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REPORT OF WHO CONSULTATION ON RABIES
(EUROPEAN BAT RABIES, POSTEXPOSURE TREATMENT AND POTENCY TESTING
FOR RABIES VACCINES)

Essen, FRG, 8 July 1988

1. INTRODUCTION

Since the meeting of the 7th WHO Expert Committee on Rabies in 1983¹ new developments in rabies research and control have called for a series of consultations and international meetings to formulate recommendations for national services and for WHO. Whereas Annex 1 of this report describes major international meetings and consultations on rabies surveillance and control in carnivores, this report deals predominantly with three subjects: postexposure treatment, potency testing for human and veterinary rabies vaccines, and European bat rabies.

The reporting during the last three years of a number of well-documented cases of rabies occurring in persons treated with modern cell culture vaccine called for a critical analysis of these cases and review of the present WHO recommendations regarding the various aspects of rabies postexposure treatment. Suggestions for the further improvement of postexposure treatment are given in the first part of this report. Another important issue concerned the significance of the NIH test and its possible replacement by *in vitro* antigenicity tests for assessing the potency of both human and veterinary vaccines. Guidance for determination of the correlation between antigenic content of rabies vaccines and immunogenicity in man and animals is provided in section 2 of this report. In addition, the increasing number of European bat lyssavirus cases reported in northern Europe, together with the recent identification of this virus in bats living in southern Europe required strengthening of the European bat rabies surveillance network of WHO as well as the initiation of further epidemiological investigations and studies for virus identification and classification. Corresponding recommendations are set out in section 3.

¹WHO Technical Report Series, No. 709, 1984

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Finally, recent findings suggested that further in vivo and in vitro studies on the neuronal effects of rabies virus infection may lead to a better understanding of rabies pathogenesis and offer new suggestions for therapy. This topic is covered in section 4 of this report.

This document has been elaborated by the directors of WHO collaborating centres (list of participants in Annex 2) on the basis of proposals formulated by working groups of the preceding Second International IMVI-Essen/WHO Symposium on Rabies (5-7 July 1988), and other earlier, special workshops.

2. POSTEXPOSURE TREATMENT

Reported rabies cases in humans after postexposure treatment with cell culture vaccine called for a thorough analysis with regard to immunization practices. A review of 17 such cases was made during a meeting of directors of WHO collaborating centres on the potency and application of rabies vaccines for human use, Annecy, 11 June 1988. The suggestions for further improvement of postexposure treatment made during the Annecy meeting were reviewed by a working group (see composition below)* during the Second International IMVI-Essen/WHO Symposium on Rabies, 5-7 July 1988, and finally during WHO Consultation, Essen, 8 July.

The participants in this Consultation recommended that:

2.1 During its next meeting the WHO Expert Committee on Rabies should consider, in its "Guide for postexposure treatment" (set out as Annex 1 in its Seventh report)¹ issuing special recommendations for postexposure treatment in countries where canine rabies is enzootic. In addition to the epidemiology of the disease, these recommendations should take into account the socioeconomic conditions prevailing in these areas as well as the costs and availability at local level of the different vaccine formulations and serum preparations.

2.2 Further emphasis be given to immediate local wound treatment and to the simultaneous and proper application of vaccine and immunoglobulin.

2.3 Inoculation of vaccine into the gluteal region should be discouraged. Vaccine should be administered exclusively into the deltoid muscle in adults or into the antero-lateral zone of the thigh in small children.

2.4 Rabies immunoglobulin and tissue culture vaccines meeting WHO requirements should be accessible to everyone.

2.5 Rabies antibody preparations (human rabies immunoglobulins (HRIG) or equine rabies immunoglobulin (ERIG)) be administered in anticipation of active immunization only under exceptional circumstances (e.g. in the absence of vaccine).

¹WHO Technical Report Series, No. 709, 1984

*P. Sureau (Chairman), G. Baer, H. Hock, E. Celis, D. Dreesen, A. Fayaz, D. Fishbein, M. Grandien, E. Gross, M. van Hedenstrom, Lin Fangtao, M. Roumiantzeff, P. Thongcharoen, O. Thraenhart, I. Vodopija and H. Wilde.

If rabies immunoglobulin (RIG) has been administered prior to vaccine it is recommended that the first dose of vaccine be increased to double or triple the normal amount and given into several locations. Increasing the initial dose of vaccine should also be considered for patients at higher risk, e.g. in the following circumstances:

- (i) in patients with underlying chronic disease (e.g. liver cirrhosis);
- (ii) in patients who are congenitally immunodeficient or suffering from Acquired Immuno-Deficiency Syndrome);
- (iii) in patients taking immunosuppressive drugs (including corticosteroids and antimalarials);
- (iv) in the severely malnourished;
- (v) in patients who attend for treatment after a delay of 48 hours or more;
- (vi) in patients where RIG is indicated but unavailable.

2.6 A skin test should be performed prior to the administration of equine serum (equine rabies serum or equine immunoglobulin). However, a positive reaction should not necessarily be regarded as contra-indication provided that all necessary precautions are taken (adrenalin, antihistamines, etc.).

2.7 The following categories of injuries, adopted by the rabies committee of the Thai Red Cross in 1987 be considered for incorporation in the current WHO guide for rabies postexposure treatment:

Category I

Touching or feeding of animals, licking by dog of healthy skin with no open wound, and no documented contact of dog saliva with mucous membrane.

Category II

Nibbling of uncovered skin, superficial scratch that does not break the skin, licking over broken skin or healing wounds, and situations as in Category I, but with unreliable history.

Category III

Single or multiple transdermal bite or scratch which penetrates the skin, at any location; lick over mucous membrane.

Considering that a bite through clothing may still be severe and sufficient saliva may have entered the wound in spite of the covering cloth, the consultation also recommends that the differentiation of bites over covered and uncovered areas be deleted from the above-mentioned WHO guide.

2.8 Cost-benefit analysis of rabies pre-exposure immunization by the intradermal route be carried out for developing countries. Consideration should also be given to rabies pre-exposure vaccination of children in hyperendemic countries.

2.9 In view of various trials indicating that abbreviated multisite regimens with cell culture vaccines of proven efficacy (potency greater than 2.5 IU/ml) evoke more rapid and sustained antibody responses than the five (or six) dose "Essen" regimen, WHO should approve the use of selected abbreviated multisite postexposure regimens (in association with RIG whenever indicated) that have undergone acceptable and successful efficacy trials such as:

- (i) the 2-1-1 dose intramuscular schedule respectively at days 0, 7, and 21;
- (ii) the multisite (e.g. 8 or 4 sites) intradermal schedule as presently used in Thailand, at days 0, 3, 7 plus 1 or 2 site(s) on day 30, but only in vaccination centres with staff well trained for intradermal injection.

More research is recommended on further reduction of the number of visits required for treating the patient, e.g. through application of the 3-1 doses schedule.

2.10 Further research be conducted to determine the possibility of replacing HRIG by rabies monoclonal antibodies. Research has to be carried out to determine which monoclonal antibody (anti-G or anti-RNP) is the most effective for postexposure prophylaxis.

2.11 It is suggested that interferon therapy be evaluated by clinical trials.

2.12 Human rabies cases reported in patients who received postexposure treatment (whatever the lapse of time between exposure and death) should not be considered as vaccine failures unless careful analysis of all circumstances of the exposure and modalities of treatment indicate that the only explanation for the disease occurrence was the lack of efficacy of the vaccine. Antigenic analysis of isolates from these cases should be carried out.

2.13 Postexposure vaccination of domestic animals, which is common even in regions with a high incidence of canine rabies, be discouraged altogether since it does not provide protection after severe exposure and it creates a false sense of security among owners of animals who may be subjected to further risk of infection.

3. POTENCY TESTING FOR RABIES VACCINES*

3.1 General considerations

During the last five years WHO has organized four consultations to review problems related to the testing for potency of human and animal rabies vaccines. According to the existing WHO requirements, potencies of inactivated rabies vaccines must be determined by a challenge method. Although the conditions for performing the corresponding tests have been specified, results may differ markedly amongst laboratories. Furthermore, some vaccines of proven efficacy do not meet minimum WHO requirements as measured by the challenge test in mice. On the other hand, in vitro tests measuring the antigenic content of vaccines have recently been developed. They may represent more rapid and cheaper methods for potency assessment

*This section is based on a text proposal prepared during the Second International IMVI-Essen/WHO Symposium on Rabies, 5-7 July 1988, by the following working group: J. Blancou (Chairman), R. Barth, A. Boge, L. Bruckner, A.M. Diaz, E. Fitzgerald, K. Haffer, K. Ramakrishnan, L. Romanova, W. Schneider, P. Sizaret, B. Wachmann.

and reduce as much as possible the unnecessary suffering of laboratory animals. It is therefore appropriate to validate, through collaborative studies, the results of such tests for antigen content. If a replacement potency test for vaccines is to be established, it should be one that could be applied worldwide and in which vaccine potencies can be expressed in international units (I.U.).

3.2 Possible sources of variation in the results of the NIH challenge test

These include: (i) weight of mice (4-week old mice were recommended, regardless of weight); (ii) strain of mice; (iii) mouse brain challenge material (dose and virus strain); (iv) interval between time of vaccine reconstitution and time of injection of diluted vaccine; (v) interval between time of challenge preparation and actual challenge of mice.

3.3 Methods available and methods under development

3.3.1 Tests based on protection of mice. The European Pharmacopoeia test which consists of challenging mice after a single injection of vaccine was discussed. It was felt that this test is less suitable than the 2-injection NIH test for vaccines with low relative potencies.

A simplified NIH test which utilizes only one dilution of test vaccine and 10 mice per test vaccine was also discussed. There is preliminary evidence suggesting that such a simplified procedure might identify vaccines with potency values less than the minimum required.

Changing the challenge virus strain may affect relative potencies obtained either in the standard NIH test or the European Pharmacopoeia test. Therefore the consultation recommends that a common CVS challenge strain should be used.

3.3.2 Test for antigenic contents (inactivated vaccines). A direct enzyme immunoassay has been developed to quantify the rabies virus glycoprotein in viral suspensions and in vaccines. This has been used successfully for in-process controls as well as for predicting potency values of given vaccines. These tests are conducted with either an anti-glycoprotein polyclonal serum prepared by the injection of purified glycoprotein of vaccine strains (ERA, LEP, PM and PV) or murine neutralizing monoclonal anti-glycoprotein antibodies specific for PM, PV, ERA and HEP strains. Regardless of the way antisera were prepared, tests were shown to be highly reproducible and precise and the results could be obtained within five hours. They can detect levels as low as 0.5 μ g of glycoprotein/ml. A reference vaccine, the titer of which has been determined by NIH test, is included in each test.

The glycoprotein content of most of the veterinary and human vaccines can be quantified by this method. It seems that the correlation between the values obtained by any of this test and those obtained by the NIH potency test are satisfactory in individual laboratories. In view of the fact that the N protein has been shown recently to contribute to the protective efficacy of rabies vaccines, the participants in the consultation recommend:

- (i) assaying the content of vaccine in both G and N protein, and
- (ii) collaborative studies examine whether estimates by various laboratories of G and N antigen contents of rabies vaccines from various origins are more comparable when expressed in comparison with appropriate international reference materials rather than individual standards.

3.4 Determination of the correlation between antigenic contents of inactivated virus vaccines and their immunogenicity in animals and man

The participants in the Consultation made the following recommendations:

3.4.1 In animals. The protective value of any vaccine to be licensed should be established on the basis of a challenge test in the vaccinated target species. These results should show that an acceptable proportion of vaccinated animals are protected against a street rabies challenge which kills at least 80% of the controls. The minimum number of animals to be used should be determined by national control authorities. The challenge should also be done at the end of the period of immunity as claimed by the vaccine producer. The batch which has been shown to protect the target species should be used as reference material by the producer in all tests for potency and/or antigen content on all further batches. The potency of such reference vaccines (product specific reference vaccine) should be determined in international units by either the NIH test or the European Pharmacopoeia test. The value obtained for the product specific reference vaccine should not be lower than the WHO recommended value of 0.3 I.U./ml (NIH test).

For batch release of licensed vaccines the NIH test could be replaced by tests for G and/or N antigen contents, under two conditions:

- (a) Establishment on at least 10 consecutive batches of vaccines of a satisfactory correlation between results of NIH tests and tests for antigenic contents.
- (b) Strict observance of the standard operating procedure (SOP) for the production and testing of the vaccine. Whenever the SOP is modified, the above-mentioned correlation should be established again. The mean geometric potency of the 10 batches tested by the challenge method should not be less than the potency determined for the "product specific reference vaccine".

All vaccines to be released on the basis of antigen determination should have an antigen content not inferior to that of the "product specific reference vaccine".

3.4.2 In humans. In spite of the availability of data on the importance of cellular mechanisms for inducing immunity against rabies, the evaluation of the antibody profile in humans has so far been the only common practice for vaccine comparison.

For the licensing and release of human vaccines produced in cell cultures:

- (a) Product specific reference vaccines to be licensed should be shown to induce (in human subjects) antibody responses which are not less in rapidity, level and duration than those induced by vaccines proven to be effective in postexposure treatment. Antibody profiles in humans should be established using a test system in which the same indicator virus for both the vaccine of proven efficacy and the vaccine to be licensed is used. Furthermore, the indicator virus should belong to a strain commonly used in such studies.
- (b) A satisfactory correlation should be established on the first 10 vaccine batches, using as reference the "product specific reference vaccine" (see 3.4.2 (a)), between the protective efficacy in mice and the antigen content .

- (c) Strict observance of the standard operating procedures (SOP) for the production and testing of the vaccine. Whenever the SOP is modified, the above-mentioned correlation should be established again. The mean geometric potency of the 10 batches tested by the challenge method should not be less than the potency determined for the "product specific reference vaccine".

For vaccines derived from CVS strains the potency of the product specific reference vaccine and of each of the first 10 vaccine batches tested in mice should be not less than 2.5 I.U./dose. In the case of vaccines produced from non-CVS strains, the potency determined by the challenge test and antigenic content determined by *in vitro* test of the first 10 batches should not be less than that of the "product specific reference vaccine" as determined in mice.

All vaccines to be released on the basis of antigen determination should have an antigen content not inferior to that of the "product specific reference vaccine".

In view of the fact that certain sub-unit rabies vaccines, e.g. nuclear protein rabies vaccine, may protect and yet be unable to elicit neutralizing antibodies, the licensing of such vaccines for human use should be granted, provided that the product is shown to protect non-human primates against lethal challenge.

4. SURVEILLANCE OF EUROPEAN BAT LYSSAVIRUS INFECTIONS*

Intensified studies on the epidemiology of chiropteran rabies in Europe are required because:

- (i) control efforts through oral immunization of carnivores is progressing rapidly in western Europe, but inadequate data exist on the potential transmission of the disease from bats to terrestrial domestic or wild animals;
- (ii) it is desirable for public health authorities to know the geographical and species distribution of bat rabies; and
- (iii) there is only limited knowledge from a comparative virological point of view about bat viruses in general.

However, the desirable intensification of bat rabies surveillance should not affect these endangered and protected animal species. The group recommends that no active surveillance of rabies in bat populations be performed; only passive surveillance in line with existing conservation measures and mainly relying on the close cooperation of bat biologists will proceed, as agreed during a meeting held in Marburg in May 1986.

*This section is based on a text proposal prepared during the Second International IMVI-Essen/WHO Symposium on Rabies, 5-7 July 1988, by the following working group: A. King, A. Wandeler, Joan Crick, J. Frost, M. Aubert, W. Muller, Monique Lafon, M. Fekadu, C. Rupprecht and Jean Smith (Chairman).

4.1 Selection of monoclonal antibodies for European bat lyssavirus identification

In Europe, there is a need to distinguish European bat lyssavirus isolates from vaccine viruses and from classical rabies virus sub-types in terrestrial animals.

The consultation recommends that reference laboratories examine their MAb panels in order to find the minimum number of MAbs required to distinguish European bat lyssaviruses from other viruses of the Lyssavirus genus. Ideally, these MAbs should react (1) positively with bat lyssaviruses and negatively with all other viruses of the rabies group (bat isolates +/terrestrial isolates -) and (2) negatively with bat lyssaviruses and positively with all other viruses of the rabies group (bat isolates -/terrestrial isolates +).

4.2 Collaborative studies on the potential transmission of bat lyssavirus to terrestrial animals

Initial surveys will be conducted in France and the Federal Republic of Germany. Approximately 250 rabid foxes, 100 domestic cats, 100 stone martens, and 50 other terrestrial species will be obtained from each country. Laboratories in Weybridge (UK), Tubingen (FRG), and Paris (France) will examine the isolates with the MAb panels to differentiate terrestrial and bat isolates. The isolates of special interest include those from terrestrial rabies cases reported outside areas with recognized lyssavirus type 1 enzootics and/or in areas where bat rabies exists. The Federal Animal Research Institute in Tubingen, the National Rabies Research Centre in Nancy and the Pasteur Institute in Paris will serve as coordinators of isolate submissions. Isolates likely to contain bat lyssavirus will be exchanged among WHO Collaborating Centres.

4.3 WHO collaborative network for European bat rabies

The Institut Pasteur in Paris and the Federal Research Institute for Animal Virus Diseases in Tubingen had so far accepted to test suspect bat isolates. It has been decided to include two additional laboratories in the WHO network, i.e. Central Veterinary Laboratory, Weybridge, UK, and the Institute of Viral Virology in Berne, Switzerland.

4.4 Taxonomy classification

It was agreed that insufficient data exist concerning the comparative nucleic acid sequences of Lyssa viruses. The classical rules of international taxonomy and systematics should be applied in the future. The participants in the Consultation agreed to compare their data in order to decide whether the European bat isolates should be termed "Duvenhage virus". In the meantime viruses from such isolates should be referred to as the "European bat Lyssavirus".

5. NEUROPHYSIOLOGY*

Research in this field, including immuno-pathology, has not received sufficient attention in the past. In line with the proposal made by the working group on neurophysiology at the Second International IMVI/WHO Symposium on Rabies, research projects should be planned by a group of specialists. WHO may wish to send the document prepared at the Second International IMVI/WHO Symposium

*This section is based on suggestions prepared during the Second International IMVI-Essen/WHO Symposium on Rabies, Essen, 5-7 July 1988 by the following group: R.L. Isaacson, M. Fekadu, Th. Hemachudha.

for complementary comments to Dr Floyd Bloom, Director, Neurophysiology Division, Scripps Clinic and Research Foundation, La Jolla, USA, and Dr Daniel Perl, Director, Neurophysiology Division, Mount Sinai Hospital, New York, USA.

Investigations by neurophysiologists should also include thorough study of human cases. A group of specialists would have to develop a suitable protocol.

6. ACKNOWLEDGEMENT

The participants of the WHO consultation wish to express their gratitude to all those who contributed to these developments through their research work and expert advice. The World Health Organization is to be commended for its sustained coordination of all their efforts.

ANNEX 1

SUMMARY OF DOCUMENTS CONTAINING CONCLUSIONS AND RECOMMENDATIONS
ON ANIMAL RABIES SURVEILLANCE AND CONTROL

Since the meeting of the WHO Expert Committee on Rabies in 1983, a number of developments have called for new recommendations in the field of rabies control and human postexposure treatment. The rapid progress in wildlife rabies elimination through oral vaccination of foxes has been recognized in a series of international meetings and consultations. Major conclusions and recommendations are or will be contained in reports of the WHO Workshop on Oral Immunization of Wildlife Against Rabies in Europe (INTORAL), October 1986 (WHO/Rab.Res./87.23), of the Meeting for Coordination of Rabies Control in Europe, June 1988 (report by WHO Collaborating Centre for Research and Management in Zoonoses Control, Nancy), and of the meeting on Oral Immunization in Wildlife, held in Montreal in August 1987 and attended by directors of WHO Collaborating Centres (report by The Wistar Institute, Philadelphia).

In recent years WHO has concentrated research efforts on the development of simple procedures for the collection and laboratory examination of brain specimens in the field. These are described in the following WHO documents: Simplified technique for the collection, storage and shipment of brain specimens for rabies diagnosis (WHO/Rab.Res./88.27) and Rapid Rabies Enzyme Immunodiagnosis (RREID) (WHO/Rab.Res./88.29).

Such improvements in surveillance components form part of WHO's efforts towards revitalization of rabies control and elimination in its canine reservoirs which still exist in 87 developing countries and territories. Emphasis has been placed on dog ecology and research on dog immunization by the oral route and two further meetings have been held, namely a WHO Consultation on Dog Ecology Studies related to Rabies Control, February 1988 (WHO/Rab.Res./88.25) and a WHO Consultation on Oral Immunization of Dogs against Rabies (WHO/Rab.Res./88.26).

LIST OF PARTICIPANTS

- Dr G. Baer, Director, WHO Collaborating Centre for Reference and Research on Rabies, Lawrenceville Rabies Facility, Centers for Disease Control, P.O. Box 363, Lawrenceville, GA 30246, USA
- Dr J. Blancou, Director, WHO Collaborating Centre for Research and Management in Zoonoses Control, National Rabies Research Centre, P.O. Box 9, 54220 Malzéville, France
- Dr B.L. Cherkasskiy, Director, WHO Collaborating Centre for Zoonoses, Central Research Institute of Epidemiology, Ministry of Public Health of the USSR, 3-a Novogizeevskaya, 111 123 Moscow, USSR
- Dr A. Fayaz, Director, WHO Collaborating Centre for Reference and Research on Rabies, Rabies Department (Research and Production), Pasteur Institute of Iran, Pasteur Avenue, Teheran, Islamic Republic of Iran
- Dr V.R. Kalyanaraman, Director, WHO Collaborating Centre for Training in Rabies Vaccine Production and Quality Control, Pasteur Institute of India, Coonoor 643 103, India
- Dr H. Koprowski, Director, WHO Collaborating Centre for Reference and Research on Rabies, The Wistar Institute, 36th Street at Spruce, Philadelphia, PA 19104, USA
- Dr W.W. Müller, WHO Collaborating Centre for Rabies Surveillance and Research, Federal Research Institute for Animal Virus Diseases, P.O. Box 1149, 7400 Tübingen, Federal Republic of Germany
- Dr L.N. Romanova, L.A. Tarasevich Institute for Standardization and Control of Medical Biological Preparations, 41 Sivtzev Vrazek, Moscow 1210.02, USSR
- Dr P. Sureau, Director, WHO Collaborating Centre for Reference and Research on Rabies, Institut Pasteur, 28 rue du Docteur Roux, 75724 Paris Cedex 15, France
- Dr O. Thraenhart, Director, WHO Collaborating Centre for Reference and Research on Neurological Zoonoses, Institute for Medical Virology and Immunology, 55 Hüfelandstrasse, 4300 Essen 1, Federal Republic of Germany
- Dr A.I. Wandeler, Director, WHO Collaborating Centre for Reference and Research on Viral Zoonoses, Institute of Veterinary Virology, 122 Langgass-Strasse, 3012 Berne, Switzerland

Observers

Dr M. Aubert, National Rabies Research Centre, P.O. Box 9, 54220 Malzéville,
France

Dr J.J. Guinet, Regional Adviser in VPH, Veterinary Public Health Programme, Pan
American Health Organization, 525 Twenty-Third Street N.W.,
Washington D.C. 20027, USA

Secretariat

Dr K. Bogel, Chief, Veterinary Public Health, Division of Communicable Diseases,
WHO, Geneva, Switzerland

Dr F.-X. Meslin, Scientist, Veterinary Public Health, Division of Communicable
Diseases, WHO, Geneva, Switzerland (unable to attend due to other
commitments)

Dr P. Sizaret, Biologicals Section, Division of Diagnostic, Therapeutic and
Rehabilitative Technology, WHO, Geneva, Switzerland

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