MINUTES, MEETING NO. 13, ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES, OCTOBER 8-10, 1968

The Advisory Committee on Immunization Practices met at the National Communicable Disease Center on October 8-10, 1968. Those in attendance were:

Committee

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

Representing the American Academy of Pediatrics

Dr. Saul Krugman

Invited Participants

Colonel Dan Crozier, Department of the Army, United States Medical Unit, Fort Detrick, Maryland
Dr. Harry Meyer, Division of Biologics Standards, National Institutes of Health, Bethesda, Maryland
Dr. Bernard Portnoy, Associate Professor of Pediatrics, University of Southern California, Los Angeles, California
Dr. Paul F. Wehrle, Chief Physician, Pediatric and Communicable Disease Services, County of Los Angeles General Hospital, Los Angeles, California

CDC Staff--Participants and Discussants

Epidemiology Program:
Dr. Alexander D. Langmuir
Dr. Elias Abrutyn
Dr. Philip S. Brachman
Dr. Roger A. Feldman
Dr. Eugene Gangarosa
Dr. George E. Hardy
Dr. A. W. Karchmer
Dr. Thomas C. Shope

Foreign Quarantine Program:
Dr. James W. Mosley

Immunization Program:
Dr. Robert Freckleton
Dr. Joel P. Friedman
Dr. Ira Kassanoff
Dr. John J. Witte

Laboratory Program:

Dr. U. Pentti Kokko
Dr. William B. Cherry
Dr. Philip H. Coleman
Dr. Andrew Fodor
Dr. Kenneth Herrmann
Dr. Steven Mostow
Dr. Roslyn Q. Robinson
Dr. Morris T. Suggs

NCDC IMMUNOBIOLOGICS ACTIVITY

The first portion of the 1968 fall meeting of the Advisory Committee on Immunization Practices was devoted to a description of NCDC's immunobiologics activity. The activity established in 1965 under the Laboratory Program, acts as a national center for storage and distribution of uncommon biological products which are primarily used in special high risk groups. Drs. Kokko, Suggs, and Fodor reviewed the concepts of the program and described the various vaccines and other biologicals which are stocked, under development, and being considered for the future. Colonel Dan Crozier, Commanding Officer, United States Medical Unit, Fort Detrick, Maryland, served as a consultant for this section of the meeting.

(See attachment "Immunobiologics Activity, Introduction.")

The Committee was unanimous in support, not only of the concept of stockpiling vaccines already developed but also of development of other antigens and antisera with value for high risk laboratory and other groups. The Committee drafted a summary comment and recommendation on its appraisal of the immunobiologics activity (see attachment) with which to encourage extension of the program.

The Committee recommended that time be set aside at future meetings for additional, systematic review of the biologics presently available so that they could be incorporated into a general plan of utilization in which the ACIP might participate.

RUBELLA VACCINE

In continuing previous discussions on rubella and development of a live, attenuated rubella virus vaccine, the Committee considered additional data on the vaccine's field testing presented by Drs. Witte, Karchmer, Herrmann, and other NCDC staff and by special consultants, Drs. Saul Krugman, Harry Meyer, Paul Wehrle, and Bernard Portnoy. The continuing evidence of efficacy and safety of the vaccine in childhood groups was notable.

In terms of vaccine application, the Committee was concerned over the established association of join reactions among large proportions of adult women receiving the antigen. Ultimate user groups and recommendations for rubella vaccination were, therefore, felt to depend on a rational and objective appraisal not only of efficacy but also of risk. In this regard, the problems of associated reactions in adult women and the presently undefined theoretical risk of vaccine antigen for the developing fetus were predominant.

In general, the Committee was impressed by the 95 to 100% rubella seroconversions in susceptible individuals and the apparently persistent antibody levels among vaccinees. The very limited data now available on natural and artificial challenge, while not entirely answering the question of durable efficacy, did indicate solid immunity among those in whom serological conversion had occurred. Data from human volunteer challenge experiments suggested that when antibodies were at a low level, a "booster effect" from a second

dose of vaccine was frequently observed. Although small numbers were involved, studies carried out in California suggested that there may indeed be a "protective" level of antibody following rubella immunization--the level probably depending on the serological test employed in the investigation.

Of interest was a single case report from Dr. Portnoy of a 50-year-old nurse with evident rubella on two occasions, both reasonably well documented serologically. The natural occurrence of second infections with rubella still appears to be rare but not altogether impossible.

The importance of improved surveillance of the congenital rubella syndrome was emphasized. Only six instances were officially reported in 1967, the first year during which this condition was nationally reportable. Obviously, such gross underreporting must be improved if the long-term benefits of rubella vaccination are to be evaluated.

No national estimates of the total number of congenitally anomalous infants and children associated from rubella are available. It is of interest in this regard, however, that Dr. Krugman indicates that since 1965, approximately 15 to 20 new cases of congenital rubella have been admitted to the New York Hospital pediatric center. About 10 of these infants are less than one year of age, giving some indication of the relative frequency of this disease even in one center in a single urban area.

Dr. Kenneth Herrmann reported to the Committee on the variations in rubella diagnostic kits being used in various

parts of the country. The Committee encouraged the Center to pursue its effort to provide adequate reagents and standardized techniques for rubella diagnosis in State health department and clinical laboratories anticipating the need for competent reference diagnosis in supporting use of rubella vaccines and in rubella surveillance.

The Committee discussed general concepts of rubella vaccine use in great detail and assigned the task of developing a first draft recommendation for live rubella vaccine use in the United States to a working group. The anticipation of licensure of vaccine within the next 6 to 8 months was felt to demand a thorough and continuing discussion and eventual adoption of a meaningful recommendation to parallel the earliest availability of the antigen.

MUMPS VACCINE

The Committee reviewed additional data on the now three-year experience with live mumps vaccine in which reports indicate solid protection and virtually complete absence of adverse reactions. Approximately 1.7 million doses have been administered at the present time, and it is expected that by the end of calendar year 1968, some 3 million doses will have been distributed.

Since licensure, only three instances of any associated vaccine reactions have been listed. These three cases of orchitic syndromes were only temporally related to vaccination, and it would seem that in all cases, a possible exposure to naturally occurring mumps had occurred simultaneous with or preceding vaccination. (These data were accumulated by Epidemic Intelligence Service Officers and

do not represent a national survey or information from the manufacturer.)

The Committee reviewed its original recommendation on live mumps vaccine and agreed that the additional year's data on efficacy and safety were adequate to modify the recommendation toward a more permissive one. A working group was charged to incorporate these concepts and submit them to the Committee for final consideration.

INFLUENZA

In view of the appearance of A2/Hong Kong/68 viruses and the special meeting of the ACIP in September 1968 to promulgate additional forecasts and vaccine recommendations, the Committee was apprised of surveillance data on the sporadic cases of Hong Kong influenza in the United States and localized outbreaks in other parts of the world which have been reported since the last review. Additional laboratory data on characterization of new strains further supported the distinctive change in A2 antigens from that seen in the United States in the winter of 1968. Although clearly an A2 virus, the Hong Kong strain continues to represent an epidemic threat to the essentially entirely susceptible population in the United States.

The Committee reaffirmed its position on using currently available bivalent and polyvalent influenza vaccines until the monovalent Hong Kong vaccine under development becomes available for widespread use.

OTHER BUSINESS AND FUTURE AGENDA

On the final morning of the ACIP meeting, draft recommendations on rubella, mumps (revised), and the comment on the immunobiologics activity of NCDC were reviewed. Editorial changes were suggested, and the Center staff was asked to circulate revised copies of both statements for additional review. It was hoped that the mumps statement could be issued in the relatively near future, following approval by the Committee and the Surgeon General.

The next meeting was scheduled for February 4-6, preceding the scheduled International Conference on Rubella Immunization. At that time, the rubella vaccine recommendation would again be reviewed. Yellow fever vaccine, vaccinia immune globulin, concepts of smallpox vaccination, and Varicella-Zoster immune globulin were also scheduled for consideration.

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

IMMUNOBIOLOGICS ACTIVITY

Introduction

The Immunobiologics Activity (IA) was established in 1965 under the Laboratory Program, National Communicable Disease Center, to act as a national center for the storage and distribution of a number of biological products to population groups engaged in research or occupations involving a high risk of exposure to certain organisms and their toxic products. In most cases, because of the limited demand for these products, licensure, commercial production and distribution have not been established nor can be expected in the predictable future. Included in this group are pentavalent botulinum toxoid, anthrax protective antigen, and tularemia vaccine.

In addition, since there is no other effective therapy for potentially fatal illness which may follow exposure to a number of agents or their toxic by-products, the IA stores and distributes a number of botulinum antitoxins produced under contract with several manufacturing organizations and, in some cases, licensed for distribution. The program has also been extended to include the collection, processing, and distribution of a number of immune globulins prepared from the plasma of immunized individuals or those convalescent from specific infections with a number of the arboviruses. These are distributed for prophylactic use on an emergency basis following accidental exposure to any of the specific agents. To these a licensed preparation of coral snake antivenin has been recently added for which the IA acts as a central repository and distributor.

In assessing a candidate vaccine, the officer in charge of the Immunobiologics Activity has the responsibility to determine the requirements for the vaccine, to evaluate safety and potency by reviewing available biological, chemical, and clinical data, and to develop liaison with organizations that represent potential sources for volume production. Before distribution of the vaccine, a Notice of Claimed Investigational Exemption for a New Drug (IND) is submitted to the Division of Biologics Standards, National Institutes of Health, with pertinent data including a description of the biological, its method of preparation, and results obtained with laboratory animals and human trials, and the biological is subsequently assigned a code number. After the application for the use of the drug for investigational purposes is approved, a system of detailed records is maintained which identifies the biological that is shipped and delivered to investigator physicians, identifying each subject treated and the results of all relevant clinical observations and laboratory examinations. Progress reports of the investigations and significant findings are submitted to the Division of Biologics Standards at yearly intervals. The NCDC has served essentially as the principal investigator for many of these biologicals.

A list of biologicals for which the IA has the responsibility to procure, maintain, and distribute, is given in Table I.

Table I

Biologicals Procured, Maintained, and Distributed by IA, NCDC, with Information about Their Source, IND Application, and Licensure

Reagent	Source	Licensed and/or IND Filed and Approved	Distribution To	Conditions for Distribution	Storage
Botulinum toxoid polyvalent (ABCDE)	Ft. Detrick (Parke-Davis)	IND approved	Investigators	Physician-to-physician basis	4°C
Botulinum horse antitoxin					
AB	Lederle	Licensed	M.D. as req.	Emergency	4°C
E	Connaught	Licensed	M.D. as req.	Emergency	4°C
ABEF (outdated)	Statens Serum Inst. Denmark	-			4°C
ABE	Connaught	Lic. pending			
ABCDEF (on order)	Statens Serum Inst.	-			
Anthrax protective antigen	Ft. Detrick (Merck & Michigan)	IND approved	Investigators	Physician-to-physician basis	4°C
Tularemia, live, attenuated	National Drug	IND approved	-	Physician-to-physician basis	-20°C
Immune Globulin					
Plasma					
EEE	NCDC	-	M.D. as req.	Emergency	-20°C
WEE	NCDC	-	"	"	"
SLE	NCDC	-	"	"	"
California E	NCDC	-	"	"	"
RSSE	MCDC	-	"	"	"
Machupo	NCDC	-	"	"	"
Junin	NCDC	-	"	"	"
VEE	Hyland	-	"	"	"
Gamma globulin	American Red Cross		"	"	
EEE	NCDC	IND approved	"	"	
Coral snake antivenin	Wyeth	Licensed	M.D. as req.	Emergency	4°C in 8 S.E. states; Calif., Ill., Md., Pa., and Texas

Subcommittee Report on Immunobiologics for Unusual Diseases

It is becoming increasingly apparent that there is a major need for a centralized resource to which both public health and practicing physicians can turn for information and guidance on the use of biologics for the prevention and treatment of infectious disease. Such assistance would provide a review of indications, contraindications, dosage schedules, adverse reactions, etc. This resource should concern itself not only with presently licensed but with investigational agents. Furthermore, it should have the capability and competence to generate new data. This resource should deal with the health professions similarly to the Division of Biologics Standards which deals primarily with the biologics industry. The NCDC would seem to be the most logical agency to develop as this resource. Information should be provided to physicians by all appropriate means including direct publications such as the Morbidity and Mortality Weekly Report and Immunization Against Disease and articles in scientific journals like JAMA, Annals of Internal Medicine and AMA Arch. Indust. Medical and Hygiene.

To implement these goals, the Committee recommends:

1) -- That NCDC consider as an additional responsibility becoming a clearinghouse for information or the current status of active and passive immunization against all diseases which, despite their rarity, are dangerous or potentially dangerous, and against which there is inadequate interest from pharmaceutical manufacturers to develop commercially available products.

2) That the value of all currently available commercial biologics products for such diseases be carefully reviewed and evaluated for effectiveness and applicability.

3) That promising products against these diseases now available for investigational use be made available to competent clinical investigators for controlled field use.

4) The active clinical investigation of products be promoted and stimulated by the NCDC. Priorities for currently available materials should be:

    1) Live, attenuated tularemia vaccine, botulinus toxoid, and anthrax vaccine.

    2) Passive immunization with human immune serum globulins against various equine encephalitides, vaccinia, varicella, and rabies.