

**REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON THE  
OIE MANUAL OF DIAGNOSTIC TESTS AND VACCINES FOR TERRESTRIAL ANIMALS:  
CHAPTER ON RABIES  
Paris, 9–11 May 2017**

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An *ad hoc* Group (AHG) on the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)*: chapter on Rabies was convened at the OIE Headquarters from 9 to 11 May 2017.

The Agenda and List of Participants are given at [Appendices I](#) and [II](#), respectively.

## **1. Opening**

Dr Matthew Stone, Deputy Director General of the OIE, International Standards and Science, welcomed the participants on behalf of Dr Monique Eloit, Director General of the OIE. Dr Stone reminded the Group of the objectives of the OIE Sixth Strategic Plan for the 5-year period 2016–2020, which emphasises a risk management approach to good veterinary governance through the development of appropriate standards that include best practices. To ensure the scientific excellence, integrity and transparency of the OIE, there must be clear documented rationale to substantiate any proposed changes to the rabies chapter.

The Group was reminded that one of the objectives of the meeting was to expand the section on oral vaccination of dogs to include details on the manufacture of the oral vaccine following adoption by the OIE Biological Standards Commission of the principle of including oral vaccination of dogs in the *Terrestrial Manual*,

The Group was also reminded of ongoing collaboration between the OIE and the WHO<sup>1</sup>, in the context of the OIE Health initiative, one of the aims of which is to eliminate dog-mediated human rabies by 2030. Part of this collaboration includes harmonising texts on rabies diagnosis and control published by both organisations.

The WHO is currently reviewing three key documents on the subject of rabies with input from OIE experts: WHO *Expert Consultation on Rabies*, WHO *Laboratory Techniques in Rabies* and *Oral Vaccination of Dogs against Rabies: Guidance for research on oral rabies vaccines and Field application of oral vaccination of dogs against rabies*. The revision of the WHO documents, the OIE *Terrestrial Animal Health Code* chapter on rabies, and the *Terrestrial Manual* chapter are an integral part of this harmonisation effort under the One Health initiative, and the Group referred to the documents throughout the meeting to ensure consistency among all the texts.

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1 WHO: World Health Organization

## 2. Appointment of chairperson and rapporteur, and review/adoption of the Terms of Reference

The meeting was chaired by Dr Thomas Müller, and Ms Sara Linnane was designated as rapporteur. The adopted Terms of Reference can be found at [Appendix III](#) to this report.

## 3. Term of Reference 1: review the introduction to Chapter 2.1.17 Rabies of the OIE Terrestrial Manual

Following in-depth discussions, the Group proposed the following amendments to the summary and introduction to the OIE *Terrestrial Manual* rabies chapter:

- To add text explaining that laboratory manipulations should be performed with appropriate biosafety and containment procedures as determined by biorisk analysis (see Chapter 1.1.4 *Biosafety and biosecurity: Standard for managing biological risk in the veterinary laboratory and animal facilities*).
- To clarify that agent identification is preferably undertaken using primary diagnostic antigen detection tests such as the direct fluorescent antibody (DFA) test and the direct rapid immunohistochemistry test (dRIT). For a large number of samples, conventional and real-time polymerase chain reaction (PCR) can provide rapid results in specially equipped laboratories.
- For serological tests, to clarify that the virus neutralisation (VN) and enzyme-linked immunosorbent (ELISA) assays are suitable tests for monitoring antibody response of vaccinated animals in the framework of rabies control. For the purposes of international animal movement and trade, only VN tests are acceptable. Serological tests should not be used for primary diagnosis.
- To clarify that for rabies vaccination in animals, inactivated virus (for companion animals and livestock), live attenuated virus (for wildlife and free-roaming dogs), or recombinant vaccines (for wildlife and dogs) are used.
- The Group undated the classification of the *Lyssavirus* genus.

## 4. Term of Reference 2: review Section B. Diagnostic techniques of Chapter 2.1.17 Rabies of the OIE Terrestrial Manual

Following discussions, the Group proposed the following amendments to *Section B. Diagnostic techniques* of the rabies chapter:

- To include the completed table of diagnostic tests rated against each of six purposes that has been introduced into each disease-specific chapter of the *Terrestrial Manual* in place of prescribed and alternative tests.
- To include updated information on the transport of specimens, together with information on suitable preservatives, etc.
- To include detailed protocols for three new diagnostic test methods following review of their validation dossiers and approval by the Biological Standards Commission: a direct rapid immunohistochemistry test (dRIT), a conventional reverse-transcriptase polymerase chain reaction (RT-PCR) and a real-time RT-PCR.
- To include a detailed protocol for the direct fluorescent antibody (DFA) test, the most widely used test for rabies diagnosis.
- For consistency, to remove Figure 1. *Proposed use of microplates for the fluorescent antibody virus neutralisation test* from the virus neutralisation (VN) test protocol because no such diagram is provided in any other chapter that include a VN test protocol.
- To remove the sentence on virus neutralisation in mice as it unethical to use mice when cell culture and enzyme-linked immunosorbent assays (ELISA) provide adequate alternatives under the 3Rs<sup>2</sup> principles.

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<sup>2</sup> The Three Rs: replacement, reduction, refinement. See Article 7.8.3 of chapter 7.8 of the OIE *Terrestrial Code*.

- To clarify that none of the available ELISAs is validated for certification of animals for international movement or trade.

The two RT-PCR protocols that are proposed for inclusion in the chapter were chosen as validated examples and their inclusion does not exclude other PCR protocols. Should a laboratory prefer to use a different PCR method, the method chosen must be validated to the same validation stage as the PCR example given in the chapter, and must show that it has equivalent sensitivity, specificity, and reproducibility.

## 5. Term of Reference 3: review of *Section C. Requirement for vaccines of Chapter 2.1.17 Rabies of the OIE Terrestrial Manual*

To ensure harmonisation of WHO and OIE texts, the Group used the WHO document: *Oral Vaccination of Dogs against Rabies: Guidance for research on oral rabies vaccines and Field application of oral vaccination of dogs against rabies* as guidance while updating this section.

Following discussions, the Group proposed the following amendments to *Section C. Requirements for vaccines of the rabies chapter*:

- To delete Table 1 *Current rabies viruses used for challenge or for vaccine manufacturing*. The Group felt that with the speed of advances in vaccine development, it would be impossible to keep this table up to date, and the table did not provide extra information of value to users of the *Terrestrial Manual*.
- To include information on oral vaccination of dogs and manufacturing methods for such vaccines.
- To include detailed information on bait requirements, coordinated with requirements given in the WHO document.

Although many new recombinant vaccines that are in development are both modified live vaccines (MLV) and biotechnology-derived vaccines (BDV), the Group decided to keep these two categories separate in the chapter.

## 6. Any other matters

The Group had a number of questions and proposals for the consideration of the OIE Biological Standards Commission.

### 6.1. Questions for the Biological Standards Commission concerning the chapter on rabies in the OIE *Terrestrial Manual*

1. Section C *Requirement for vaccines* includes the requirements for tests on the final product. The Group asks what the final product is. Is it the vaccine bait (as stipulated in the European Pharmacopoeia) or the bait in primary packaging (blister/sachet)?
2. The WHO recommends that safety tests be carried out in non-human primates (NHPs). The Group noted that there are international efforts currently being undertaken regarding this sensitive issue. As oral vaccination of dogs is a complementary control measure, the Group asks if such safety tests are really justified. The Group also pointed out that to have confidence that the residual pathogenicity is <1%, at least 300 animals would need to be tested. Finally, the Group requested the rationale for testing NHPs and immunocompromised mice for human safety.
3. In Section C.3.2.2. *Method of manufacture*, iii) *Final product batch/serial tests*, e) *Batch/serial potency*, the Group asks why the potency of BDV is measured by seroconversion while the potency of MLV is not.
4. The chapter states that tests for reversion to virulence of modified live vaccines (MLV) should be undertaken (in accordance with chapter 1.1.8) in the target species and, if not possible, they should be undertaken *in vitro*. The *European Pharmacopoeia* (EP) states that such tests should be undertaken in suckling mice. Should the chapter be modified according to the requirements of the EP?

5. Section 3.1.3 of the WHO document: *Oral Vaccination of Dogs against Rabies: Guidance for research on oral rabies vaccines and Field application of oral vaccination of dogs against rabies on Safety for non-target species* states that dogs should be given ten times the field concentration of the vaccine. It also states that “Categories that might be more susceptible (e.g. young, pregnant) or more likely to transmit vaccine virus to humans must be included in such studies”. The Group felt that choosing young or pregnant animals is indefensible scientifically.
6. Section 3.3.2 *Safety requirements*, i) *MLV*, a) *In target species* it states “For the overdose safety test, a 10 × minimum effective dose is administered, preferably using a syringe, via the oral route to ten animals (less than 6 months of age for wild animals and less than 10 weeks for dogs)”. The Group asks why the difference in age between wild animals and dogs.
7. Section 3.3.2 *Safety requirements*, i) *MLV*, b) *In non-target species* animals are observed for 30 days post-vaccination, while in Section 3.3.2 *Safety requirements*, ii) *BDV*, b) *In non-target species* animals are observed for 14 days post-vaccination. The Group asks why this difference.

## 6.2. Recommendations concerning the disease-specific chapters in the OIE Terrestrial Manual

1. The Group proposed that the Commission consider removing the detailed test protocols from the chapter proper and including them as appendices at the end of the chapter.
2. The Group proposed including a flow chart to illustrate the order in which diagnostic tests should be undertaken taking into account the purpose of testing and the results obtained.

## 7. Finalisation and adoption of the draft report

The *ad hoc* Group finalised and adopted the draft report.

The proposed revised chapter will be circulated to all OIE Reference Laboratories for rabies so that they can collaborate to submit a consensus version for review by the Biological Standards Commission at its meeting in September 2017. If endorsed by the Commission, it will then be sent for Member Country comment with the aim of proposing it for adoption in May 2018.

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.../Appendices

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**Agenda**

1. Opening
  2. Appointment of chairperson and rapporteur
  3. Term of Reference 1: Review the introduction to Chapter 2.1.17 *Rabies* of the OIE *Terrestrial Manual*
  4. Term of Reference 2: review *Section B. Diagnostic techniques* of Chapter 2.1.17 *Rabies* of the OIE *Terrestrial Manual use*
  5. Term of Reference 3: review of *Section C. Requirement for vaccines* of Chapter 2.1.17 *Rabies* of the OIE *Terrestrial Manual*
  6. Any other matters
  7. Finalisation and adoption of the draft report
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Appendix II**REPORT MEETING OF THE OIE AD HOC GROUP ON THE  
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Appendix III

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**Terms of Reference**

To thoroughly review and update the following sections of *Terrestrial Manual* chapter on rabies:

*Introduction*

*Section B. Diagnostic techniques:* including incorporating newly developed validated tests and deleting obsolete tests or tests no longer in use

*Section C. Requirements for vaccines:* including oral vaccination of dogs and manufacturing methods for such vaccines

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