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DIVISION OF BIOLOGY AND AGRICULTURE

Laboratory and Field Testing of a Foot-and-Mouth Disease Vaccine for Potency, Viability, and Immunity Duration

FINAL REPORT

Contract AID/csd-2273

Advisory Committee on Foot-and-Mouth Disease

September 25, 1970

A.I.D.
Reference Center

BACKGROUND

The problem of foot-and-mouth disease (FMD) has been under surveillance by the Argentine-U.S. Joint Commission on FMD since it was established in 1961 by action of the governments of the two countries. Studies on the persistence of virus in vaccinated animals as it relates to the meat packing industry and a serologic survey of animals on Tierra del Fuego, were completed during 1964. The results of these studies, supported by NAS-AID contract AID/LA-4, involving scientific collaboration between laboratory and field personnel in Buenos Aires, Tierra del Fuego, the Pan American Health Organization Foot-and-Mouth Disease Center (PAHO,FMDC) in Rio de Janeiro and USDA have been published in the National Academy of Sciences (NAS) Publication 1343, 1966.

In 1965, following the expressed wishes of the governments of the United States and Argentina, the National Academy of Sciences Division of Biology and Agriculture proposed an expanded program for the U.S. Advisory Committee on FMD to include subcommittees on meat technology, animal virology, and epidemiology, and to give particular attention to training of Argentine scientists and technicians.

At the third official meeting of The Argentine-United States Joint Commission on Foot and Mouth Disease (FMD) in Buenos Aires, Argentina 30 November-2 December 1966, its Committee on Vaccines and Virology recommended that a project on "Comparative antigenic evaluation of oil-adjuvant and aluminum hydroxide vaccines" be initiated. The project, as outlined, was designed to compare an oil-adjuvant vaccine being developed at Plum Island Animal Disease Laboratory (PIADL) with the Frenkel-type

aluminum hydroxide vaccine in common use in South America. The Committee recommended that cattle be tested in Argentina and that the PAHOFMD Center coordinate with this project its research on immunization of swine and sheep.

The FMD Vaccines Evaluation Project suggested by the Joint Commission has been in effect for over two years, and is concerned with the comparison of vaccines prepared by PIADL with vaccines in use in Argentina and Brazil. Two objectives of these trials are: 1) to develop a vaccine which is more immunogenically effective than the ones now in use, and 2) to increase the period of immunity. Presently it is considered necessary for livestock owners to revaccinate their herds every three to four months. The PIADL vaccine being used in the South America trials gives promise of producing immunity for six months or longer.

Two phases of the project have been active. Phase I has been concerned with cooperative trials started in 1968 and confined to Brazil, under the auspices of PAHOFMD Center in Rio de Janeiro. Phase II, the cooperative field trials in Argentina, was started in 1969. Both phases have been partially supported with funds made available to NAS by AID through contract AID/LA-4 and the subject contract AID/csd-2273, with the cooperation of USDA, PAHO and the Argentine government.

Sufficient funds were not available through AID/LA-4 contract in 1969 to completely support a proposal to expand the cooperative FMD Vaccine Evaluation Trials, so the subject contract AID/csd-2273 was negotiated. Because of complexities of negotiating the research and testing program in Argentina, and because of unforeseen problems, it has become desirable and necessary to continue the program beyond 1970. Since funds for

continuation of the project have now been made available under the AID/LA-4 contract, the subject contract was allowed to terminate on 30 June 1970.

FMD VACCINES EVALUATION STUDIES

Phase I - Brazilian Trials

It was realized early in 1968 that it would be impossible to initiate the planned cooperative FMD vaccine evaluation trials in Argentina for at least one year because of failure of the Argentines to complete their arrangements to furnish cattle and to house them. After discussions with all agencies concerned, it was agreed that a series of trials should be conducted at the PAHOFMDC using swine, sheep and cattle. These trials were made with the concurrence of Argentine AID and the Argentine government on the basis that the information obtained would aid in the planning of the trials in Argentina. Since swine and sheep are not to be used in Argentina, the data obtained with these species will supplement the Argentine information. As stated above, this project, later to be known as Phase I of the Argentina-Brazil trials, was first supported by a cooperative funding by USDA, PAHO and NAS-AID under contracts AID/LA-4. From 1 July 1969 to 30 June 1970 funds from the subject contract AID/csd-2273 have also contributed to its support. An agreement was negotiated between NAS and USDA (No. 12-14-100-9774) for USDA participation on a matching fund basis. PAHOFMD Center has contributed an approximately equivalent amount in terms of manpower, laboratory facilities and animals. Over 600 animals (swine, sheep and cattle) were involved in the initial trials started in May 1968. At least that many more have been used since then.

Two trivalent vaccines, prepared with A, O, and C types of FMD virus of South American origin were used. One of these was the Frenkel aluminum hydroxide saponin adjuvant formalinized type made at the PAHOFMD Center. The other vaccine was an experimental PIADL oil adjuvant type inactivated with acetylethyleneimine (AEI) prepared by PIADL. This vaccine later became known in the Phase II Argentine trials as FMD vaccine No. 3.

A member of PIADL staff went to Rio de Janeiro on 15 May 1968 to aid in the vaccination of the animals and to represent USDA and NAS in the project. Swine and sheep were vaccinated on 17 May, and cattle were vaccinated on 18 May. Blood samples were collected from all animals previous to vaccination, as well as from all control animals. These blood samples were tested for antibodies to insure that all animals were free of evidence of FMD at the time of vaccination.

All of the animals vaccinated in May 1968 were held for 30, 60 or 90 days before being challenged with FMD virus. The summarized results of these tests as well as those of subsequent trials are not included but are available.

Sheep were very well protected by both vaccines. On the basis of the vaccination results obtained, PAHOFMD Center now recommends vaccination of sheep against FMD.

The immunity produced in swine was not as good as anticipated. One group vaccinated with aluminum hydroxide vaccine was not protected against challenge with FMD virus 30 days post-vaccination. Two groups challenged three months after vaccination, one with each type of vaccine, were not protected and developed generalized FMD lesions. Swine revaccinated after 30 days with the same vaccine and challenged 30 days after the second vaccination likewise had poor immunity. The group vaccinated with oil-adjuvant vaccine (PIADL #3) showed some degree of protection.

At challenge, three months after vaccination, 11 of 15 cattle vaccinated with the aluminum hydroxide vaccine developed secondary lesions, while 10 of the 15 cattle vaccinated with the oil-adjuvant vaccine also had secondary lesions.

The studies in Brazil are being continued and are expected to be partially supported by NAS under contract AID/LA-4 and USDA under the NAS-USDA cooperative agreement. Considerable progress with swine has been made in trials subsequent to those reported above but the research is not yet far enough along to permit recommendations for this species.

The Brazilian trials on cattle yielded data which will be valuable to supplement those obtained in Argentina, but as yet do not warrant definite conclusions.

Phase II

At a meeting of representatives of PIADL, NAS, and Argentine veterinarians held at Plum Island, New York, 10-16 July 1968 plans were formulated for conducting field trials in Argentina to evaluate four FMD vaccines. The following persons were present:

Dr. J. M. R. Quevedo, Instituto Nacional de Tecnologia Agropecuaria, (INTA), Argentina
Dr. S. Rivenson, INTA, Argentina
Dr. E. G. Charles, Sanidad Animal Servico de Luchas Sanitarias, (SELSA), Argentina
Dr. J. J. Callis, PIADL, USDA
Dr. J. J. Hyde, PIADL, USDA
Other PIADL staff members
Dr. M. S. Shahan, NAS
Dr. W. R. Hinshaw, NAS

The final plans for the proposed trials designated as Phase II were formulated at a meeting of the Argentina-U.S. Joint Commission on FMD held in Buenos Aires 27 January-1 February 1969. At this meeting, the technical staff of INTA, SELSA, USDA PIADL, and PAHO FMD Center developed the protocols

for the evaluation trials which were finally accepted by the Joint Commission members present.

The participants at the 27 January-1 February meeting were:

USDA

J. J. Callis, Director, PIADL
P. D. McKercher, PIADL
P. Sutmoller, PIADL
E. F. Schultz, Jr., Director, Biometrical Services, USDA

Pan American Foot-and-Mouth Disease Center

M. V. Fernandes, Head, Division of Research

Argentine Technicians

S. Rivenson, Director, Foot-and-Mouth Disease Institute, INTA
E. G. Charles, Central Laboratory, SELSA
A Garcia Pirazzi, Director, Central Laboratory, SELSA
C. M. Caggiano, Central Laboratory, SELSA
Martina Segura de Aramburu, FMD Institute, INTA
Eda Adler, FMD Institute, INTA
Violeta Sonvico, Statistics, INTA
Norma Pizarro de Pereira, Statistics, INTA

Argentine U.S. Joint Commission on FMD

M. Shahan - U.S.
V. Deulofeu - Argentina
C. Brandariz - Argentina
W. R. Hinshaw - U.S.
A. L. Durlach - Argentina

It was agreed that the four products to be tested in preliminary trials would be:

1. Formalinized Frenkel-type virus, incorporated with saponin and aluminum hydroxide.
2. Formalinized Frenkel-type virus, incorporated with INTA oil adjuvant.
3. AEI-inactivated, BHK virus, incorporated with INTA oil adjuvant.
4. AEI-inactivated, BHK virus, incorporated with PIADL oil adjuvant.

The Argentine technicians agreed that a product satisfactory for use in Argentina should protect at least 75% of the vaccinated cattle against normal challenge procedures applied not less than 3 months after vaccination,

in contrast with an expected 10-15% protection after the same interval following vaccination with products currently in use.

If all 4 vaccines pass the prescribed requirements at 30 days post-vaccination, comparable numbers of cattle will be vaccinated with the same products, these animals to be exposed 6 months post-vaccination. The two best vaccines, as measured by the challenge 6 months post-vaccination, will then be considered for study in more detail.

Representatives of the Pan American Foot-and-Mouth Disease Center recommended that the following virus strains, all of South American origin, be used in the tests and have provided samples of each to Plum Island and INTA:

Type A Vallee, Subtype A_{24}, strain Cruzeiro.
Type O Vallee, Subtype O_1, strain Caseros.
Type C Waldwann, Subtype C Rezende.

It was agreed that vaccines 1, 2 and 4 as listed above would be prepared in the laboratories of the INTA, FMD Institute, Buenos Aires, with the cooperation of PAHOFMD Center. The FMD viruses for vaccines 3 (PIADL) and 4 (INTA) were produced and inactivated with AEI at PIADL. They were sent to Buenos Aires for inocuity testing and for adjuvanting.

Cattle for the vaccination trials were purchased by the Argentine Government in the province of Chubut where foot and mouth disease was not known to exist. They were held in quarantine until the date of vaccination and then taken to the Valdez Peninsula Puesto Larralde Experimental Outpost, for vaccination and observation. This "outpost" was built specially for these trials, and was managed under a strict safety program throughout the holding period. Previous to vaccination all animals were tested serologically to determine the absence of FMD antibodies.

According to the protocols, 3 groups of cattle were to have been vaccinated and held 30 days, 60 days and 6 months respectively at the "outpost." At the end of each of these periods, the cattle were to be transported to Buenos Aires for challenge by inoculation of FMD viruses. Actually, only one group of 135 cattle was vaccinated. This group was vaccinated on 27-29 October 1969. On 28-30 November 1969 these animals were transported by truck to Buenos Aires and challenged for the 30 day potency test. Final observation was made on 8 December. Because of the conflicting results observed at the end of 30 days, it was decided to postpone further vaccinations for the 60 day and 180 day immunity tests until serological data were available and until a meeting of the Joint Commission and Technical Staff of INTA, SELSA, PIADL and PAHOFMDC could be called to review and evaluate the 30 day period test results. Such a meeting was called for the week of 2 March 1970 in Buenos Aires.

The attendees at this meeting included all members of the Argentine sections of the Joint Commission, the participating technical staff members of INTA and SELSA, Dr. M. Fernandes, PAHOFMDC, and the following U.S. persons, Drs. J. J. Callis, P. D. McKercher and E. F. Schultz, USDA; and Drs. C. A. Brandly, M. S. Shahan and W. R. Hinshaw, U.S. section of the Joint Commission. The conclusions made after evaluation of the results as determined by challenge at 30 days by statisticians and review by the attendees were:

1. The Frenkel-formalin-aluminum-hydroxide-saponin vaccine (No. 1) exhibited good potency in animals exposed 30 days after vaccination, thus, confirming previous laboratory reports and field experiences.

2. Frenkel-formalinized-oil vaccine (No. 2) was of low potency.

3. The BHK-AEI PIADL (No. 3) and INTA (No. 4) vaccines were of moderate potency against O type virus, and slightly better against C type virus. The potency against A type virus could not be evaluated because, as it was subsequently determined, that the challenge virus contained components of A_{24} and A_{25} virus while some of that used for vaccine production contained only A_{24}.

PERSONNEL TRAINING

Aid in improving the level of the technical knowledge of the professional staff in both the fields of meat technology and animal disease control has been one of the priority missions of the Joint Commission. The U.S. group has cooperated in this training program by aiding the Argentines in locating available candidates in U.S. Universities, and to a minor extent in furnishing funds from the AID/LA-4 contract budget. At least 10 persons have been aided by the U.S. group in getting training of some type in U.S. since 1962. Mr. G. Zuloaga of the INTA staff is an example. He has just returned to Buenos Aires after spending two years at Texas A&M University School of Veterinary Medicine, where he received an M.S. degree in Veterinary Microbiology. Before returning to Buenos Aires he spent three weeks at the Plum Island Animal Disease Laboratory and six days at the Pan American Health Organization FMD Center in Rio de Janiero.

Other examples include:

Dr. S. Rivenson and Dr. J. M. Quevedo of INTA and Dr. E. G. Charles of SELSA in July 1968, spent 10 days at PIADL visiting the laboratories and conferring on the proposed FMD vaccines evaluation project.

Dr. Eda Adler, a chemist employed by INTA, spent three weeks at PIADL in January 1969 learning the techniques of the oil adjuvant vaccine formulation.

Dr. Auge de Mello, a member of the staff at PAHOFMD Center spent a month at PIADL during the spring of 1970 learning the techniques for vaccine formulation.

PIADL staff members have also gained technical training by spending time during the past two years in both Brazil and Argentina as members of the project team. Dr. J. J. Callis, Director of PIADL, has stated that his staff has gained most valuable experience from these associations.

PIADL staff members who have spent more or less time in Brazil and Argentina include the following:

Dr. K. M. Cowan, an Immunochemist, spent two weeks at each of the INTA Laboratories in Buenos Aires and at the PAHOFMC Center in Rio de Janeiro.

While visiting at these laboratories, he demonstrated various immunochemical techniques, especially the agar gel precipitin test.

Dr. D. O. Morgan, spent about 6 weeks at the PAHOFMD Center working with Dr. de Mello and his staff in preparation of experimental vaccines.

Dr. John Graves, Dr. P. D. McKercher, Dr. P. Suttmoller and Dr. H. Cunliff have spent a total of several weeks in Brazil and Argentina as members of the Cooperative Project.

RECOMMENDATIONS

It was anticipated originally that all three groups of animals would be vaccinated and challenged before January 1970.

The Joint Commission finally recommended at the advice of the Technical Staff members present that the planned 60 and 180 day immunity tests with these 4 vaccines be abandoned. One of the reasons for abandonment was the fact that the vaccines which had been prepared for the entire project were reaching the end of their safe "shelf life." The Joint Commission also recommended that the cooperative evaluations should be continued but only after a thorough review and general approval of a modified plan of operation.

In the meantime it was urged that evaluation studies in progress at the PAHOFMD Center be continued. The Argentine representatives expressed a desire to continue the cooperative studies and assured the U.S. delegation that the animal holding facilities on the Valdez Peninsula would continue to be available. Continued support of the program by the Argentine Government has been assured.

It was on the basis of these results reported and the recommendations that the U.S. Argentine AID Mission agreed to make additional funds available to finance under contract NAS-AID/LA-4 the continuation of NAS-USDA support on a matched fund basis. It was because this money became available that NAS decided to allow contract AID/csd-2273 to terminate on 30 June 1970 without requesting additional funds for continued support. Plans for a new series of trials to test the value of FMD vaccines in Argentina are now in the final discussion stages. It is expected that new field trials will be started late in 1970 or early in 1971.

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W. R. Hinshaw/dc