. Archie L. Gray
Dr. Hugh H. Hussey
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Dr. Frederick C. Robbins

Members: Advisory Committee on Immunization Practice

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RECOMMENDATION CONCERNING THE PROPHYLAXIS OF RUBELLA

The epidemic of rubella in the United States in 1963-64 has highlighted the importance of reviewing current recommendations for the use of human immune (gamma) globulin in the prevention of rubella during pregnancy. In the absence of definitive data to support or reject its use, physicians have continued to use it in the hope that a few malformations might be prevented. This creates an acute shortage of human immune globulin in epidemic years, a useless expense for families if it is not effective and diverts the product from other diseases where it is of established value.

Recent experimental studies utilizing serologic tests and virus isolation in patients injected with immune globulin and rubella virus suggest that immune globulin may suppress only the clinical manifestations of rubella without preventing the occurrence of infection or viremia. It has not been established whether such viremia, in the absence of other manifestations of rubella in the first trimester of pregnancy, can be associated with fetal damage.

In the light of recent data there is less reason than before to justify the use of immune globulin for susceptible women exposed to rubella during the first trimester of pregnancy. Physicians and others charged with responsibility for advising patients should make their decisions and recommendations for management on the assumption that there is still no firm evidence that immune globulin is effective in reducing the risk of congenital anomalies.

Combined statement by the Committee on the Control of Infectious Diseases and the Committee on Congenital Malformations, American Academy of Pediatrics.

December 7, 1964

RECORD COPY

DEPARTMENT OF
HEALTH, EDUCATION AND WELFARE
Public Health Service Communicable Disease Center
Atlanta, Georgia 30333

August 7, 1964

TO : Participants of Advisory Committee Meeting on Oral Poliomyelitis Vaccines

FROM : Secretary, Advisory Committee on Immunization Practices

SUBJECT: Final Clearance of Report

Enclosed is a further revision of the report based upon replies to the memo of July 20 and further comments received after distribution of the memo of July 28 transmitting the letters of Drs. Ager and Sabin.

It is our belief that the revisions of the wording that have been incorporated into this draft make the document acceptable to the great majority of the participants.

We would appreciate your prompt review of this "Draft for Final Clearance" and would like to receive your comments by Monday, August 17. It is our proposal to forward this report to the Surgeon General at that time along with a summary of the reactions of each member of the group.

Release of the report can be expected shortly after the Surgeon General returns from Europe at the end of this month.

Donald A. Henderson
by AHL

Donald A. Henderson, M.D.

P.S. - Both Dr. Goddard and I will be on leave this week. Do not hesitate to phone Alex Langmuir if there are any points or issues you wish to discuss.

D.A.H.