

Pan American Health Organization

PAHO/ACMR 15/10
Original: English

FIFTEENTH MEETING OF THE
ADVISORY COMMITTEE ON MEDICAL RESEARCH

Brasília, D.F., Brazil
14-17 June 1976

REPORT OF THE SCIENTIFIC ADVISORY COMMITTEE
TO THE PAN AMERICAN FOOT-AND-MOUTH DISEASE CENTER

The issue of this document does not constitute formal publication. It should not be reviewed, abstracted, or quoted without the consent of the Pan American Health Organization. The authors alone are responsible for statements expressed in signed papers.

REPORT OF THE SCIENTIFIC ADVISORY COMMITTEE
TO THE PAN AMERICAN FOOT-AND-MOUTH DISEASE CENTER*

The Scientific Advisory Committee (SAC) to the Pan American Foot-and-Mouth Disease Center met November 10-14, 1975 inclusive. Dr. Acha gave the official welcome on behalf of the Director of the Organization, Dr. Hector Acuña Monteverde. Satisfaction was expressed for support given by the Inter-American Development Bank (IDB) to the countries for development of animal health programs.

Investment of the governments to control foot-and-mouth disease has reached a level higher than \$200,000,000. IDB has supported the activities of the Center and member countries in the organization in control efforts for foot-and-mouth disease (FMD). Chile is an example, where progress was made for FMD has not occurred there the previous 18 months.

The SAC recommended that the Evaluation Guide on FMD control programs prepared by a working group of PAHO should be revised. It has been used extensively by Brazil, Chile and Paraguay.

The Committee learned of plans for a regional laboratory in Panama for diagnosis of vesicular diseases. The diagnostic work and studies to be conducted at this laboratory would partially relieve the Center in Rio of some responsibilities and would permit the much needed expansion in vesicular disease surveillance.

Reference was made to the fact that epidemiological patterns of FMD in South America are still not clearly defined. It was suggested all opportunities to collect additional quantitative data be utilized.

*Prepared by Dr. Jerry J. Callis, Director, Plum Island Animal Disease Center, Greenport, New York, U.S.A.

Disease reporting by South American nations provides essential information for the disease security of all nations. A few countries report on the number of cases of FMD by geographic location each week, others every two weeks, and some only every sixteen weeks. The current situation is an improvement over that of the past but greater uniformity of reports and increased frequency of reporting is desirable. Ongoing training programs in epidemiology and diagnostic methods should help toward the goal of increased disease reporting and gathering of epizootiologic information in every nation in the Hemisphere.

In consultation with the IDB, a proposal for determining the physical losses from FMD in milk and beef herds on selected farms in the state of Rio de Janeiro was reviewed. The Committee recommended this study to provide information on losses from FMD which can be interpreted into economic terms.

Several years ago, a pilot study was undertaken in the province of Buenos Aires, Argentina in which FMD vaccine is administered by government personnel over a program in which the administration is left in the hands of farmers. The same vaccine was used in both instances and prevalence of the disease was ten times less in herds in the supervised area. When the result is confirmed in other studies it may suggest need for a fundamental change in control programs in South America.

The PAHO-FMD Center has had interest for many years in oil adjuvanted FMD vaccines. The Committee emphasized the importance of field testing this vaccine as soon as possible, and recommended tests be carried out using vaccine manufactured under strict control of the Center including the potency testing by challenge. A two year study was projected which should give excellent information on the comparative value of oil adjuvanted and aluminum hydroxide vaccines.

The potential value of computer based methods in the research of the Center was reviewed and the Committee recommended that the Center staff continue to assist developments in this area.

The Center staff have been leaders in introduction of cell culture techniques into the continent. There were lengthy discussions of this subject at the meeting. The Committee reviewed a number of specific recommendations with the staff relative to continuing to examine cell lines for propagation of FMD virus and use of anchored cells for production of FMD virus which is then used for vaccine production purposes.

The Committee learned of the ambitious program which the Center has undertaken to develop improved methods for evaluating the serological relationship of FMD virus strains within a single type, as well as to determine the degree of cross protection afforded by the individual strains against others within the same immunologic type. In view of the expected benefits, the project should be continued and extended to include information on a bank of sera against all subtypes existing among the three immunologic types of FMD virus in the Hemisphere.

Studies at the Center on modified live virus vaccine should be continued as an integral part of the Center's research.

The group discussed in length that approximately 300 million doses of FMD vaccine are being used each year in South America and considered this quantity may increase in the next few years; therefore the Center should continue to take the necessary leadership on vaccine innocuity and potency evaluation and methodology. This work should include information on minimal requirements for FMD vaccines.

The Committee heard plans for investigation of the role of milk and milk products in the spread of FMD virus. The work projected was reviewed and is considered a worthy project.

Since the last SAC meeting, two years ago, the training activities have increased tremendously. These activities are a fundamental service to the member countries and should be maintained and expanded if possible. The Center was encouraged to work with other branches of PAHO in expanding opportunities for postgraduate study. The SAC heard of the Center's plans for support of field programs in expanding mass communications, and recommended developing materials and techniques for mass communication including such things as media for radio, film, posters and circulars.

The Committee learned that during 1976, the PAHO-FMD laboratory in Rio will celebrate its 25th anniversary. This occasion should be celebrated by organizing a symposium dealing with several general areas or disciplines, and in addition the Center should elaborate on its accomplishments toward FMD control in South America.

The PAHO-FMD Center, as all parts of PAHO, has responsibility for furthering the broad goals of the organization in ways that do not jeopardize the original objectives of the Center. The SAC believes this could be done and recommend expansion as much as possible in the use of the available PAHO services and programs in epidemiological surveillance, viral diagnosis, laboratory services, computer services, training and scientific publications.



PAN AMERICAN HEALTH ORGANIZATION



WORLD HEALTH ORGANIZATION

IX INTER-AMERICAN MEETING, AT THE MINISTERIAL LEVEL, ON FOOT-AND-MOUTH DISEASE AND ZOOZOSES CONTROL

CARACAS, VENEZUELA, 5-8 APRIL 1976

Provisional Agenda Item 7

RICAZ9/4 (Eng.)
4 March 1976
ORIGINAL: ENGLISH

RESEARCH PROGRAM OF THE PAN AMERICAN FOOT-AND-MOUTH DISEASE CENTER

PAHO SCIENTIFIC ADVISORY COMMITTEE FOR THE
PAN AMERICAN FOOT-AND-MOUTH DISEASE CENTER

Report to the Director

1975

PAHO SCIENTIFIC ADVISORY COMMITTEE
FOR THE PAN AMERICAN FOOT-AND-MOUTH DISEASE CENTER

REPORT TO THE DIRECTOR

1975

PAHO SCIENTIFIC ADVISORY COMMITTEE FOR THE
PAN AMERICAN FOOT-AND-MOUTH DISEASE CENTER

November 9-15, 1975

Dr. Otto Bier, Director*
Instituto Butantan
Caixa Postal 65
05504 São Paulo, SP, Brazil

Dr. Giuseppe Mario Boldrini
Secretary
European Commission for the Control
of Foot-and-Mouth Disease - FAO
Via delle Terme di Caracalla
Rome, Italy

Dr. J. B. Brooksby, Director
The Animal Virus Research Institute
Pirbright, Woking
Surrey, England

Dr. Jerry J. Callis, Director
(Chairman)
Plum Island Animal Disease Center
U.S.D.A.
Agricultural Research Service
Greenport, Long Island
New York 11944, USA

Dr. Harry Eagle
University Professor
Director, Cancer Research Center
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, N.Y. 10461, USA

Dr. Emilio Gimeno
Facultad de Ciencias Veterinarias
Universidad Nacional de La Plata
Calle 60 y 119
La Plata, Argentina

Dr. Robert Hanson (Rapporteur)
Department Veterinary Science
University of Wisconsin
1655 Linden Drive
Madison, Wisconsin 53706, USA

Dr. Hilary Koprowski, Director
The Wistar Institute
Thirty-sixth Street at Spruce
Philadelphia, Pa. 19104, USA

Dr. Stewart H. Madin*
Biomedical Laboratory Science Division
School of Public Health
Earl Warren Hall
University of California
Berkeley, California 94720, USA

Prof. Dr. Anton Mayr, Direktor*
Institut für Mikrobiologie und
Infektionskrankheiten der Tiere
8 München 22, Veterinärstrasse 13
München, Germany

Dr. Roger Morris
Veterinary Epidemiology and
Preventive Medicine Unit
University of Melbourne
Veterinary Clinical Centre
Werribee, Victoria 3030
Australia

Dr. William M. Moulton
Chief International Operations
Veterinary Services
U.S. Department of Agriculture
Hyattsville, Maryland 20782, USA

Dr. Carlos A. Palacios, Director*
Centro Nacional de Investigaciones
Agropecuarias
El Limón, Maracay, Aragua
Venezuela

Dr. Calvin W. Schwabe
Department of Epidemiology and
Preventive Medicine
School of Veterinary Medicine
University of California
Davis, California 95616, USA

Dr. J.G. van Bekkum, Director
Central Veterinary Institute
Virology Department
39 Houtribweg
Lelystad, Holland

*Could not attend the meeting

SECRETARIAT

Dr. Pedro N. Acha, Chief
Division of Disease Control
Pan American Health Organization
525 Twenty-third Street, N.W.
Washington, D.C. 20037, USA

Dr. James O. Bond
Department of Communicable Diseases
Pan American Health Organization
525 Twenty-third Street, N.W.
Washington, D.C. 20037, USA

Dr. Louis Greenberg
Health Laboratory Services
Division of Disease Control
Pan American Health Organization
525 Twenty-third Street, N.W.
Washington, D.C. 20037, USA

Dr. Luis V. Meléndez
Department of Human and
Animal Health
Pan American Health Organization
525 Twenty-third Street, N.W.
Washington, D.C. 20037, USA

Dr. Ramón Rodríguez, Director
Pan American Zoonoses Center, PAHO
Casilla de Correo No. 3092
Ramos Mejía, Buenos Aires
Argentina

Dr. Juan A. Zapatel
Zone V Veterinary Advisor
Repartição Sanitária Pan-Americana
Caixa Postal 04-0229
70.000 Brasília, DF, Brazil

FINAL REPORT

The Scientific Advisory Committee (SAC) met during the period of November 10 to 14 inclusive. All Committee members were present with the exception of Drs. O. Bier, S. H. Madin, A. Mayr, and C. A. Palacios.

The S.A.C. had this year four new members: Drs. G. M. Boldrini, H. Eagle, R.P. Hanson, and R. Morris.

Dr. Jerry J. Callis was elected Chairman of the meeting and Dr. R. P. Hanson, the Rapporteur.

Dr. Pedro N. Acha, Chief of the Division of Disease Control of the Pan American Health Organization, gave the welcome to the members of the S.A.C.

Dr. C. Schwabe congratulated Dr. Acha on behalf of the members of the S.A.C. for his new appointment as Chief of the Division of Disease Control recently established by the Organization.

Mr. Reinhart Helmke gave his greetings to the S.A.C. members on behalf of the United Nations Development Program Representative, Dr. L. M. Ramírez-Boettner. He indicated that it was most important for the adequate development of the activities of the Pan American Foot-and-Mouth Disease Center to have them reviewed biennially by such a distinguished group of internationally known scientists whose scientific capability is without question.

Mr. Helmke indicated that the UNDP is highly interested in a continued support of the activities of the Pan American Foot-and-Mouth Disease Center.

Dr. Acha gave the official welcome to the members of the S.A.C. on behalf of the Director of the Organization, Dr. Héctor Acuña Monteverde. He indicated that the recommendations of the S.A.C. to the Director of the Organization are highly beneficial and well recognized by the Member Governments of the Organization. He indicated that in spite of the shortage in funds and human resources the Center has continued giving assistance to the countries in the establishment and/or development of their programs for the control and prevention of foot-and-mouth disease. Dr. Acha informed the members of the S.A.C. that the Director of the Organization is very much satisfied with the support given to the countries, for the development of their animal health programs, by the Inter-American Development Bank. The investment of the Governments to control foot-and-mouth disease has reached a level higher than \$200,000,000. The activities of the Center and the support given to the countries and the Organization by the IDB has helped very much in the control of foot-and-mouth disease in Chile. This country has been now free of an outbreak of foot-and-mouth disease for the last 14 months. Chile has now an area free of the disease for a period longer than

four years. Dr. Acha also informed the Committee that the activities of the Center have been seriously hampered because flexibility of available funds were restricted by the new increase in the salary scale imposed at the international level by the United Nations.

Dr. Acha acknowledged with thanks on behalf of the Director of the Pan American Health Organization the continued support given to the activities of the Center by the UNDP, and indicated that this financial support is going to be increased in the near future.

Dr. Mário V. Fernandes presented to the members of the S.A.C. a summarized review of the activities of the Center during the last two years.

He indicated that the assistance given to the countries during this period has not been without serious difficulties. These have originated from the constant inflation and the increase in the salaries and expenditures during this period. The latter condition is an obvious result of the former one. These difficulties have been partially overcome by voluntary contributions provided particularly by the Governments of Brazil and Venezuela. He expressed his recognition to both countries for their collaboration. He especially emphasized the support given to the Center by the Government of Brazil which has allowed the purchasing of supplies for transportation and animal feeding.

Dr. Fernandes also thanked the members of his staff for the support given to the Center activities that are now suffering difficult budgetary restrictions.

He also expressed his thanks to the United States Air Force for the excellent assistance provided through Dr. P. W. Schilling in the development and improvement of the laboratory animal management and facilities.

Dr. Fernandes indicated that one of the positive actions of establishing national programs for the control and prevention of foot-and-mouth disease is the development of an infrastructure which can be utilized for the development of other animal disease control programs like those involving tuberculosis, brucellosis, hydatidosis, etc. Such a case is being observed in Brazil where a National Program of Animal Health (PRONASA) will replace the former national program for foot-and-mouth disease control.

Dr. Fernandes also indicated that the Center will reach its 25th year of existence during 1976, and he would like to request from the members of the S.A.C. whether they would consider a special scientific meeting on foot-and-mouth disease a proper celebration of this date.

Two seminars were presented during the meeting of the S.A.C. One was conducted by Dr. J. J. Callis and the other by Dr. R. J. Morris.

The Committee divided into two groups on the second day: one to consider the laboratory and research activities and the other to deal with the field and training activities of the Center.

The discussions and deliberations during the next three days resulted in the following conclusions and recommendations:

I. FIELD ACTIVITIES

A. Continuing Program

1. Guidelines

The Evaluation Guide of Foot-and-Mouth Disease Control Programs recommended in the last report was prepared by a working group in February 1974 and published by PAHO. It has been used during the past year by three nations: Brazil, Chile, and Paraguay. The Guide was found to be very useful in identifying inadequacies in information needed for thorough evaluation and in establishing deficiencies in programs. On the bases of the experienced gained, it is recommended that the program evaluation process be carried out continuously by the national program staff so that documents will be available for grantor review. It is also important that the criteria used for evaluation be greatly simplified. Therefore, it is recommended that the Center staff, with the assistance of a few consultants, revise the Guide within the next two years.

2. Pilot Programs

Four programs, each having as its purpose the comparison of two systems of vaccine distribution and administration, are under way in Argentina, Bolivia, Brazil and Paraguay. The results, already available, appear to have significance for countries planning control programs. It is recommended that the Center assemble and evaluate data from these studies and make the results more generally available.

3. Epizootiological Studies

At the recommendation of the Central American nations, a proposal has been submitted for the funding of a regional laboratory to be located in Panama and operated by the Center which would be charged with assisting in the diagnosis of vesicular diseases and conducting epizootiologic studies. Every effort should be made to see that this new laboratory operates within the existing mutual assistance agreements between the Central American nations and the

United States of America. The studies that would be conducted at this laboratory on vesicular stomatitis and other diseases enzootic to the area would partially relieve the Center at Rio of some responsibilities and would permit a much needed expansion in vesicular disease research.

The Committee notes that the epidemiological patterns of FMD in South America are still far from being clearly defined. It recognizes that such studies require access to resources on too large a scale for detailed investigations to be undertaken in the near future. However, the Committee suggests that all opportunities to collect additional quantitative data at low cost be utilized and epidemiological studies be initiated when vaccination programs have been undertaken for a sufficient period for the epidemiological pattern under such circumstances to have stabilized. Where possible, such studies should be developed as an integral part of multipurpose field studies, subject to the proviso that the workload of such studies does not become excessive due to the inclusion of the additional investigations.

4. Disease-Reporting

Disease-Reporting by South American nations provides information essential for the disease security of all nations, and reporting of disease becomes increasingly important as control programs become more successful. A few nations report information on the number of cases of FMD and geographical location of these cases each week. Other nations report every two weeks, and some only every 16 weeks. The current situation is an improvement over that of the past, but greater uniformity of reports and increased frequency of reporting is desirable. Several nations have initiated a program of exchanging information weekly or sometimes daily about outbreaks on their mutual borders. This practice is to be highly recommended.

Disease-reporting and gathering of epizootiologic information could be improved in every nation in this Hemisphere, but the need is clearly greater in some nations. Ongoing training programs in epidemiology and diagnostic methods should help toward this goal. The Center, in cooperation with CEPANZO, should give consideration to providing advice on ways of developing an adequate infrastructure for disease-reporting and a uniform system of reporting.

5. Physical Losses

The Center, in consultation with the IDB, has prepared a proposal for funding that would measure the physical losses from foot-and-mouth disease in milk and beef herds on selected farms in the State of Rio de Janeiro. This proposal is now under consideration. The intention is that records of herds suffering outbreaks of FMD and paired herds having similar characteristics other than

the presence of FMD would be compared over a period of one year. Details of the experimental design are being completed. This study should provide long-needed base line information on losses from FMD that can be interpreted in economic terms. The essential nature of economic information in the justification of national disease control programs should be recognized by everyone. However, this is a preliminary study, and planning should be initiated for studies designed to measure important parameters beyond the scope of the present investigation.

6. Pilot Study Conducted in Argentina (Henderson)

The study conducted in the province of Buenos Aires, Argentina, with the collaboration of the Center, has already amassed evidence from three years of observation that indicated a clear superiority of a program in which the vaccine is administered by government personnel over a program in which the administration of vaccine is left in the hands of farmers. The same vaccine was used in both instances, and the prevalence was 10 times less in herds in the supervised area. If the result is confirmed in the other studies, it suggests the need for a fundamental change in control programs in South America.

7. Oil Vaccine

The Committee emphasized the importance of field-testing of the oil adjuvant vaccine as soon as possible. These tests should be carried out in two phases, using vaccine manufactured under strict control of the Center, including the potency testing by challenge.

In Phase 1, an evaluation of vaccine safety in the Center's test population in Bage, Rio Grande do Sul, cattle will be immunized by Center staff during one year period, and all untoward reactions carefully monitored. At the end of this period, rates of occurrence of untoward reactions will be calculated by appropriate categories.

Six months after initiation of Phase 1, an evaluation of the field efficacy of this vaccine will be initiated in two other counties of Rio de Janeiro State (Population I, A & B). These counties are now serving the Center as a field investigation area. Phase 2 of field testing, as outlined below, will be repeated in three other countries, so that overall evaluation of the field efficacy of the oil vaccine may be appraised under a range of ecological and husbandry conditions and a range of systems for delivery of vaccine.

Phase 2 is essentially an in-herd study of the level of "herd immunity" realized under field conditions. It will be carried out on herds subject to FMD attack during the one-year test period.

Herd immunity is an epidemiological measure of the proportion of a population unit resistance to natural challenge and, in this instance, is an appropriate proxy for field efficacy of vaccine. Herd immunity represents the product of: (1) the potential efficacy of the vaccine determined under strictly controlled laboratory circumstances, expressed as percent protection; times (2) the percentage of animals initially in the herd which are actually vaccinated (corrected for numbers of unvaccinated animals introduced during the observation period); times (3) percent of immunologically competent animals; times (4) percent of vaccine doses maintained in optimal condition; times (5) percent of vaccine doses administered properly, etc. In this type of study of attacked herds, herd immunity is measured by the secondary attack rate (clinical cases) and the secondary infection rate.

Oil vaccine prepared under Center control will be administered to cattle in population II A and comparable aluminum hydroxide vaccine to cattle in population II B. Administration of both vaccines will be according to the delivery system currently employed throughout Brazil. All outbreaks will be carefully monitored and subjected to intensive epidemiological investigation. In addition to determination of and comparisons between the secondary occurrence rates in outbreak herds in populations II A & B, appropriate sampling procedures will assess humoral antibody response in the two vaccinated populations, and rates of untoward vaccine reactions will be calculated for both populations. Because of the low incidence of herd attacks expected, such prospective trials are unlikely to yield a sufficient quantity of data to compare herd or animal attack rates under these two vaccination regimens.

In addition to the above stated objectives of Phases 1 and 2, these populations will serve at the same time as sources of data for appropriate studies on the epidemiology of FMD and on its economic impact. The Committee emphasizes the importance of this "peripheral fallout" from these tests; for example, under the various vaccination regimens of Phases 1 and 2, comparisons using multivariate analytic methods such as multiple regressive discriminant analysis and factor analysis could be made between herds in which outbreaks occurred and those in which outbreaks did not. The objective of such studies is the tentative identification of measurable factors of husbandry, herd characteristics, health management and the like, which tend to increase or decrease risk of FMD occurrence.

In addition, data contributed during the test period could be used too as part of elementary time series studies (i.e., calculation of "typical seasonals" based upon moving averages of different periodicities) to begin to identify any seasonal, cyclic and secular trends of occurrences of FMD. A number of other valuable analytical possibilities would occur to Center epidemiological staff.

The Committee also recommends that an effort be made to challenge some of the animals with virus. These animals should be randomly selected from a group recently vaccinated and from another group which had been vaccinated at least six months previously.

8. Provision of Computer Facilities for Disease Modelling and Monitoring

The potential value of computer-based methods in the research of the Institute is recognized. In particular, the application of statistical and mathematical skills of Center staff to the development of improved understanding of the quantitative epidemiology of FMD is supported.

With the aim of assisting development in this area, it is recommended that access to computer services on the site be sought by the Center, provided that the cost of such services is not excessive in relation to the severe limitations on the financial resources of the Center.

II. LABORATORY ACTIVITIES

A. Techniques of Cell Culture

1. Cell Strains Used for Preparation of Vaccine in Suspension Culture

a) Only two strains had been studied at the Center before the BHK-21 cells were selected for vaccine production. It was the general consensus that additional cell lines should be tested by the Center in the hope that vaccines of higher quality might be produced without some of the problems which attend the use of BHK cells.

Among the cells that may be tested are the following:

- i) A hog cholera free kidney clone (MPVK⁷) developed at Plum Island Animal Disease Center if (as seems likely) it can be adapted to growth in suspension.
- ii) BHK-S, a BHK subline which can be grown without serum (PIADC).
- iii) A cow brain cell line developed at Wistar Institute which may be adapted to growth in suspension.
- iv) A hog cholera free line of pig kidney which can be grown in suspension. (Biological Institute in São Paulo).

b) As they become available, these cell lines should be tested for the production of immunizing virus. For the present, however, it was the consensus that the Center should not be charged with the responsibility of developing new cell lines, but should test the susceptibility of lines developed in South America which cannot be exported.

2. A Fresh Approach to the Use of Anchored (Monolayer, Multi-layer) Cultures for Vaccine Production

a) Reasons for Reexamination of the Monolayer System

A number of considerations suggest that the growth of cells for vaccine production in suspension culture should not be considered a closed issue, but that the possible use of monolayer cultures should be reconsidered.

i) There may be unpredictable and uncontrollable changes in the properties of the virus produced in suspension.

ii) A number of laboratories in Europe are finding that, particle for particle, vaccines produced in monolayer may be more immunogenic than those produced in suspension. The details of those findings and procedures upon which they are based should be requested by the Center staff, since their own preliminary studies do not show such differences.

iii) New techniques have been developed for monolayer culture which make that technique at least competitive with suspension cultures in terms of the time, effort, and cost required to produce a given number of cells.

- A new multichannel apparatus has been developed under the joint auspices of the Mexican Government and the Pan American Health Organization which enormously increases the cellular yield. That apparatus is already being used in Mexico for production of polio virus, and can be made available to the Center by PAHO for exploratory studies.

- The "Microcarrier" technique was developed some five years ago, and is currently being used by the Massachusetts Institute of Technology in its cell production program. This technique involves the use of suspensions of minute spheres to which the cellular inoculum adheres and which the cells cover as they multiply. In effect, this is a monolayer culture on substrates in suspension.

- A perfusion cylinder¹ and a monolayer system² have been developed which similarly permit a greater yield in time labor and costs.

III. RECOMMENDATIONS

1. Representative(s) of the Center should go to Mexico and to the MIT laboratories to familiarize themselves with the operation of the mass monolayer culture systems being used in those laboratories prior to the procurement of the machines for exploratory use in the Center.
2. A number of candidate cell lines growing in monolayer should be examined for viral susceptibility and propagation, and for the quality of the viral antigens produced. Although much of that work could be done in other laboratories, preliminary studies could be done at the Center with a number of cell lines selected by the staff or suggested by outside consultants.
3. Candidate cell lines which appear promising should then be adapted to growth in mass monolayer culture, preliminary to the production of pilot lots of vaccine.
4. If the thesis is validated that monolayer cultures produce virus which is more immunogenic than that produced in suspension, experiments should be undertaken to determine the basis of that difference.
5. The presence of mycoplasma contaminants adversely affects the quantity and quality of monolayer and suspension culture of cells and on the virus produced therein. The Committee again recommends the Center give attention to testing for mycoplasma in its teaching program on tissue culture and in the culture produced at the Center for assay on virus production purposes.

IV. SELECTION OF VIRUS STRAINS FOR VACCINE PRODUCTION

The Center has undertaken an ambitious program with a view to develop improved methods for evaluating the serological relationship of FMDV strains within a single type and as well to determine the degree of cross protection afforded by the individual strains against others within the same type.

¹Amicon

²Connaught Laboratories

Using C.F.' tests and 9 types C strains of different origins it has already been established that there is considerable serological crossing between these strains.

To ascertain the spectrum or protection afforded by the individual strains, groups of 12 cattle are being inoculated with single strain vaccines; the cattle are being bled at intervals of 30, 60, and 90 days, and the mouse protection index is being established for the homologous and heterologous strains- thereby allowing for selection of strains for vaccine production with the broadest spectrum.

Further, adequate supplies of the above sera will be collected and kept in the frozen state. These sera are being kept as a bank for MPI testing against newly isolated strains in epidemics. The results can be used as an indicator of the value of existing vaccines for a specific outbreak. Since the results can be available within a few weeks of receipt of the causal FMD strain, this procedure represents a very practical approach for selecting the virus that can be expected to give the best results when incorporated in vaccines to be used in a given epizootic.

To date, 5 group C strains have been catalogued as noted above, and present plans at the Center are to include all other FMD strains which have possible vaccine value.

This project involves much work; however, in view of the expected benefits, it is the opinion of the Committee that this project should be continued and extended to include the formation of a bank of sera against the A and O types as well.

V. STUDIES ON MODIFIED LIVE VIRUS

The Committee noted with great interest results of experiments on intranasal immunization of cattle with A₂₄ attenuated virus and their resistance to challenge with virulent homologous virus.

The Committee recommends that the investigations on modified live virus vaccines be continued as an integral part of the research program of the Center.

The following plan of studies is recommended:

- a) The experiments should be undertaken in cattle immunized and challenged by intranasal route only.
- b) In addition to A₂₄ strain, attenuated O and C viruses should be used for vaccination of animals; these should be followed for the duration of their carrier state and for resistance to challenge with virulent homologous virus.

- c) Viruses should be isolated from the nasopharynx of the vaccinated animals at the latest stage of their OP positive period.
- d) Although the Committee recommends that nasopharyngeal secretions and sera of the vaccinated animals should be checked for antiviral antibodies, it recognizes that difficulties may be encountered in determining presence of such antibody until radioimmune assays for FMDV become available at the Center.
- e) Attenuated live virus could be used for intranasal instillation into cattle during an FMD outbreak in an effort to terminate the epizootic. However, conduct of the experiment poses several problems that should be carefully examined before its initiation.
- f) Studies of modified live virus as a method of prophylactic vaccination of cattle should be continued. These investigations should emphasize duration of immunity following intranasal vaccination, resistance of vaccinated animals to homologous and heterologous challenge, and the role of local versus systemic immunity in protecting the animals against virulent virus.

VI. OIL VACCINES

The Committee acknowledged the important progress made in the development of an oil emulsion vaccine destined for the protection of cattle.

However, it felt that further information regarding the innocuity and potency of vaccines of this type should be obtained before the Center can take responsibility for the recommendation to use them in the field.

It was also considered necessary to collect further data on the innocuity of emulsion type vaccines prepared with virus produced in BHK suspension cultures because much of the virus incorporated in the vaccines now in use in Latin America is grown in BHK-cells in suspension cultures and such antigens administered in the form of Al gel vaccines have caused allergic reactions in repeatedly vaccinated cattle in other parts of the world.

The Committee recommended that workers at the Center make themselves familiar with methods for the evaluation of antigenic mass in virus preparations destined for vaccine production that are now becoming established in European production laboratories. The necessary equipment should be procured.

The Committee noted with interest the efforts made within the Center to concentrate its research efforts in certain areas of great practical importance for Latin America. It strongly supports this policy.

The Committee considers it important that the Center direct attention to methods for assay of large numbers of sera for antibody using all available tests such as metabolic inhibition and microtiter. In this connection, consideration might be given to collaborating with other institutions where the sophisticated equipment required for conduct of some of the tests, such as radio-immune assay, is available. Cooperation of this type would allow the Center to evaluate these tests for the purposes of the Center.

VII. VACCINE INNOCUITY AND POTENCY TESTING

Approximately 300 million doses of FMD vaccine are being used each year in South America, and this quantity may increase in the next few years. For this reason the Committee continues to recommend that the Center provide the necessary leadership on vaccine innocuity and potency evaluation methodology. The Committee reiterates comments on this subject which was included in the two previous reports. It is recognized that it is difficult, if not impossible, to obtain appropriate numbers of cattle for evaluation of every batch of vaccine. This makes even more urgent the introduction of the technology for evaluation of the antigenic mass of vaccine. Similarly, the new technology recently developed in Europe, and mentioned elsewhere in the report, of innocuity-testing of vaccines in tissue cultures should be included in the recommendations of the Center to the countries where FMD vaccine is used. The Committee also still considers it advisable for the Center to develop minimal requirements for FMD vaccines.

VIII. FOOT-AND-MOUTH DISEASE VIRUS IN MILK AND MILK PRODUCTS

The Center's plans for the investigations of the role milk or milk products could play in the dissemination of FMD-virus were discussed.

They were outlined as follows:

1. Determination of the amount of virus arriving at the industrial processing plants in endemic areas.
2. Survival of FMD virus during the processing of milk products under industrial conditions.

3. If the final products are found to be infectious, estimation of the risk of introducing FMD into free areas by such products.

As to objective 1, it was felt that there are three stages for which infectivity levels should be determined:

- a) Output from infected farms;
- b) Amount of virus arriving at dairy cooperatives;
- c) Amount of virus arriving at processing plants.

At the farm level, one or more infected herds must be located. From these herds, a composite milk sample will be taken every three days. Daily milk sample will be taken from approximately five cows at risk until two weeks after appearance of clinical signs of the disease.

At the cooperative and processing plant levels, weekly samples will be collected from all suppliers regardless of whether or not they have reported clinical disease.

Samples for the isolation of infectious FMD virus should be taken at the normal sampling points in the production process so as not to interfere with the regular operations of the plant. At these points, samples are routinely obtained in order to determine pH, bacterial content, dry matter, etc.

If final products are still found to contain infectious foot-and-mouth disease virus, further experimentation of these products will involve exposure of susceptible animals to these products. The results of these studies will be evaluated in terms of the final use of the product and the possibilities of altering production conditions so as to guarantee the safety of the product.

The following supportive investigations are planned:

1. Kinetics of FMD virus inactivation under the conditions at which milk arrives at the processing plant (pH 6.3-6.6 at 10° C). This investigation will be done to determine what happens to the virus under the conditions occurring during the transportation of the raw milk from the cooperative to the processing plant. Results will also serve to determine the choice of strains to be used in further experiments, such as those now under way in Argentina on casein production.

2. The role of antibodies in milk with regard to reduction of levels of infectivity.

3. Determination of most suitable methods for the detection of minimal amounts of foot-and-mouth disease virus in milk or milk products.

In the discussion it was pointed out that nonantibody neutralizing activity has been detected in human milk against polio virus and in cow milk against VSV. Such activity directed against FMD-virus has so far not been found in milk from FMD-susceptible Irish cows.

It became apparent that all milk batches used in the study will routinely be pH-tested.

It was suggested that the herds in which outbreaks were diagnosed be sampled for serological testing, but this was considered to be difficult to carry out under field conditions in most instances. Serum samples will be collected at the end of the outbreak for testing against VIA-antigen and other antigens.

The importance of developing sensitive methods for the detection of small quantities of virus in milk was stressed, as it was considered likely that the concentrations of virus in commercial milk would, as a rule, be very low due to dilution and other factors.

This is a worthy project which will require a great deal of effort on the part of the staff. The scheduling of this project should be based upon demand for its initiation, availability of support, and the requirements of other projects, several of which are of high priority.

IX. TRAINING

The Committee is impressed by the training activities that have been carried out since the last meeting. These training activities are a fundamental service provided to the countries. The completion of the new training building will contribute greatly to the development of educational programs.

The Committee recommends that training activities be maintained and expanded, if possible, in courses, seminars, and individual training in the field of tissue culture, vaccine production and related techniques, diagnostic procedures, epidemiology, field exercises, statistics, laboratory animal medicine, and mass communications. It also recommends that the interaction and coordination of the Center with other PAHO programs be increased and more exchange of assistance be encouraged.

In keeping with the greater efforts over the next few years in the training of large numbers of national FMD program staffs, the Committee also recommends a continuance and strengthening of the relationship with universities and other institutions, in order to organize with them the delegation of responsibility of some of the training activities, under the supervision and coordination of the Center.

The Committee learned that scheduling of training requires a heavier commitment of time from the technical staff which, at times, necessitate restrictions of the investigative and research function and seriously delays the preparation of research reports. It is suggested that the Center study ways of relieving this situation.

Centers of excellence in special areas of science and technology in South America that relate to disease control should be identified, and an effort should be made to develop training programs that utilize these centers in fulfilling the objectives of both human and animals disease control efforts. The Center should be encouraged to work with other branches of PAHO in expanding opportunities for postgraduate study in South America.

X. COMMUNICATIONS

The recognition by the Center of special need in the area of mass communication for support of field programs by the appointment of a communication specialist is commended. The Center is urged to expand this effort to assist nations in developing both materials and techniques for mass communication. The materials should include message as well as format and the techniques should include such media as radio, film, poster and circulars. This could be accomplished by training courses, special scholarships, and special commissioning of materials. International organizations and national institutes that have special expertise should be invited to contribute services of consultants.

The Committee supports the efforts directed toward making available library service and the publication of technical materials which are used throughout the Continent, in the form of the Bulletin, the Epidemiological Report, the scientific monographs, and the technical services. The improvement of publication activities should be given priority at the Center and accomplished by seeking support from the countries and also from international institutions.

The request of the Center for a communication specialist in scientific literature who would enable the Center to make full use of worldwide computer network through a terminal at São Paulo is supported. This would aid the Center in providing all nations with a more complete and a more rapid access to world literature.

Publication of Results of Laboratory and Field Research

The Committee understands that the relative infrequency of publication by Center staff of findings from laboratory and field studies results from the multiple pressures of training programs, consultations and other necessary ongoing activities in addition to research programs per se. We know that many valuable results, including epidemiological studies, now exist in the Center which demand completion and publication without undue delay in referred international journals or, as appropriate, in the Center's Bulletin. The director and members of the staff have indicated their full appreciation of this problem and present lack of time necessary for such activities.

The Committee wishes merely to reinforce this recognized need in connection with conduct of scientific research generally, and feels that staff activities connected with bringing study goals to periodic fruition in suitably published forms requires some priority consideration. We would emphasize the particular dearth of useful epidemiological literature on foot-and-mouth disease and this Center's special role in developing this type of information.

XI. TWENTY-FIFTH ANNIVERSARY OF THE CENTER

The Committee recognizes the importance of the 25th Anniversary of the Center and recommends that PAHO and the Center celebrate this occasion by organizing a symposium dealing with general areas of biological research such as immunology, virology, molecular biology, and epidemiology.

The accomplishments of the Center on FMD control in South America should also be elaborated at this meeting. A special budget should be provided for this symposium at an early date to allow for orderly planning.

XII. COORDINATION OF THE ACTIVITIES OF THE CENTER WITH OTHER DIVISIONS OF PAHO

The Center, as part of PAHO, has a responsibility for furthering the broad goals of the Organization in ways that do not jeopardize its original objectives. Initiation of activities that are not in conflict with these objectives appears to be reasonable.

The Center appears to be able to provide training in animal medicine that would support other animal and human health programs. On the other hand, current commitments to national FMD programs do not appear to permit training of additional individuals in virology or epidemiology during the next two years. Expansion of such training programs would require additional facilities and staff. Transshipment of cell cultures and other biologicals by Center support

staff, as currently provided, can be continued indefinitely. However, the establishment of the Center as a reference and storage center for cells or reagents should be examined very carefully as it has undesirable as well as desirable features. At the very minimum, it would require the erection of a maximum security facility at the Center to meet standards expected of international health organizations.

The Center should expand as much as possible the use of the available PAHO services and programs in epidemiological surveillance, viral diagnosis, biological center, international laboratory services, computer services, fellowship training, and scientific publications, in order to strengthen or supplement the Center's program and primary objectives.