THE STATUS OF MEASLES VACCINES

A Technical Report*

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PREFACE

Licenses for the manufacture of two types of measles vaccines, you are no doubt aware, were approved on March 21, 1963, by Secretary of Health, Education, and Welfare Anthony J. Celebrezze on the recommendation of the Public Health Service.

Merck, Sharp, and Dohme of Philadelphia has been licensed to market a live attenuated measles vaccine and Charles Pfizer, Inc., of New York an inactivated vaccine.

Both vaccines stem from the work of Dr. John Enders of Harvard University, and an associate, Dr. Thomas Peebles who isolated a strain of the measles virus in 1954, and Dr. Samuel L. Katz who worked with Dr. Enders to effect the attenuation of the live virus.

Although the national death rate for measles in the United States is relatively low, its after effects in deafness and mental crippling can, as you know, be serious. It is, of course, a major threat to many parts of the world. In Africa and South America the death rate among children may be as high as 25 percent.

Early this year, in anticipation of licensing, I asked a group of distinguished virologists and experts in the field of measles to meet with me and with staff members of the Public Health Service to review all of the data associated with the field trials here and abroad and to make recommendations on the use of the vaccines.

For your information, I am making available the full text of their report.

Surgeon General.

STATEMENT ON THE STATUS OF MEASLES VACCINE

In order to make available to the health profession concise information regarding the status of inactivated and live attenuated measles virus vaccines and their appropriate application, an Advisory Committee to the Surgeon General was convened on February 25 to appraise the available data. Considerable research has been carried out by many investigators in developing and testing these vaccines. Additional studies are planned or are in progress to define and clarify many practical questions relating to their use, such as, optimal immunization schedules, relative efficacy and safety, and others. The present report is an interim statement based on all of the current, available information.

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 approximately 25,000 persons in the United States, either alone or in combination with gamma globulin. The vaccine induces active immunity following a single dose and produces in the recipient a mild or inapparent, noncommunicable measles infection. 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 2 to 5 days. However, even those with high fever may experience relatively little disability. In 30 to 60 per cent a modified measles rash is seen which, unlike true measles, 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 per cent of susceptible children. Measured as late as 4 years later, the 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 as long as 3 years and 8 months 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 per cent demonstrate fever over 103° F (rectal); the duration of fever is shortened and the incidence of rash is reduced. Although the frequency of serological conversion is the same as that following attenuated vaccine alone, the level of induced antibody attained appears to be slightly decreased. Antibody titers have been shown to persist for at least 3 years and protection against the naturally occurring disease has been noted for at least 2 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 reported.

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 per cent 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. Preliminary data, however, indicate that these children, although without detectable antibody,

* The following statement, in major part, is as prepared by an Ad Hoc Committee on Measles Control, advisory to the Surgeon General.

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 per cent during the immediate 6 months following administration. Whether the protective effect of the vaccine persists beyond this time is not yet known.

C. *Combination Schedules Employing Inactivated and Live Attenuated Virus Vaccines*

If live attenuated vaccine is administered 1 to 3 months after one or two doses of inactivated vaccine, clinical reactions caused by the live vaccine are sharply reduced; resultant antibody titers are sharply boosted over those produced by the inactivated vaccine alone and appear to be equivalent to those observed following the administration of live vaccine with gamma globulin. Less than 10 per cent demonstrate fevers over 103° F (rectal); rash, cough, and coryza are rarely observed. Serological conversion occurs in 95 per cent given this combination; information as to the duration of antibody persistence is not yet available.

Under natural challenge, this combination has demonstrated an efficacy of over 97 per cent during the 6 months following administration. Although the protective effect of this vaccine combination may persist beyond this time, substantiating data are not yet available.

D. *Recommendations for Vaccine Use*

(1) *Age.*—Over 90 per cent of children will, at some time, have clinically evident measles. Marked by severe constitutional symptoms and a 7- to 14-day course, the disease is of additional concern because of secondary complications such as bronchopneumonia and encephalitis. The vast proportion of cases of measles occurs 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; it should be administered to those without a history of measles, at 9 months of age or as soon thereafter as possible. Those younger than 9 months frequently fail to respond to immunization with the attenuated virus vaccine because of the presence of residual maternal antibody. Vaccination of adults is rarely indicated since all but a very small percentage are immune. Limited data indicate that in the adult, reactions to the vaccine approximate those seen in children.

(2) *High Risk Groups.*—Immunization against measles is particularly recommended for those prone to develop serious complications should they acquire natural measles infection. Specifically, these include institutionalized children and those with cystic fibrosis, tuberculosis, heart disease, asthma and other chronic pulmonary diseases.

(3) *Prevention of Natural Measles Following Exposure.*—Limited studies 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.*

(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 Sensitivity.* 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) *Contraindications—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 Study*

A number of studies are currently in progress which will serve to provide a better measure of the efficacy of the different vaccine schedules. It is important that children in these trials be followed for many years to determine the durability of immunity conferred, both in terms of serological response and in terms of protection against naturally occurring disease. Studies to evaluate the possible use of inactivated vaccine for infants less than 9 months of age are in progress.

Although approximately 25,000 children in the United States have reecived the live, attenuated vaccine, and a somewhat smaller number the inactivated vaccine, without serious complications, careful surveillance for significant adverse reactions is of the utmost importance as

* 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.

the number immunized is extended. It is important that any serious reactions be carefully evaluated and reported in detail to local and State health officials. The Communicable Disease Center specifically is requested to assume a continuing active role in maintaining a close surveillance of all such cases.

The members of the Ad Hoc Advisory Committee on Measles Control are as follows:
JAMES L. GODDARD, M.D., *Chairman*—Chief, Communicable Disease Center, Public Health Service, Atlanta 22, Ga.
DONALD A. HENDERSON, M.D., *Secretary*—Chief, Surveillance Section, Epidemiology Branch, Communicable Disease Center, Public Health Service, Atlanta 22, Ga.
JOHN F. ENDERS, M.D., Chief, Research Division, Infectious Diseases, Children's Hospital, Boston, Mass.
HARRY A. FELDMAN, M.D., Professor and Chairman, Department of Preventive Medicine, State University of New York, Syracuse, N. Y.
ARCHIE L. GRAY, M.D., Secretary and Executive Officer, State Board of Health, Jackson 5, Miss.
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SAUL KRUGMAN, M.D., Professor and Chairman, Department of Pediatrics, New York University School of Medicine, New York, N. Y.
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RODERICK MURRAY, M.D., Director, Division of Biologics Standards, National Institutes of Health, Public Health Service, Bethesda, Md.
FREDERICK C. ROBBINS, M.D., Professor of Pediatrics, Western Reserve School of Medicine, Cleveland 9, Ohio.

Schedule	*Type of Vaccine*	*Doses* and Administration*	*Comment*
1	Live, Attenuated Vaccine	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 reactivity.
2	Live, Attenuated Vaccine plus Measles Immune Globulin.	1 plus Measles Immune Globulin (.01 cc per pound at different site with different syringe).	
3	Inactivated Vaccine	3** (monthly intervals)	In view of the rapid fall off in antibody and lack of data regarding persistence of immunity beyond 6 months, use of this vaccine is not preferred at this time except for special groups in which live attenuated vaccine is contraindicated.
4	Inactivated Vaccine followed by Live, Attenuated Vaccine.	Pending	This approach to measles immunization appears promising; recommended schedules will be developed as more data becomes available.

* Manufacturers directions regarding volume of dose should be followed.
** In view of rapidly declining antibody levels, it would appear that one or more subsequent booster doses will be necessary. Data are not yet available to indicate when or with what frequency these will be required.

Medical Education

HOWARD UNIVERSITY COLLEGE OF MEDICINE

Alpha Omega Alpha. The annual initiation banquet of Gamma Chapter of the District of Columbia was held on April 20, 1963. MISS PAULINE Y. TITUS and MISS JOANNE B. EWING, of the class of 1964, were initiated at this time. DR. JOHN L. PARKS, dean of the College of Medicine of George Washington University, delivered the address of the evening. His subject was "Live to Learn." MR. JAMES R. MATHEWS, president of Gamma Chapter, presided. Presentation of candidates for membership into AOA was conducted by DR. JOHN W. LAWLAH, faculty counselor. Mr. Mathews and DR. JOSEPH L. JOHNSON, secretary-treasurer of AOA, awarded keys and certificates to the initiates. DR. ROBERT S. JASON, dean of the College of Medicine, gave the charge to the initiates and Miss Titus responded.

In addition to the initiates the roster of Gamma Chapter consists of the following students. JAMES R. MATHEWS, FRANK D. HARRISON, MELVIN J. SPICER and WILLIAM A. STALLWORTH of the Class of 1963.

Honors and Oath Day. The annual exercises were held on June 6, 1963. DR. CHARLES D. WATTS, '43, of Durham, North Carolina, addressed the class. He was introduced by DR. CHARLES C. HUNT, '43. MR. RAFAEL LINARES, president of the Class of '63, presented the class gift and the Medical School Choral Group under the direction of MR. WAYNE P. WEDDINGTON, '63, rendered musical selections. MR. MICHAEL SERBER, '63, played a violin solo. DR. ROBERT S. JASON, dean of the College of Medicine, presided. Recipients of prize-awards were as follows: