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REPORT OF THE MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION

Paris, 2–5 February 2016

The OIE Biological Standards Commission met at the OIE Headquarters from 2 to 5 February 2016. Dr Monique Eloit, Director General of the OIE, welcomed the Members of the Commission, Dr Beverly Schmitt, President, Dr Franck Berthe and Dr Hualan Chen, Vice-Presidents, and Dr Peter Daniels, Dr Mehdi El Harrak and Dr Anthony Fooks, members of the Commission.

Dr Eloit informed the Commission of the proposed roadmap for the implementation of the Sixth Strategic Plan 2016–2020. She reminded the Commission that the four OIE Specialist Commissions are currently managed by two Departments (the International Trade Dept and the Scientific and Technical Dept), and it will be proposed to merge all four secretariats into one new department of standards, to reinforce the consolidated secretariats and thereby to improve their capacity. These and other changes would not be implemented until after the General Session in May.

Regarding the agenda item on vaccinating dogs against rabies (agenda item 2.4), Dr Eloit reminded the Commission of the WHO[1]/OIE Conference on Rabies, Global Elimination of Dog-Mediated Human Rabies, which was held from 10 to 11 December 2015 in Geneva, Switzerland. She informed the Commission that in the light of this Conference, the OIE would launch a second call for tender for a vaccine bank against rabies.

Dr Eloit further acknowledged that the Commission would review the guidelines for applicants for OIE Reference Laboratory status and the procedure for designating laboratories (agenda items 3.1 and 3.2). She stressed the importance of this network to the OIE and its Member Countries. The OIE depends very heavily on its designated Reference Laboratories and disease experts for scientific advice and support. OIE Reference Laboratories must therefore have a high level of expertise to ensure the scientific excellence of the OIE.

Regarding the replacement International Standard Bovine Tuberculin (agenda item 4.1), Dr Eloit informed the Commission that the Headquarters had begun to contact possible donors in an effort to ensure that this project could begin as soon as possible.

Finally Dr Eloit told the Commission that the OIE and the WHO are working together on the control of MERS (Middle East Respiratory Syndrome), and are considering the development of a vaccine for use in camels. The Commission would be informed of further developments in this project.

Dr Brian Evans, Deputy Director General and Head of the OIE Scientific and Technical Department, who joined the meeting on the second day, informed the Commission that the OIE Council had requested more interaction with the four Specialist Commissions. To improve communication between the four Commissions joint meetings, meetings of the Presidents and sharing of meeting agendas were planned. The Biological Standards Commission should clearly define its role, its working procedures and work plan, and also the skill sets that would be required of future members.

The Agenda and List of Participants are given at Annexes 1 and 2, respectively.

[1] WHO: World Health Organization

1. Brainstorming: In-depth discussion on the Commission's activities, modus operandi and working procedures

The two topics discussed in-depth by the Commission were the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*) and the OIE Reference Laboratories (see agenda item 2.1 and 3.1, respectively.

2. *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*

For this agenda item, the Commission was joined by the Consultant Editor of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*), Prof. Steven Edwards.

2.1. Extensive review of the structure and content of the *Terrestrial Manual*

A primary responsibility of the Biological Standards Commission is to consider and prepare advice regarding the *Terrestrial Manual*, both with respect to overall aspects and the content of individual chapters, noting that the *Terrestrial Manual* is a Standard published by the OIE in line with its responsibilities as the WTO[2] reference organisation for standards relating to animal health and zoonoses.

After extensive discussion, the Commission agreed the following regarding the *Terrestrial Manual:*

1. At the General Session in May this year, the Assembly will consider proposed definitions of an OIE Standard and of an OIE Guideline to distinguish between texts adopted by resolution of the Assembly and those endorsed without adoption by resolution. Given that the guidelines in Part 3 of the *Terrestrial Manual* have all been adopted by resolution, the title of Part 3 would be changed to *General Recommendations* and the guidelines it contains would be renamed as chapters.

2. Part 2 of the *Terrestrial Manual* is currently entitled: OIE Listed Diseases and Other Diseases of Importance to International Trade. Recognising that the OIE mandate is broader than trade issues and includes matters such as food safety, animal welfare, zoonotic diseases and new and emerging diseases, the words "to International Trade" should be deleted from the title.

3. The titles of disease chapters in the *Terrestrial Manual* should be maintained and the *Terrestrial Animal Health Code* title should be added in brackets when relevant, e.g. Chapter 2.2.2 American foulbrood (Infection of honey bees with *Paenibacillus larvae*). The Code Commission and the Biological Standards Commission should keep each other informed of changes to disease chapter titles in the *Terrestrial Code* and *Terrestrial Manual*, respectively.

4. The schematic representations of the application of laboratory tests for determining evidence of infection for various purposes should remain in certain disease-specific chapters of the *Terrestrial Code*. Generic terms should be used to designate the tests in these flowcharts, e.g. "serological test" rather than "ELISA"[3]. In this way the focus of the *Terrestrial Manual* would remain as a standard on how to perform the tests described.

5. If at the next General Session in May the Assembly adopts the Code Commission's proposal to delete *Terrestrial Code* chapter 1.3 *Prescribed and alternative diagnostic tests for OIE listed diseases*, the corresponding table and all reference to prescribed tests for international trade would be removed from the *Terrestrial Manual*, i.e. the label "prescribed tests for international trade" would be deleted and the protocol of tests previously designated in this way would no longer be written in blue.

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[2] WTO: World Trade Organization
[3] ELISA: enzyme-linked immunosorbent assay

6. Given the importance of molecular tests, the instructions for authors should require the inclusion in the disease-specific chapters of current molecular tests such as PCR[4]-based approaches (including real-time PCR) and isothermal amplification methods, specifying primer sequences and reaction conditions. The text should state the stage of validation of the assay as defined in Chapter 1.1.5 *Principles and methods of validation of diagnostic assays for infectious diseases*. Where relevant to the purpose of the tests as described in the *Terrestrial Manual*, partial or whole genome sequencing should be included with a description of the appropriate methodology.

The Commission reiterated its decision to abandon the Enlarged Bureau Group, which had been formed to review the draft chapters and propose them to the Commission for circulation or for further revision as this task is a fundamental responsibility of and should be undertaken by the Commission supported by the Consultant Editor. External experts could be invited to future meetings if their expertise was to be requested; the decision would be taken on a case-by-case basis.

2.2. Review of first-round Member Country comments on draft chapters

The Commission reviewed 22 draft chapters and approved 21 chapters for circulation, some subject to clarification of certain points by the experts, for second-round Member Country comment and proposal for adoption by the Assembly in May 2016.

The batch of draft chapters included two new chapters: Chapter 1.1.8 *Minimum requirements for the organisational management of a vaccine manufacturing facility*, and Chapter 1.1.9 *Minimum requirements for the production and quality control of vaccines*. The Commission agreed that these two chapters should be added to Part 3 of the *Terrestrial Manual*, newly entitled *General Recommendations*, that the summaries of both chapters should be expanded and include cross references to Chapter 1.1.0 *Management of veterinary laboratories* and Chapter 1.1.6 *Principles of veterinary vaccine production*, and that the Appendix 1.1.9.1 *Minimum requirements for the production and quality control of vaccines: aseptic production* should be removed from chapter 1.1.9 and added to Part 3 of the *Terrestrial Manual* as a stand-alone chapter. These three chapters would be preceded by an introductory note, *Recommendation for the manufacture of vaccines*, similar to the note that precedes the validation chapters (formerly guidelines).

The Commission noted the comments on Chapter 1.1.11 *Standards for high throughput sequencing, bioinformatics and computational genomics* (HTS-BCG), which will be taken into account by the *ad hoc* Group in future revisions. The intention of the chapter is to give an overview of the topic and it will be revised regularly as new advances are made. The chapter was approved to be sent for second-round Member Country comment and proposal for adoption by the Assembly in May 2016.

For sections of chapters that are currently marked as "under study" (e.g. vaccine section of chapter 2.1.7 *Japanese encephalitis* or diagnostic techniques section of chapter 2.1.15 *Rinderpest*), the Commission agreed it would be clearer to state "This section was adopted in YEAR, and is currently being considered for revision".

Regarding chapter 2.1.15 *Rinderpest*, one Member Country had asked whether it was appropriate to retain a full chapter on this disease in the *Terrestrial Manual.* The Commission agreed that it was important to maintain the chapter and would ask the Reference Laboratory experts to review the section of the chapter on diagnostic tests. The Commission considered that for maintenance of freedom it is important to have a standard protocol for rapid molecular testing for this pathogen.

2.3. Terms from Validation Guideline 3.6.8 proposed to be added to the glossary

The Commission reviewed a short list of terms from the proposed Chapter 3.6.8 *Comparability of assays after minor changes in a validated test method* and agreed that the following should be included in the Glossary:

[4] PCR: polymerase chain reaction

Comparability: the preferred term when performance characteristics of a new test, which has undergone a minor change, are as good as those of a validated test within statistically defined limits.

Ct value: the number of PCR cycles required for fluorescent signal to exceed the background.

Limit of detection (*LOD*): the LOD is the estimated amount of analyte in a specified matrix that would produce a positive result at least a specified per cent of the time and is a measure of the analytical sensitivity.

Receiver operating characteristic (*ROC*): ROC analysis provides a cut-off-independent approach for evaluation of the global accuracy of a test where results are measured as ordinal or continuous values. The area under the ROC curve provides a single numerical estimate of overall accuracy ranging from 0.5 (useless test) to 1 (perfect test).

Validation: is a process that determines the fitness for purpose of an assay, which has been properly developed, optimised and standardised, for an intended use.

Verification: represents evidence that the performance characteristics, e.g. accuracy and precision of a validated assay, are comparable when used in another laboratory.

These definitions will be circulated for first-round comment as part of the 2016/2017 review cycle.

2.4. Proposal to include in the *Terrestrial Manual* oral vaccination of dogs against rabies

A report had been received from a commercial company on a study it had undertaken to immunise dogs against rabies using oral vaccination. The document included information on the vaccine, including background on the strain, safety studies and efficacy studies, on the bait and on the distribution system. The company was requesting that the Commission consider amending the *Terrestrial Manual* chapter on rabies to include the principle of oral vaccination of dogs as currently the *Terrestrial Manual* only provides for parenteral vaccination of dogs and the references for oral vaccination are applicable only to wildlife.

In the past, the OIE has endorsed the use of oral vaccination of dogs against rabies, in combination with other measures such as parenteral vaccination or chemical or immunological contraception, as part of a rabies control programme (e.g. see the recommendations of the Global Conference on Rabies Control, Incheon, Seoul, Korea [Rep. of], 7–9 September 2011). The Commission agreed to seek the advice of the OIE Reference Laboratory experts before taking a final decision.

The report was also forwarded to the Terrestrial Animal Health Code Commission for consideration of inclusion of this vaccination strategy in the *Terrestrial Code*.

2.5. Request for review of the vaccine section of the chapter on Rift Valley fever

In view of the possible establishment of an OIE regional vaccine bank for Rift Valley fever (RVF), the Commission was requested to review the vaccine section of the RVF chapter to ensure that it is reflective of current RVF vaccine knowledge and technologies. The Commission did not recommend an update at present, but would commission one should there be major advances in the future in vaccine development.

2.6. Question regarding the primer sequence given in the peste des petits ruminants chapter

A reader of the *Terrestrial Manual* had queried the accuracy of the primer sequence given in the RT-PCR protocol in the chapter on peste des petits ruminants (PPR). It would appear that the misunderstanding arose as the sequence published in the *Terrestrial Manual* is *based on* the original publication, but has been modified as indicated in the chapter, and is the sequence currently recommended by the Reference laboratory. A response would be sent to the reader explaining the *Terrestrial Manual* text.

2.7. Review of draft form for submission of new test methods and validation data

At its last meeting, Dr François Diaz from the OIE Headquarters had proposed to draft a form that would accompany a submission of a new test method for consideration for inclusion in the *Terrestrial Manual*. The form would be based on Chapter 1.1.5 *Principles and methods of validation of diagnostic assays for infectious diseases* and also on the existing form that is part of the procedure for the registration of diagnostic kits. The Commission reviewed the proposed form and agreed that it represents an excellent development that will reassure the public that there is a consistently applied procedure for accepting new validated tests. The form can be found at Annex 3.

2.8. Validation dossier for a group-specific real-time reverse-transcription polymerase chain reaction (RT-qPCR) for African horse sickness virus (AHSV)

At its last meeting in September 2015, the Commission was updated on the outcome of an international ring trial on the performance variability of 10 different RT-PCR protocols used in the main AHS diagnostic laboratories. The study had identified one method, namely the "Agüero method", for full validation and the Commission reviewed and accepted the validation dossier. The OIE Reference Laboratory experts were asked to update the *Terrestrial Manual* chapter to provide a more complete protocol for this test along with text explaining that the protocol had been identified in a comparative ring trial to be one among other top-ranking protocols.

In line with this conclusion, a validation dossier had been received from Prof. A.J. Guthrie for a group-specific real-time RT-PCR AHSV. As the level of validation was equivalent to the "Agüero method", the Commission accepted the assay for inclusion in the *Terrestrial Manual* chapter. The OIE Reference Laboratory experts would be asked to further update the *Terrestrial Manual* chapter to include this protocol. It was also decided that the chapter should have a table of the PCR methods that have been developed and validated that gives the primer sequences, annealing temperatures, number of amplification cycles, and that identifies the test as group specific or type specific. The sensitivity and specificity of the tests should also be indicated.

2.9. Comment from Singapore on equine diseases

The Delegate of Singapore had a question regarding the complement fixation test (CFT) for glanders. The OIE *Terrestrial Manual* states that the CFT is an accurate and reliable serological test for diagnosing glanders. However, the test is unable to differentiate serologically between *Burkholderia mallei* and *B. pseudomallei*, which presents a problem for countries that are endemic for melioidosis as horses that carry *B. pseudomallei* antibodies can react positively in the glanders CFT. These horses cannot be confirmed conclusively as being infected with *B. mallei* due to the cross-reactivity of the two bacteria. The Delegate asked if the OIE Reference Laboratories could provide comments on the interpretation of positive CFT results when such countries submit samples for confirmatory testing. He also questioned the suitability of the use of glanders CFT as the only prescribed test for international trade. Finally he proposed that the OIE Reference Laboratories consider establishing an assay with a high sensitivity and specificity for differentiating between these two bacteria, and organise an inter-laboratory proficiency test programme that will help participating laboratories validate their tests and assess the reliability of their test results. The advice of the OIE Reference Laboratory experts would be sought.

The Delegate also requested access to the protocols and scientific data from the ring trial of the 10 RT-PCR protocols for AHS (see item 5.2.7 of the report of the meeting of the Biological Standards Commission, September 2015). The Commission noted that publication of the study is in process.

3. OIE Reference Centres

3.1. Extensive review of the approval and maintenance of Reference Centre status procedures

The Commission agreed that clear criteria and procedures for designation and de-listing of OIE Reference Laboratories were needed. With regard to designation of new laboratories, the Commission discussed several possibilities, for example organising on-site visits to applicant laboratories, but such a step is not foreseen in the *Basic Texts*.

The Commission agreed that new applications for OIE Reference Laboratories would only be considered at its August/September meetings. Furthermore, the Commission set a deadline of 45 days before the scheduled August/September meeting to receive applications for OIE Reference Laboratories. This deadline would need to be strictly observed to allow a full evaluation of the applications by the Commission members prior to this meeting. Applications received after the deadline would be examined in the next August/September meeting of the Commission.

For de-listing, and with reference to a previously proposed decision tree on how to evaluate and react to under-performing Reference Laboratories (Annex 4 of the report the February 2014 meeting of the Commission), the Commission identified two critical points for initial evaluation of an laboratory's performance. These critical points were: i) lack of submission of an annual report and ii) no progress or explanation provided on achievement of accreditation to the ISO 17025 or equivalent quality management system in their diagnostic laboratories. Any OIE Reference Laboratory scoring negatively when measured against either or both of these points could be deemed to be failing to fulfil the Terms of Reference and could progress down the pathway towards potential de-listing.

The Commission decided to further discuss the overall item at its next meeting in September 2016 so as to develop standard operating procedures for designation of OIE Reference Laboratories.

The Commission reviewed the work that had been accomplished on Reference Centres and networks and noted that discussion could usefully be held regarding whether the current system met all the evolving needs of the OIE and the Member Countries, and whether that was achieved in the most effective manner. The Commission decided to hold over a more detailed consideration of such matters to its next meeting, to be addressed under a specific agenda item.

3.2. Specific issues related to Reference Centres: guidelines for applicants

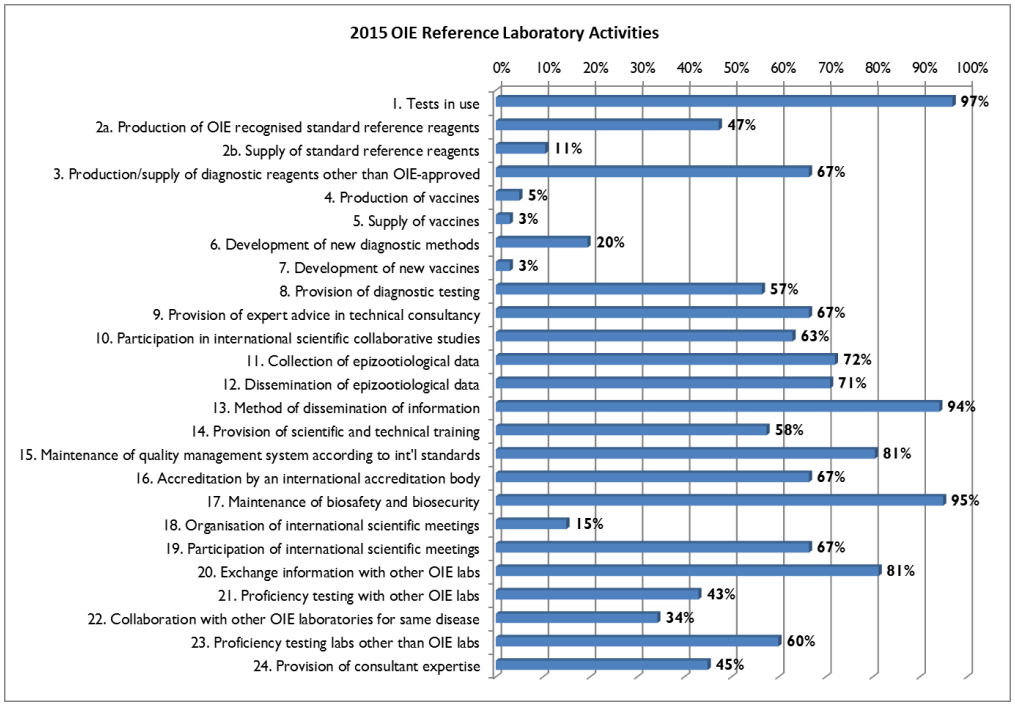
The Commission was reminded of the current status of the *Guidelines for applicants for OIE Reference Laboratory status*, which it had first updated at its January 2015 meeting. At this meeting, the Commission further modified the guidelines based on the current Terms of Reference and taking into consideration feedback received from the Council in February 2015. The Commission decided to include a paragraph on the timeline to receive applications: 45 days before the date scheduled for its August/September meeting. This deadline was set to provide sufficient time for the OIE to screen, translate when necessary, and process the dossiers, and for the members of the Commission to fully evaluate the applications prior to its meeting. Applications received after the deadline would be examined at the next August/September meeting of the Commission (see also agenda item 3.1). The Commission also amended the guideline to improve clarity. The document will be submitted to the Council and, if approved, would be uploaded onto the OIE website. The document can be found at Annex 4 for information.

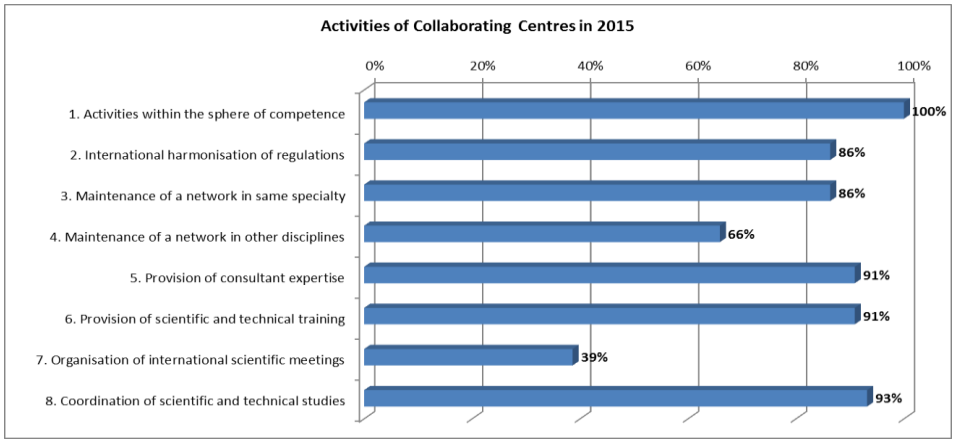
3.3. Annual reports of Reference Centre activities for 2015

Dr Min-Kyung Park, Scientific and Technical Department of the OIE, joined the meeting for this agenda item. Dr Park presented an analysis of the activities based on the annual report submitted by the OIE Reference Centres for terrestrial animals. As of 31 January 2016, 172 out of 211 (81.5%) Reference Laboratories and 33 out of 47 (70.2%) Collaborating Centres had submitted annual reports for 2015 to the OIE.

The activities relevant to the Terms of Reference of OIE Reference Centres for terrestrial animals are summarised in the following graphics overleaf.

The Commission expressed its on-going appreciation for the support and expert advice given to the OIE by the Reference Centres. The Commission appreciated the increase in the positive responses received regarding having an internationally recognised quality management system. With reference to the recommendation approved at the 3rd Global Conference of OIE Reference Centres, that: *"OIE Reference Centres achieve or maintain accreditation to the ISO 17025 or equivalent quality management system in their diagnostic laboratories"* (a 3-year deadline to achieve this standard was given for existing OIE Reference Laboratories, i.e. by end December 2017), the Commission is aware that the deadline is approaching and that it needs to develop a procedure to review and react to Reference Laboratories that do not meet the requirement on time. The Commission decided to follow-up on an individual-laboratory basis by electronic consultation in March 2016. A letter, including a reminder of the deadline to achieve or maintain accreditation to the ISO 17025 or equivalent quality management system, would be sent to those laboratories concerned.





3.4. Applications for OIE Reference Centre status

The Commission recommended acceptance of the following applications for OIE Reference Centre status:

OIE *Reference Laboratory for porcine reproductive and respiratory syndrome*
Veterinary Diagnostic Laboratory, China Animal Disease Control Center, NO.17Tiangui Street, Biomedical Base, Daxing District, Beijing 102618, CHINA (PEOPLE'S REP. OF)
Tel.: (+86-10) 59.19.88.98; Fax: (+86-10) 59.19.88.99;
E-mail: zhaixy2010@sina.cn
Designated Reference Expert: Dr Kegong Tian.

OIE *Reference Laboratory for rinderpest*
National Reference Laboratory for Rinderpest, Exotic Disease Research Division, National Institute of Animal Health (NIAH), National Agriculture and Food Research Organization, Josuihoncho 6-20-1, Kodaira, Tokyo, 187-0022, JAPAN
Tel.: (+81-42) 321.1441; Fax: (+81-42) 325.5122;
E-mail: yoshidak@affrc.go.jp; Website: http//niah.naro.affrc.go.jp/index.html
Designated Reference Expert: Dr Kazuo Yoshida.

OIE *Reference Laboratory for highly pathogenic avian influenza and Newcastle disease*
Laboratório Nacional Agropecuário em Campinas – Lanagro-SP, Unidade de Sanidade Aviária, Rua Raul Ferrari, s/n°, Jardim Santa Marcelina, CEP 13100-105, Campinas, SP, BRAZIL
Tel./Fax: (+55-19) 32.52.31.74 / 32.52.48.35;
E-mail: avi.lanagrosp@agricultura.gov.br; Website: http//www.agricultura.gov.br
Designated Reference Expert: Dr Dilmara Reischak.

An application had been received for an OIE Reference Laboratory for brucellosis (*Brucella abortus, B. melitensis, B. canis*) and another application from a different country for an OIE Reference Laboratory for classical swine fever. In both cases, a twinning project had previously been undertaken in the countries for these diseases, but the twinning projects had been with institutions other than the applicant laboratories. Given that the Internal Rules for OIE Reference Laboratories limits them to one per country per disease, the Commission would seek confirmation from the Delegates that the applicant laboratories were indeed the ones chosen in their countries to host an OIE Reference Laboratory.

An application had also been received for an OIE Reference Laboratory for infectious bursal disease. The Commission noted that the applicant had completed 2 years of a 3-year twinning project. It believed that it was too soon to review the application, but would welcome a submission once the twinning project is complete and the final report has been received and reviewed.

Another application had been received for an OIE Reference Laboratory for brucellosis (*Brucella abortus, B. melitensis*) following completion of a twinning project. The final report of the project identified some issues that the laboratory should address, for example the capacity to produce reagents for use in diagnostic tests. The Commission felt it was too soon to endorse the application, but would welcome a future re-submission after the laboratory has developed and strengthened its post-twinning activities.

Finally, a country had submitted the supplementary information requested in support of an application for an OIE Collaborating Centre for Management of Quality Systems in Testing Laboratories. The Commission found that the application still lacked sufficient evidence of sustained leadership in the region in the area of quality management systems. The Commission would suggest that the applicant expand its activities, in particular by providing proficiency panels and conducting proficiency tests for various diseases, by providing training courses on all the components of a quality management system, including on auditing and document management. The applicant needs to provide more evidence of its broad expertise and track record in its chosen specialty. The Commission did not yet endorse the application, but awaits more information on the items mentioned above.

The Commission noted that the following OIE Reference Centres had asked to be removed from the lists: OIE Reference Laboratory for Echinococcosis/hydatidosis at the Rakuno Gakuen University in Japan following the retirement of the designated expert; OIE Reference Laboratory for theileriosis at the Institute of Tropical Medicine in Antwerp, Belgium following the retirement of the designated expert; OIE Reference Laboratory for paratuberculosis at the Department of Economic Development, Jobs, Transport and Resources in Victoria, Australia following a change of role within the department of the designated expert; and the OIE Collaborating Centre for Research and Training in Population Animal Health Diagnosis and Surveillance Systems at the International Epilab, Technical University of Denmark in Copenhagen, Denmark due to lack of activity in this field.

The Commission also noted that there are currently no OIE Reference Laboratories for the following diseases and invites applications from Member Countries where expertise exists:

i) Old world screwworm (*Chrysomya bezziana*)
ii) Haemorrhagic septicaemia
iii) Nairobi sheep disease
iv) Porcine cysticercosis
v) Avian infectious bronchitis
vi) Avian infectious laryngotracheitis
vii) Duck virus hepatitis
viii) Fowl typhoid
ix) Pullorum disease

3.5. Changes of experts at OIE Reference Laboratories

The Delegate of the Member Countries concerned had submitted to the OIE the following nominations for changes of experts at eight OIE Reference Laboratories. The Commission recommended their acceptance:

Rift Valley fever and Crimean–Congo haemorrhagic fever
Dr Noël Tordo to replace Dr Michèle Bouloy at the Institute Pasteur, Paris, FRANCE.

Echinococcosis/hydatidosis
Dr Hamid Sahibi to replace Prof. Allal Dakkak at the Institut Agronomique et Vétérinaire Hassan II, Rabat-Instituts, MOROCCO.

Contagious bovine pleuropneumonia
Dr Massimo Scacchia to replace Dr Attilio Pini at the Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise (IZSAM), Teramo, ITALY.

Leptospirosis
Dr Marga Goris to replace Dr Rudy Hartskeerl at the Royal Tropical Institute (KIT), Amsterdam, NETHERLANDS.

Avian chlamydiosis and Enzootic abortion of ewes (*Ovine chlamydiosis*)
Dr Christiane Schnee to replace Dr Konrad Sachse at the Friedrich-Loeffler-Institute, Jena, GERMANY.

3.6. Review of new and pending applications for laboratory twinning projects

Dr Gounalan Pavade from the OIE Scientific and Technical Department updated the Commission on the OIE Laboratory Twinning programme. As of 4 February 2016, 28 projects have been completed and 35 projects are underway.

In November 2015, the OIE conducted technical and financial audits of two twinning projects, namely UK – Botswana for avian influenza and Newcastle disease and Canada – Colombia for avian influenza and Newcastle disease. The Commission requested that the final audit reports of these two projects be shared with the Commission to update the members on the performance of the candidate laboratory.

In December 2015, the OIE adopted management procedures for the OIE Laboratory Twinning Programme, which includes a section on *Ethical rules and avoidance of conflicts of interest*. The President of the Commission should ensure that Commission members having a personal interest abstain from taking part in the procedure for reviewing and approving a Laboratory Twinning Project. If necessary, the President of the OIE Commission may consult and seek advice from the Director General of the OIE.

Two new twinning proposals were presented to the Commission for technical review.

- ***France – Kuwait*** for diseases of small ruminants (PPR and contagious caprine pleuropneumonia [CCPP]): the Commission supported the technical contents of this project and stressed that the work programme should include training on quality assurance and risk management in all steps of the project.

- The Commission reviewed another twinning project proposal and noted that the objective was uniquely to undertake an efficacy study of a recombinant capripox vaccine, which does not correspond to the usual objectives of the laboratory twinning programme, which are of improving capacity building and expertise. The Commission therefore did not consider that this project met the criteria of a laboratory twinning project, and did not support it.

Three twinning proposals were resubmitted following revision based on the Commission's comments made at the September 2015 meeting.

- ***UK/USA – India*** for rabies: the Commission approved the project's technical programme. To improve the project the Commission proposed that training in quality assurance be considered a higher priority in the project's programme. Stage three of the workplan should be further elaborated to include more information on the hands-on training of the candidate laboratory. The proposed start date (April 2016) for this project was confirmed.

- ***Italy – Brazil*** for bluetongue: the Commission reviewed the supplementary information requested regarding the facilities, research activities and publications of the Brazilian laboratory and on how this twinning project will improve the existing facilities. The Commission approved the technical contents of the project with the suggestion that the project focus on quality assurance and accreditation of its quality management system, consistent with its aim of achieving OIE Reference Laboratory status.

- At its last meeting, the Commission had reviewed a twinning proposal for bluetongue and West Nile fever in a country in Asia-Pacific and requested more justification on the rationale for this project. The Commission was not satisfied with the justification submitted and continues to maintain that West Nile fever is not a priority disease in the country. It also observed that the laboratory is already engaged in a similar twinning project on emerging infectious diseases that could very well cover the objectives of this project.

The Commission was presented with the full technical programme of the ***Italy – United Arab Emirates*** twinning proposal for camel diseases that was approved at the September 2015 meeting. The Commission commented that all the tests performed under this twinning project should be accredited to a quality management system from the beginning of the project.

3.7. Mission to candidate laboratory

In September 2015, an expert mission had been organised to evaluate the facilities at an institute that had applied to be recognised as OIE Reference Laboratories for Avian influenza and Newcastle disease following a twinning project with the Istituto Zooprofilattico Sperimentale delle Venezie, Padua, Italy.

The Commission reviewed the report of the mission report, which documented improvements at the institute, for example in diagnostic capabilities. The report included a number of recommendations, which the Commission endorsed. Once the recommendations had been fully implemented, the institute would be in a position to submit a strengthened application for review. The Commission is particularly interested in two areas: the institute's capacity to receive samples and its quality management system (ISO 17025 or equivalent).

3.8. Offer from WHO to share tools for the implementation of a quality management system towards accreditation to ISO17025

A WHO Collaborating Centre in the Netherlands had developed a stepwise implementation tool for implementation of a quality management system toward accreditation to ISO 15189 for medical laboratories. The tool is available online for all laboratories. WHO asked if the OIE would be interested in developing a similar tool for veterinary diagnostic laboratories for accreditation to ISO 17025. The Commission felt that a number of such tools already exist and that those laboratories that need assistance to achieve ISO 17025 accreditation would be better served by undertaking a twinning project. Regarding collaboration with the WHO in the development of other laboratory tools, the members of the Commission would review existing WHO tools and take a decision at the next meeting in September.

As noted in the report of meeting of the Biological Standards Commission in February 2013, the OIE publication: OIE *Quality Standard and Guidelines for Veterinary Laboratories: Infectious Diseases*, 2008, had been withdrawn from sale and should therefore no longer current and should not be used in accreditation programmes.

4. *Ad hoc* Groups

- **Past *ad hoc* Group meetings: reports for adoption**

4.1. Report of the meeting of the *ad hoc* Group on Replacement International Standard Bovine Tuberculin, 24–26 November 2015

Upon receipt of assurances regarding the proposed procedure for producing the Replacement International Standard Bovine Tuberculin, the Commission adopted the report, which can be found at Annex 5 of this report.

4.2. Report of the meeting of the *ad hoc* Group on High Throughput Sequencing and Bioinformatics and Computational Genomics (HTS-BCG), 7–9 December 2015

Dr Peter Daniels briefed the Commission on this activity. The Commission supports the project to create an OIE Platform for the collection and management of genomic sequences in animal health and recommends that the OIE take it forward without too much delay. The Commission adopted the report, which can be found at Annex 6 of this report.

4.3. Report of the meeting of the *ad hoc* Group on Vaccination, 17–19 November 2015

See agenda item 8.1.1.

5. International Standardisation/Harmonisation

- **Diagnostic tests**

5.1. OIE Register of diagnostic kits

5.1.1. Update and review of applications

Dr François Diaz, Scientific and Technical Department of the OIE, updated the Commission on the current status of the dossiers submitted according to the OIE Procedure for Registration of Diagnostic Kits.

He informed the Commission that evaluation of the dossier on "BIONOTE® – Rapid MERS-CoV Ag test kit" had been completed. Based on the final report from the expert evaluation panel, the Commission provided a favourable opinion for the inclusion in the OIE register of this diagnostic kit with the following purposes:

The Bionote Rapid MERS-CoV Ag Test Kit is fit for the qualitative detection of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) antigens from nasal swab in dromedary camel for the following purposes:

i) Detection of MERS CoV infected herds (herd test) with acutely infected animals with high virus loads, e.g. during or shortly after the calving period;

ii) When used as a supplemental test, to estimate prevalence of infection to facilitate risk analysis, e.g. surveys, herd health schemes and disease control programmes.

Further to the approval of the OIE Director General, this would be proposed for adoption by the Assembly at the General Session in May 2016.

An abstract sheet of the validation data of the "BIONOTE® – Rapid MERS-CoV Ag test kit" kit, drafted in collaboration with the diagnostic kit manufacturer and the expert evaluation panel, and endorsed by the Commission, is included at Annex 7 of this report.

According to the procedure, each kit included in the OIE Register must have its registration renewed every 5 years. Dr Diaz informed the Commission that one diagnostic kit (*Mycobacterium bovis* Antibody Test Kit), added to the OIE Register in 2012, was reaching the end of the 5-year term; the renewal would take place under the aegis of this Commission. In accordance with protocol, the kit manufacturer had been contacted to indicate whether it wished to maintain the same purposes for which its kit had been certified as validated or to add new purposes. The OIE experts for the diseases targeted by the kit had also been contacted and asked their opinion on the need for a new evaluation of the purposes for which the kit had been certified as validated. Based on this information, the Commission decided to propose to the vote of the Assembly in May 2017 the renewal of the registration of the *Mycobacterium bovis* Antibody Test Kit in the OIE register for the same purposes and for 5 additional years.

5.2. Standardisation programme

5.2.1. Update on progress on developing guidelines for antigen standards

Dr Peter Daniels had begun to draft guidelines for the preparation and validation of antigen standards but due to the complexity of the subject matter further inputs are required. Dr Anthony Fooks would now assist in progressing the draft document.

5.2.2. Need for guidelines for other reference standards

The Commission agreed that guidelines for the preparation and validation of reagents for molecular tests were useful, and identified an OIE Reference Laboratory expert who will be approached to assist with their preparation.

5.2.3. Project to establish a virtual OIE Biobank: next steps

Since the last meeting in September 2015, a questionnaire had been sent to those OIE Reference Centres that had indicated previously that they have a biobank to collect information on their IT (information technology) systems, and also to collect any datasheets the Centres have for their biological resources. Dr Maura Ferrari of the OIE Collaborating Centre for Veterinary Biologicals Biobank had analysed the responses and found that around 50% of these Reference Centres do not have a computerised system for managing biological resources. Another known difficulty in the establishment of a biobank is the variation in national laws and local practices regarding processing and storage of biological samples, and in the specific information that should be provided with samples. Based on this information, the Commission recommended that an *ad hoc* Group be convened and proposed the following draft principal Terms of Reference:

i) identify which types of biological material should be included in the OIE biobank;

ii) define the quality requirements;

iii) define the metadata attached to the biological material;

iv) review the IT options and propose preferred option;

v) propose standard MTA;

vi) define the steps that are needed for implementation of the biobank database.

The Commission is aware of other existing projects, such as EVAg[5], which will come to an end in 4 years' time, and of the various problems of maintaining and sustaining operable biobanks. OIE Reference Laboratories are mandated to develop reference materials, so it would be an expectation of the OIE that the Reference Laboratories provide information on the reagents they produce that could be included in the OIE biobank. The Commission felt that the development of an OIE material transfer agreements (MTA) could be useful if it were to speed up transfer of materials between OIE Reference Laboratories, but acknowledged that for legal reasons Member Countries may not use it.

- **Biosafety/Biosecurity**

5.3. Feedback on ISO Technical Committee meeting, 11–13 November 2015, Geel, Belgium

Dr Diaz informed the Commission about the follow-up meeting of the joint project between ISO/TC 212 (Standardization and guidance in the field of laboratory medicine and *in vitro* diagnostic test systems) and ISO/TC 34 (Food products) intended to convert the CEN Workshop Agreement 15793 (CWA 15793) on Laboratory Biorisk Management to an ISO deliverable (ISO 35001 document) for all laboratories and related facilities that handle, store, transport, or dispose of biological agents or toxins, including veterinary laboratories.

6. Resolutions for the General Session

6.1. Resolutions that will be presented in May 2016

The Commission noted that the following resolutions would be proposed for adoption at the General Session in May 2016:

- A resolution proposing the adoption of the 20 draft chapters and one validation guideline for the *Terrestrial Manual*;
- A resolution proposing the new OIE Reference Laboratories;
- A resolution proposing the addition of two diagnostic kits to the OIE Register and the renewal of an already registered kit.

7. Conferences, Workshops, Meetings

7.1. Update on training for Focal Points for Veterinary Laboratories

Dr Diaz informed the Commission that the next first-cycle regional training seminar (Asia and the Pacific region) for OIE National Focal Points for Veterinary Laboratories will be held in Republic of Korea in April 2016. He briefly presented the provisional programme. He also provided the dates of the next regional training seminars to be organised in 2016 for the Americas and African regions so that a member would attend these meetings as a representative of the Commission and a speaker on relevant topics.

7.2. COMPARE meeting

Dr Franck Berthe and Dr Elisabeth Erlacher-Vindel briefed the Commission on the COMPARE[6] initiative. Founded in 2014, COMPARE is a European Union funded project for the detection of emerging and foodborne diseases using advanced technologies such as HTS-BCG. Both the OIE and EFSA[7] are represented on the advisory panels. COMPARE is a flexible information-sharing platform linked to the GMI[8] initiative (see agenda item 7.3). Dr Erlacher-Vindel will report on developments at the next Commission meeting in September.

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5 EVAg: European Virus Archive goes Global

6 COMPARE: COllaborative Management Platform for detection and Analyses of (Re-) emerging and foodborne outbreaks in Europe

7 EFSA: European Food Safety Authority

8 GMI: Global Microbial Identifier

7.3. GMI meeting, GMI9, 23–25 May 2016 at FAO[9] premises in Rome, Italy

Although the main focus of the GMI initiative is food safety, it also has activities in animal health and the OIE is a member of the Steering Committee. The next meeting will take place in May 2016 and a member of the Commission would attend this meeting as a representative of the Commission.

7.4. Update on 8th Meeting of the FAO/OIE Joint Advisory Committee on Rinderpest, OIE Headquarters, 4–5 November 2015

Dr Beverly Schmitt updated the Commission on this meeting.

At the General Session in 2015, the OIE Assembly adopted by Resolution approved rinderpest holding facilities. Since then, countries are being encouraged to send their isolates to one of these facilities where they will be sequenced and destroyed, and progress is being made in this area.

The Joint Advisory Committee (JAC) discussed the need for rapid molecular assays using non-infectious controls. Proposals from the holding facilities are being considered for approval by the Rinderpest Secretariat.

Finally, regarding an international preparedness plan, the FAO is working on the components of the contingency plan, including diagnostics and vaccine reserves.

8. Liaison with other Commissions

8.1. Horizontal issues among the Specialist Commissions

For this agenda Item the Commission was joined by Dr Etienne Bonbon, President of the OIE Terrestrial Animal Health Code Commission. Dr Bonbon updated the Commission on the current and future *Terrestrial Code* chapters that the Code Commission is working on for which input from the Biological Standards Commission is and will be requested.

8.1.1. Proposed *Terrestrial Code* chapter on vaccination: outline of chapter as developed by the *ad hoc* Group

Dr Franck Berthe presented the outcomes of the first meeting of the *ad hoc* Group on vaccination and the proposed outline of the chapter. The Commission provided some technical comments and agreed to review the draft chapter at its next meeting.

The Commission also commented on draft definitions proposed for inclusion in the chapter. These definitions would be cross checked with the *Terrestrial Manual* chapter on vaccine banks to ensure consistency. Once adopted, the definitions would be added to the *Terrestrial Manual* glossary.

Finally, the Commission amended its draft chapter on vaccine banks in the light of the *ad hoc* Group report (see also agenda item 2.2).

8.2. Scientific Commission for Animal Diseases (Scientific Commission)

Matters from the Scientific Commission to the Biological Standards Commission

8.2.1. Proposal to update the *Terrestrial Manual* chapter on lumpy skin disease

The Scientific Commission forwarded a request from an *ad hoc* Group to update the lumpy skin disease (LSD) chapter from the *Terrestrial Manual* in line with a proposed update to the *Terrestrial Code* chapter. The *Terrestrial Manual* chapter had been updated and was currently in the review cycle with the aim of proposing it for adoption in May this year. The Biological

[9] FAO: Food and Agriculture Organization of the United Nations

Standards Commission proposed that the update be provided to the *ad hoc* Group members to verify that the amendments they recommended had been addressed. If the chapter needed further important amendments, it would be put forward to the 2016/2017 review cycle.

Follow-up from last meeting

8.2.2. Practicability of requiring FMD vaccine manufacturers to supply sera for test calibration

At the last meeting in September 2015, the Biological Standards Commission reviewed the advice of the OIE Reference Laboratories for foot and mouth disease (FMD), regarding a proposal to amend the *Terrestrial Manual* chapter on FMD to include the requirement that vaccine manufactures provide, on request of the vaccine purchaser, post-vaccination sera produced during final product batch testing for potency. The Commission believed that it would be useful scientifically to have such sera and would request the OIE Reference Laboratories to update the *Terrestrial Manual* chapter to include this proposal.

At this February 2016 meeting, the Scientific Commission further proposed that the chapter mention that this serum could also be produced and distributed by OIE Reference Laboratories, while acknowledging the additional funding requirements of this request. The Biological Standards Commission agreed to this proposal; the OIE Reference Laboratories would be requested to include it in the *Terrestrial Manual* update.

8.2.3. Update on the revision of the bovine spongiform encephalopathy chapter in the *Terrestrial Manual* to include a description of the available tests to discriminate atypical from classical BSE

The Biological Standard Commission had agreed that the revision of the bovine spongiform encephalopathy (BSE) chapter of the *Terrestrial Manual* should include descriptions of the available tests able to discriminate atypical from classical BSE. The OIE Reference Laboratory experts had been asked to update the chapter to include information on the suitable tests to be used to discriminate atypical from classical BSE. The chapter had been circulated to Member Countries for first-round comment and would be proposed for adoption in May 2016.

8.2.4. Update on Replacement International Standard Bovine Tuberculin

See agenda item 4.1.

8.3. Terrestrial Animal Health Standards Commission

Matters from the Terrestrial Animal Health Standards Commission to the Biological Standards Commission

8.3.1. Infection with bluetongue virus

Member Countries had submitted a proposal to the Code Commission to exclude "non-pathogenic serotypes" of bluetongue virus (BTV) from *Terrestrial Code* Chapter 8.3 *Infection with bluetongue virus*.

The Code Commission had also received conflicting comments from Member Countries on the need to include or exclude naturally transmitted vaccine strains from the bluetongue case definition.

The Biological Standards Commission agreed to ask the experts on the *ad hoc* Group if any BTV strains are considered to be non-pathogenic, and also to request the scientific evidence for the continued exclusion of vaccine strains from the BTV case definition.

8.3.2. Infection with *Mycobacterium tuberculosis* complex (draft new Chapter 8.X.)

The Code Commission referred some Member Country comments on the rationale for listing New World camelids as "under study" in the case definition in the draft chapter the Infection with *Mycobacterium tuberculosis* complex. The Biological Standards Commission agreed to seek the advice of experts from the OIE Reference Laboratories and *ad hoc* Group on diseases of camelids.

Follow-up from last meeting

8.3.3. Discrepancies between the *Terrestrial Code* and *Terrestrial Manual* regarding collection and processing of bovine, small ruminant and porcine semen

In follow up to a Member Country comment that there are discrepancies between the *Terrestrial Code* and *Terrestrial Manual* regarding collection and processing of bovine, small ruminant and porcine semen, the Consultant Editor of the *Terrestrial Manual* had reviewed the chapters and written a report. The report was endorsed and provided to the Code Commission for consideration.

8.3.4. Definition of OIE Standard and OIE Guideline

See agenda item 2.1.1.

8.3.5. Update on the revised bovine spongiform encephalopathy chapter in the *Terrestrial Manual*

See agenda item 8.2.3.

8.3.6. Naming of diseases

See agenda item 2.1.3

8.3.7. Coordination of work programme between Code and Biological Standards Commissions

For future meetings, Dr Bonbon agreed to inform the Biological Standards Commission of which *Terrestrial Code* chapters had been identified by the Assembly for update, and of any other priorities.

Both Commissions would share their meeting agendas and any other information of importance.

9. Matters of Interest for Information

9.1. Update on OFFLU[10]

Dr Peter Daniels updated the Commission on OFFLU. Routine OFFLU activities have continued during the reporting period, including participation in the WHO Vaccine Composition Meetings (VCM) process, and meetings of the swine influenza technical activity and the influenza in wildlife technical activity.

It has been noted that although, through OFFLU, the animal health sector undertakes to report to the WHO on zoonotic influenza viruses being currently transmitted in livestock populations that in fact the number of isolates and associated genetic sequences reported by animal health sector to the public health sector is quite small. The data being made available from the animal health sector in support of pandemic preparedness may be considered to inadequately represent relevant influenza infections in animals. OFFLU must continue to advocate greater data and isolate "sharing" among its members, and request the formal assistance of the OFFLU parent organisations, the FAO and the OIE, to support these matters.

[10] OFFLU: Joint OIE-FAO Network of Expertise on Animal Influenza

9.2. Progress on implementation of a regional CBPP Scientific Network Pilot Activity Project

The Commission noted this activity.

9.3. GF-TADs (Global Framework for the Progressive Control of Transboundary Diseases) Sub-Regional Conference on Camel Diseases, Abu Dhabi, United Arab Emirates, 14–16 February 2016

Dr Mehdi El Harrak briefed the Commission on this upcoming meeting. Organised by the OIE Regional Representation for the Middle East, to bring together the network of expertise in this area and implement a regional camel disease control plan, Dr El Harrak will present the work of the OIE *ad hoc* Group on Diseases of Camelids. Within the next 3 years it is envisaged that an OIE Collaborating Centre for the Diagnosis and Control of Diseases of Camelids can be designated.

9.4. Update on Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Dr Gounalan Pavade updated the Commission on recent OIE activities on MERS-CoV.

In December 2015, the OIE participated in a WHO consultative meeting to develop a roadmap for research and product development against MERS-CoV. There was broad consensus within the scientific community that recent research findings show that dromedary camels are the main animal reservoir. The recommendations of the OIE *ad hoc* Group on MERS-CoV regarding further research studies in animals were shared. A number of diagnostic tests are available for MERS-CoV testing in animals, and validation of these tests is essential. A vaccination research trial in camels using modified vaccinia virus Ankara, which also provides protection against camel pox, has shown capacity to prevent MERS-CoV viral shedding in camels; more research is needed on its applicability.

In January 2016, the OIE assisted WHO in a high level mission to Riyadh, Saudi Arabia to monitor progress made by the Saudi Ministry of Health and the Ministry of Agriculture on the prevention and control of MERS-CoV. There is improved collaboration between both Ministries on investigating suspected camel-acquired human cases. The Ministry of Agriculture has initiated target-based surveillance in a number of camel farms and shared the data. It was recommended to reinforce collaboration on joint investigations of cases, research projects that address issues at the human–animal interface, and improving the diagnostic facilities at the veterinary laboratory level.

In January 2016, the OIE attended a meeting hosted by FAO on *Understanding MERS-CoV at the Animal–Human Interface*. FAO is embarking on a field programme in collaboration with various institutes to better understand the disease dynamics at the interface between humans and camels in Africa and the Middle East. The creation of a scientific MERS-CoV network based on the OFFLU network model was discussed and will be explored further. The animal health community is looking forward to an updated case definition for reporting positive MERS-CoV in camels to the OIE based on recent research findings.

The need for an *ad hoc* Group was discussed and the Commission decided not to take further action at this time.

9.5. Update on Ebola

Dr Mariano Ramos updated the Commission on an FAO Technical Meeting "Understanding Ebola Virus at the animal-human interface" that had been held at the FAO Headquarters in Rome, Italy, 19–20 January 2016. One of the purposes of the meeting was to better understand the disease dynamics at the interface between animals and humans through sharing information on ongoing research projects and studies on the role of livestock and wildlife in the epidemiology of Ebola virus disease. Knowledge gaps in the disease dynamics at the human-wildlife-animal interface were also identified.

The need for an *ad hoc* Group to review diagnostic tests used in animals was discussed and the Commission decided not to take further action at this time.

10. Any Other Business

10.1. Workplan

The updated work plan was agreed and can be found at Annex 8.

10.2. Dates of the next Biological Standards Commission meeting

The Commission noted the dates for its next meeting: 30 August – 2 September 2016.

11. Adoption of the Report

The report was adopted by the Commission.

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.../Annexes

Annex 1

MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION

Paris, 2–5 February 2016

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Agenda

1. Brainstorming: In-depth discussion on the Commission's activities, modus operandi and working procedures

2. *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*

2.1. Extensive review of the structure and content of the *Terrestrial Manual*
2.2. Review of first-round Member Country comments on draft chapters
2.3. Terms from Validation Guideline 3.6.8 proposed to be added to the glossary
2.4. Proposal to include in the *Terrestrial Manual* oral vaccination of dogs against rabies
2.5. Request for review of the vaccine section of the chapter on Rift Valley fever
2.6. Question regarding the primer sequence given in the peste des petit ruminants chapter
2.7. Review of draft form for submission of new test methods and validation data
2.8. Validation dossier for a group-specific real-time reverse-transcription polymerase chain reaction (RT-qPCR) for African horse sickness virus (AHSV)
2.9. Comment from Singapore on equine diseases

3. OIE Reference Centres

3.1. Extensive review of the approval and maintenance of Reference Centre status procedures
3.2. Specific issues related to Reference Centres: guidelines for applicants
3.3. Annual reports of Reference Centre activities for 2015
3.4. Applications for the status of OIE Reference Centre
3.5. Changes of experts at OIE Reference Centres
3.6. Review of new and pending applications for laboratory twinning projects
3.7. Mission to candidate laboratory in Vladimir, Russia
3.8. Offer from WHO to share tools for the implementation of a quality management system towards accreditation to ISO17025

4. *Ad hoc* Groups

Past *ad hoc* Group meetings: reports for adoption

4.1 Report of the meeting of the *ad hoc* Group on Replacement International Standard Bovine Tuberculin, 24–26 November 2015
4.2 Report of the meeting of the *ad hoc* Group on High Throughput Sequencing and Bioinformatics and Computational Genomics (HTS-BCG), 7–9 December 2015
4.3. Report of the meeting of the *ad hoc* Group on Vaccination, 17–19 November 2015

5. International Standardisation/Harmonisation

- **Diagnostic tests**

5.1. OIE Register of diagnostic kits
  5.1.1. Update and review of applications
5.2. Standardisation programme
  5.2.1. Update on progress on developing guidelines for antigen standards
  5.2.2. Need for guidelines for other reference standards
  5.2.3. Project to establish a virtual OIE Biobank: next steps

- **Biosafety/Biosecurity**

5.3. Feedback on ISO Technical Committee meeting, 11–13 November 2015, Geel, Belgium

6. Resolutions for the General Session

6.1. Resolutions that will be presented in May 2016

7. Conferences, Workshops, Meetings

7.1. Update on training for Focal Points for Veterinary Laboratories
7.2. COMPARE meeting
7.3. GMI (Global Microbial Identifier) meeting, GMI9, 23–25 May 2016 at FAO premises in Rome, Italy
7.4. Update on 8th Rinderpest Joint Advisory Committee Meeting, OIE Headquarters, 4–5 November 2015

8. Liaison with other Commissions

8.1. Horizontal issues among the Specialist Commissions
  8.1.1. Proposed *Terrestrial Code* chapter on vaccination: outline of chapter as developed by the *ad hoc* Group
8.2. Scientific Commission for Animal Diseases
  8.2.1. Proposal to update the *Terrestrial Manual* chapter on lumpy skin disease
  Follow-up from last meeting
  8.2.2. Practicability of requiring FMD vaccine manufacturers to supply sera for test calibration
  8.2.3. Update on the revision of the bovine spongiform encephalopathy chapter in the *Terrestrial Manual* to include a description of the available tests to discriminate atypical from classical BSE
  8.2.4. Update on Replacement International Standard Bovine Tuberculin
8.3. Terrestrial Animal Health Standards Commission: joint meeting with the President
  8.3.1. Infection with bluetongue virus
  8.3.2. Infection with *Mycobacterium* tuberculosis complex (draft new Chapter 8.X.)
  Follow-up from last meeting
  8.3.3. Discrepancies between the *Terrestrial Code* and *Terrestrial Manual* regarding collection and processing of bovine, small ruminant and porcine semen
  8.3.4. Definition of OIE Standard and OIE Guideline
  8.3.5. Update on the revised bovine spongiform encephalopathy chapter in the *Terrestrial Manual*
  8.3.6. Naming of diseases
  8.3.7. Coordination of work programme between Code and Biological Standards Commissions

9. Matters of Interest for Information

9.1. Update on OFFLU
9.2. Progress in implementation of regional CBPP Scientific Network Pilot Activity Project
9.3. GF-TADs (Global Framework for the Progressive Control of Transboundary Diseases) Sub-Regional Conference on Camel Diseases, 14–16 February 2016
9.4. Update on Middle East respiratory syndrome coronavirus (MERS-CoV)
9.5. Update on Ebola

10. Any Other Business

10.1. Workplan
10.2. Dates of the next Biological Standards Commission meeting: 30 August – 2 September 2016

11. Adoption of the report

Annex 2

MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION
Paris, 2–5 February 2016

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Annex 3

FORM FOR SUBMISSION OF A NEW TEST METHOD FOR THE OIE *MANUAL OF DIAGNOSTIC TEST METHODS AND VACCINES FOR TERRESTRIAL ANIMALS*

Chapter 1.1.5 *Principles of validation of diagnostic assays for infectious diseases* of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* should be read (available on the OIE website at: http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/). It deals with principles of validation and therefore could be helpful when filling in this form. Further guidance is given in the set of *Validation Guidelines* in Part 3 of the *Terrestrial Manual.*

Test should be described in sufficient detail to enable a laboratory to set it up and validate it for local use. Therefore a stepwise description of the procedure should be provided

All test descriptions should include (when relevant):

- Type of the test method
- Intended purpose(s) (The diagnostic test method needs to be defined in terms of a purpose, target animal species, target pathogen(s) and target specimen(s))

  The most common purposes are:

  1. Population freedom from infection (non-vaccinated animals)
  2. Individual animal freedom from infection prior to movement
  3. Contribute to eradication policies
  4. Confirmation of clinical cases
  5. Prevalence of infection – surveillance
  6. Immune status in individual animals or populations post-vaccination

- Special precautions required for sampling
- Protocol including: Preparation of antisera, antigens, primers, etc. / Availability of international standards / Incubation times/temperatures / Essential equipment, reagents and supplies / pH and molarity of buffers / units of biological activity / washing techniques
- interpretation of the results
- "DIVA" tests for differentiating vaccinated from infected animals may be used and will usually fall within one or more of the above purposes. Their performance characteristics should be aligned with the appropriate vaccine which should be described in section C of the relevant chapter of the *Manual.*

Any new test procedure proposed for inclusion in the chapter must be accompanied with a summary of its performance characteristics (see below the template for providing the performance characteristics). All reagents should be described with scientifically accurate generic names. Commercial names for reagents, diagnostic kits or vaccines should not be used.

For examples of diagnostic test method description, please see the part B of disease specific chapters of the *Manual of diagnostic tests and vaccines for terrestrial animals* (http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/)

TEMPLATE FOR PROVIDING THE PERFORMANCE CHARACTERISTICS

1. Analytical characteristics

1.1. Analytical sensitivity

The limit of detection (LOD) is a measure of the analytical sensitivity (ASe) of an assay. The LOD is the estimated amount of analyte in a specified matrix that would produce a positive result at least a specified percent of the time.

1.2. Analytical specificity

Analytical specificity (ASp) is the ability of the assay to distinguish the target analyte (e.g. antibody, organism or genomic sequence) from non-target analytes, including matrix components.

1.3. Repeatability

Repeatability is the level of agreement between results of replicates of a sample both within and between runs of the same test method in a given laboratory. Repeatability is estimated by evaluating variation in results of replicates.

2. Diagnostic characteristics

2.1. Cut-off determination (if relevant)

2.2. Diagnostic sensitivity

Proportion of known infected reference animals that test positive in the assay. The number of positive reference animals, used to calculate the diagnostic sensitivity, have to be mentioned.

2.3. Diagnostic specificity

Proportion of known uninfected reference animals that test negative in the assay. The number of negative reference animals, used to calculate the diagnostic specificity, have to be mentioned.

3. Reproducibility

Reproducibility is the ability of a test method to provide consistent results, as determined by estimates of precision, when applied to aliquots of the same samples tested in different laboratories, preferably located in distinct or different regions or countries using the identical assay (protocol, reagents and controls).

If it was not possible to undertake a full reproducibility study, at least preliminary reproducibility estimates of the candidate assay has to be done using the select panel of well-characterised samples to enhance provisional acceptance status for the assay. The candidate test method is then duplicated in laboratories in at least two different institutes, and the panel of samples is evaluated using the candidate assay in each of these laboratories, using the same protocol, the same reagents as specified in the protocol, and comparable equipment. This is a scaled-down version of the reproducibility study in Stage 3 of assay validation.

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Double-underlined text: BSC January 2015
Grey highlighted text: Council February 2015
Yellow highlighted text: BSC February 2016

Guidelines for applicants for OIE Reference Laboratory status

OIE Reference Laboratories must provide evidence of scientific leadership and of the capability to fulfil the ToR (*link to page with ToR*): all applicants should preferably be the national reference ~~laboratory and must demonstrate that they are a reference point for the disease in the region in question~~; they should be able to receive samples from other countries for diagnostic testing; they should demonstrate the capability and willingness to organise rather than just participate in proficiency tests; they should be capable of providing confirmatory diagnostic services, reference materials, training, etc., ~~internationally~~ internationally; and the designated expert should have a number of recent relevant publications in peer-reviewed journals.

Applications should be submitted 45 days before the date scheduled for the August/September meeting of the relevant Commission (Biological Standards Commission and Aquatic Animal Health Standards Commission for OIE Reference Laboratories terrestrial and aquatic animal diseases, respectively). The 45-day period gives the OIE sufficient time to screen, translate into English when necessary, and process the dossiers for the Commission's evaluation. Deadlines must be strictly observed to allow a full evaluation of the dossiers by the members of the Commission prior to its meeting. Applications received after the deadline are examined in the next August/September meeting of the Commission, after the General Session in May.

Applications shall be submitted in accordance with Article 1 of the Internal Rules and should include the following information:

1. Name of expert (a~~n informal~~ curriculum vitae using this template (*link to template provided*) ~~and documented proof of international recognition for his/her expertise, e.g. publications in peer-reviewed journals, awards, membership in high profile academic boards, should be included~~).

2. Name and address of laboratory (telephone and e-mail address [fax numbers or Web site, if available]).

3. Name of the Head of laboratory (Responsible Official).

4. ~~Relevant~~ Demonstrate that legal and budgetary provisions are in place that provide assurance on the sustainability and functioning of the laboratory.

5. Provide ~~D~~documented proof (certificates) of accreditation to the ISO 17025 or equivalent quality management system in diagnostic laboratories. *Reference made to the 3rd Global Conference of OIE Reference Centres*

6. Give details of ~~E~~experience in diagnostic testing for the disease according to the OIE Standards nationally ~~and internationally~~ and internationally (approximate number of tests performed annually for each technique).

7. Provide ~~A~~additional information on expertise in diagnostic techniques (agent characterisation techniques, molecular techniques, monoclonal antibody techniques, etc.), epidemiology and control of the disease.

8. Give details of ~~E~~experience in standardisation and validation of diagnostic tests.

9. Demonstrate ~~R~~reagent production capability (provide details of current stock of reagents for the disease).

10. Demonstrate ~~C~~capability for timely international shipment and receipt of samples in accordance with the requirements for postage and packaging of biological materials described in the *OIE Manual of Diagnostic Tests and vaccines for Terrestrial Animals*, and the *OIE Terrestrial Animal Health Code* or the *OIE Aquatic Animal Health Code*.

11. Provide ~~G~~guarantees to ensure that staff respect the confidential nature of certain subjects, results or communications.

12. Provide a list of ~~Current and~~ completed research and methods development projects on the disease, including a list of relevant publications.

13 Provide a list of ~~Organisation and participation in regular~~ inter-laboratory proficiency tests~~ing~~ that the laboratory regularly organises and participates in.

14. Provide a list of ~~C~~collaboration with other laboratories, centres or organisations.

15. Give details of ~~T~~training and consultation experience for the disease in the last 2 years (courses provided, number of people trained, examples of international consultation).

16. Provide a list of ~~Organisation and participation in~~ scientific meetings that the laboratory has organised and participated in.

17. Provide a list of ~~C~~contributions to the preparation or reviewing of reference documents (chapters for the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*, *OIE Manual of Diagnostic Tests for Aquatic Animals*, disease cards, etc.).

The application will be processed by OIE in accordance with Articles 2, 3 and 4 of the Internal Rules.

A short summary of activities of relevance to the status of OIE Reference Laboratory (no more than one page) should be included.

Applications must be no longer than 15–20 pages in A4 format, single-spaced using Times New Roman font size 10 pt. Relevant appendices (curriculum vitae of the proposed reference expert, accreditation certificates) may be attached to the core document. The core document must be prepared in one of the official languages of the OIE (English, French or Spanish).

Annex 5

Original: English
November 2015

REPORT OF THE MEETING OF THE OIE *AD HOC* GROUP ON REPLACEMENT OF THE INTERNATIONAL STANDARD BOVINE TUBERCULIN

Paris, 24–26 November 2015

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An *ad hoc* Group (AHG) on Replacement of the International Standard Bovine Tuberculin was convened at the OIE Headquarters from 24 to 26 November 2015.

The Agenda and List of Participants are given at Appendices I and II, respectively.

1. Opening

Dr Brian Evans, OIE Deputy Director General and Head of the Scientific and Technical Department, welcomed the participants of the meeting on behalf of Dr Bernard Vallat, Director General of the OIE, and of Dr Monique Eloit, Director General elect who would begin her 5-year term of office in January 2016. Dr Evans reminded the Group that the OIE is the international standard-setting organisation in the field of animal health and welfare. Dr Eloit's vision for the OIE Member Countries was to continue to strengthen its scientific excellence, credibility and integrity. Dr Evans reminded the Group of the importance of their task: an international standard tuberculin is an essential tool for OIE Member Countries to help them combat or eradicate bovine tuberculosis, a priority disease for both animal and human health.

2. Appointment of chairperson and rapporteur

The meeting was chaired by Dr Steven Edwards, and Prof. Glyn Hewinson was designated as rapporteur.

3. Presentations providing background information on the international standard bovine tuberculin

Presentations were given to the Group, the first by Dr Mei Mei Ho, MHRA-NIBSC[1], and the second by Dr Douwe Bakker, providing background information on the international standard bovine tuberculin (BIS) and the rationale for the requirement for a new standard.

In 1982, WHO[2] proposed the establishment of a BIS. The first BIS was originally produced in 1983 and donated by the Central Diergeneeskundig Instituut, Rotterdam, The Netherlands. It was evaluated on behalf of WHO by the Central Veterinary Laboratory (CVL), Weybridge, UK, through coordination of an international collaborative study, and was then adopted and designated by WHO. At that time (1986), CVL was a WHO Reference Laboratory for International Biological Standards. Subsequently, around 1999, CVL withdrew from that designation, and the role and all the reference materials, approximately 2900 ampoules of BIS, were transferred to MHRA-NIBSC, which is the leading WHO Collaborating Centre and International Laboratory for Biological Standards. The reference materials have subsequently been stored at –20°C and distributed on request by MHRA-NIBSC. The BIS is intended for use in the calibration of the contents of national or working standard preparations in International Units (IUs).

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1 Medicines and Healthcare products Regulatory Agency-National Institute for Biological Standards and Control, Potters Bar, Hertfordshire EN6 3QG, United Kingdom

2 World Health Organization

The BIS preparations have the following characteristics: they are contained in clear/neutral glass ampoules, formulated in glucose phosphate buffer containing phenol and have been lyophilised and sealed under vacuum. Each ampoule contains 1.8 mg (Standard Deviation [SD] 0.024%) of bovine PPD (purified protein derivative) equivalent to 58,500 IU. The ampoules are stored at –20°C in assured, temperature-controlled storage facilities and shipped at ambient temperature.

In view of the declining stocks of BIS, Dr Ho and Dr Bakker mentioned that a new standard was needed and that this would require an international collaborative study to determine the unitage and suitability of such a new replacement standard. Dr Bakker highlighted the considerable differences in tuberculin potency (100 fold differences) that have been observed worldwide emphasising the continuing requirement for a BIS and for more prescriptive tuberculin potency testing protocols.

Dr Bakker outlined the requirements for potency testing in guinea-pigs and mandatory testing in cattle in order to calibrate a new replacement BIS. As there are a limited number of laboratories that can carry out guinea-pig potency testing using live AN5, validation and subsequent adoption of the use of heat-killed *Mycobacterium bovis* AN5, rather than live *M. bovis* AN5, to sensitise guinea-pigs for the tuberculin potency test is necessary and would have several advantages in terms of greater reproducibility, safety and cost. Dr Bakker also reported the left-right effect observed for guinea-pigs in which the response is not bilaterally symmetrical and so a Latin square design for the inoculation sites in potency testing is essential. Dr Carmen Casal commented that in cattle the response to tuberculin varies depending on the position of injection in the neck and thus a Latin square design for potency testing is also essential. Additionally Dr Casal presented some differences in the protocols currently in use for the validation of the biological potency of bovine PPD and some discrepancies in the interpretation of the assays.

Finally, Dr Bakker drew the attention of the *ad hoc* Group to the sources of variation for the potency assays in guinea-pigs and cattle to help inform the subsequent design of the potency tests for a new replacement BIS. He highlighted that not all strains of *M. bovis* AN5 used by manufacturers were identical.

4. Presentations on the current status of the international standard bovine tuberculin

Dr Ho and Dr Bakker provided background information on the current situation regarding the existing BIS, which is now about 30 years old. Stocks are getting low and, in recent years, there have been concerns about the quality of some ampoules. The content of some concerned ampoules are no longer completely water soluble, some may contain nanoparticles, and some ampoules mayhave leaked and are in visibly poor condition due to increased moisture content. After visual inspections, approximately 1000 good ampoules are left. Over the past 2 years, 200 ampoules per year have been requested. At this rate the current stock will last 4–5 years.

5. Evaluation of the current situation regarding the availability of international standard bovine tuberculin

The Group reflected on the current situation regarding the availability of BIS.

The Group advised that the tuberculin skin test will be required as a front line test for the control of bovine tuberculosis for the foreseeable future. The Group also stressed that although the interferon gamma release assay (IGRA) is recommended as an adjunct to the skin test, the IGRA also relies on the use of bovine tuberculin. Thus without a suitable international standard, there is a serious threat for the future of bovine tuberculosis diagnosis and control.

The Group discussed the timescale that would be required to produce a new replacement BIS and noted that work should begin immediately on the production of a replacement to prevent supply of the current standard running out. In the meantime the Group recommended that the current BIS should be used sparingly as a primary reference preparation. Manufacturers should be encouraged to produce their own internal reference standards calibrated against the BIS.

In 1986, the OIE had not yet developed the concept of Reference Laboratories, let alone designated standard reference materials, so WHO was filling the gap by establishing certain veterinary reference materials, some of which continue to be managed by the WHO. With the strengthening of the OIE in recent years, and the stronger focus by WHO on human diseases (including One Health issues) the Group agreed that it seemed appropriate that any new International Standard Bovine Tuberculin should be evaluated and calibrated through an OIE agreed-led international collaborative study guided by a study expert panel that could be formed from the members of this *ad hoc* Group. This approach was supported by the WHO representative Dr David Wood.

The Group agreed that a new standard should be produced and that a sufficient number of final filled containers should be available to meet the estimated demand, preferably for the next 20 years, which is estimated to be about 5,000 ampoules. Each ampoule should contain 2 mg of protein of not less than 30,000 IU/mg. The bulk material should be produced from *M. bovis* AN5 using OIE-approved processes.

The Group recommended that a standardised panel of sensitising agents and defined protocols for potency assays should be produced and used for the international collaborative study.

In addition, a standard program for the analysis of parallel line assays should be used and the study expert panel should select the program to be used after comparative evaluation of available software packages.

The Group developed a tentative timescale for producing a new BIS shown below:

- Approval of the proposal for establishing a new replacement BIS, by OIE Biological Standards Commission – February 2016.
- Define selection criteria for bulk material – February 2016.
- The OIE write to manufacturers requesting bulk materials with a written submission including technical data and the OIE also write to preliminary testing Reference Laboratories – March 2016.
- Testing protocol defined by September 2016.
- Bulk material selected and supplied to MHRA-NIBSC – September 2016.
- Call for participants for International Collaborative Study – September 2016.
- Trial fill of ampoules - January 2017.
- Validation of trial fill preparation by two Reference Laboratories – September 2017.
- Definitive fill of about 5,000 ampoules – December 2017.
- Prepare standard immunisation doses – heat-killed *M. bovis* AN5 and live *M. bovis* AN5 strain for guinea-pigs – December 2017.
- International collaborative study – 2018.
- Written report submission to the OIE Biological Standards Commission January 2019 and endorsement by the World Assembly – May 2019.
- Peer-reviewed paper on characterisation of new replacement BIS.

6. Development of a protocol for evaluation and adoption of a new international standard bovine tuberculin

The Group developed a protocol for the evaluation and adoption of a new replacement BIS (see Appendix III).

7. Development of guidance and discussions on who could undertake the task and how this project could be funded

The Group noted a further issue: because of the nature of the proposed standard, it will be necessary to carry out animal studies in cattle and guinea-pigs, and that will cost considerably, as well as being quite a lengthy process. Ethical issues related to the 3Rs (replacement, reduction, refinement) should also be considered. This is going beyond the level of funding normally available to run a Reference Laboratory, and the OIE should therefore give consideration to how such a project could be funded bearing in mind the high importance of bovine tuberculosis to global animal and human health and the serious threat posed by the potential lack of

BIS as mentioned in Section 5 above. Two of the OIE Reference Laboratories are in Europe and one in the Americas. Some involvement from other regions would be essential. It should also be borne in mind that tuberculin (working product, not the international standard) needs a product licence/marketing authorisation in the countries where it is used. The standard therefore has to be designed with the requirements of regulators in mind.

8. Other matters

8.1. Alternative to tuberculin with other specific *Mycobacterium bovis* antigens and DIVA (detection of infection in vaccinated animals) strategy

Information had been submitted on a potential new approach to bovine tuberculosis diagnosis using defined *M. bovis* antigens. The Group considered that these show promise for the future, but that the antigen mixture does not correspond to tuberculin. This should therefore be considered as a new diagnostic approach. If it is intended to replace the current tuberculin test, it should be validated for this purpose according to the OIE validation pathway. Use as a DIVA test would require separate validation for that purpose.

9. Conclusions

9.1. Principle recommendations

The Group recommended that:

1. A new replacement BIS should be evaluated and calibrated through an international collaborative study, and then endorsed by the OIE Biological Standards Commission.

2. The current BIS should be used sparingly as a primary reference preparation. Manufacturers should be encouraged to produce their own internal reference standards calibrated against the BIS.

3. Members of this *ad hoc* Group should oversee the implementation of this study.

4. A standardised panel of sensitising agents and defined protocols for potency assays should be produced and used for the international collaborative study.

9.2. Other recommendations from the Group

The Group recommended that the section on tuberculin production and potency testing in the OIE *Terrestrial Manual* should be revised to be more prescriptive to reduce variation in the quality of PPD tuberculin and that the chapter should be updated using the current OIE template. Draft revision to the texts should be completed by September 2016. The Group also recommended that OIE Reference Laboratory experts and members of this *ad hoc* Group be asked to undertake this task.

The revision of the *Terrestrial Manual* chapter should take account of other national and international written standards.

The Group recommended that the OIE should inform the European Pharmacopoeia of the proposed new replacement BIS and also the intention to revise the *Terrestrial Manual* inviting them to coordinate revisions of their text with the updated OIE chapter.

The strain of AN5 used to produce tuberculin and for sensitisation in potency assays should be traceable to its original source. The Group recommended that the European Union Reference Laboratory for Bovine Tuberculosis (EURL) should hold stocks of the primary source of AN5 and that this strain should be sequenced.

The Group recommended reviewing the current status and future requirements for the Avian Tuberculin International Standard (AIS).

The Group recommended that studies to replace the use of live animals with *in-vitro* assays for future tuberculin standardisation should be encouraged.

The Group further recommended that the EURL should be encouraged to apply to be an OIE Reference Laboratory.

Finally the Group recommended that MHRA-NIBSC should continue to hold and distribute the new replacement BIS after its establishment.

10. Finalisation and adoption of the draft report

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

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…/Appendices

Appendix I

AD HOC ON REPLACEMENT INTERNATIONAL STANDARD BOVINE TUBERCULIN

Paris, 24–26 November 2015

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Agenda

1. Opening
2. Appointment of chairperson and rapporteur
3. Presentations providing background information on the international standard bovine tuberculin
4. Presentations on the current status of the international standard bovine tuberculin
5. Evaluation of the current situation regarding the availability of international standard bovine tuberculin
6. Development of a protocol for evaluation and adoption of a new international standard bovine tuberculin
7. Development of guidance and discussions on who could undertake the task and how this project could be funded
8. Other matters
9. Conclusions
10. Finalisation and adoption of the draft report

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Appendix II

AD HOC ON REPLACEMENT INTERNATIONAL STANDARD BOVINE TUBERCULIN

Paris, 24–26 November 2015

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Appendix III

Protocol for the evaluation and adoption of a replacement International Standard Bovine Tuberculin

The 1st International Standard for purified protein derivate (PPD) of bovine tuberculin was designated by WHO[3] in 1986 and is currently held at the WHO International Laboratory for Biological Standards, MHRA-NIBSC[4], UK. Due to the declining stocks of the International Standard Bovine Tuberculin, a proposal has been developed for the evaluation and calibration of a replacement standard. The aim is to produce a new International Standard Bovine Tuberculin sufficient to meet global requirements for the next 20 years. The task will require animal studies, and therefore funding. It is agreed that the OIE should take the lead in evaluating and designating the replacement standard. A study expert panel should direct and oversee the study. Partners in the study will include the OIE Reference Laboratories for bovine tuberculosis, other recognised experts, and MHRA-NIBSC (as holders of the current standard and experts in the evaluation, designation and storage of standard reference preparations). The protocol for the proposed study is given below.

1. Production

Tuberculin manufacturers will be invited to donate a bulk candidate material along with certificates of analysis that should include toxicity, sterility, sensitising effect, specificity and potency. At least two candidate materials will be selected for further processing and evaluation using methods that are in conformity with recognised production processes. The tuberculin will be obtained from the water-soluble fractions prepared by heating in free-flowing steam and subsequently filtering cultures of *M. bovis* strain AN5 grown in a liquid synthetic medium. The active fraction of the filtrate, consisting mainly of protein, will be isolated by precipitation, washed and re-dissolved in glucose-phosphate buffer without preservative. The final sterile preparation will be stored at MHRA-NIBSC as bulk material pending calibration of the new standard. A small number of lyophilised test ampoules, each containing 2 mg of protein, will be produced for initial analysis. The bulk stock of candidate preparations that give satisfactory performance in the preliminary evaluation will then be lyophilised into 2 mg ampoules. These will be used in an international collaborative study to determine the unitage/potency of the preparations, one of which will be selected as the replacement International Standard Bovine Tuberculin. It will be defined in International Units by calibration against the current Standard.

2. Preliminary evaluation

The aim of the preliminary evaluation is to validate the lyophilisation process and the suitability of the candidate preparations. One or two recognised Reference Laboratories for bovine tuberculosis will be invited to carry out a preliminary evaluation in guinea-pigs sensitised with inactivated *M. bovis* AN5 strain. They will be supplied with the current International Standard and the pre-lyophilised and freeze-dried preparations of the two candidate preparations, which will be evaluated as follows.

2.1. Potency

For each candidate preparation sensitise not fewer than nine albino guinea-pigs, each weighing 300 g to 500 g, by the deep intramuscular injection of a suitable dose of heat-inactivated *M. bovis* strain AN5 suspended in buffer and made into an emulsion with Freund's incomplete adjuvant. Not less than 4 weeks after the sensitisation of the guinea-pigs, shave their flanks to provide space for not more than four injection sites on each side. Prepare dilutions of the preparation to be examined and of the reference standard preparation using isotonic phosphate-buffered saline (pH 6.5–7.5) containing 0.005 g/litre of polysorbate 80. Use not fewer than three doses of the standard preparation and not fewer than three doses of the candidate preparation to be examined. Choose the doses such that the lesions produced have a diameter of not less than 8 mm and not more than 25 mm. Allocate the dilutions randomly to the sites using a Latin square design. Inject each dose intradermally in a constant volume of 0.1 ml or 0.2 ml.

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3 World Health Organization

4 Medicines and Healthcare products Regulatory Agency - National Institute for Biological Standards and Control, Potters Bar, Hertfordshire EN6 3QG, UK

Measure the diameters of the lesions after 24 to 28 hours and calculate the result of the test using the usual statistical methods and assuming that the diameters of the lesions are directly proportional to the logarithm of the concentration of the tuberculins.

The test is not valid unless the fiducial limits of error ($p = 0.95$) are not less than 50% and not more than 200 per cent of the estimated potency, where the stated potency of the standard represents 100%. The estimated potency is not less than 66 per cent and not more than 150 per cent of the stated potency. The stated potency is not less than 30 000 IU/mg.

The results and raw data will be submitted to MHRA-NIBSC for analysis and evaluated by the study expert panel.

This will require 38 albino guinea-pigs per laboratory.[5]

2.2. Specificity

The candidate standards are assayed against the standard for avian PPD tuberculin by a four-point assay in guinea-pigs sensitised with *M. avium* (strain D4ER), comprising two dilutions at 25-fold intervals of each tuberculin. Quantities of 0.03 mg and 0.0012 mg of test avian PPD tuberculin corresponding to approximately 1500 and 60 IU, are chosen because these doses give good readable skin reactions. In one assay, the candidate standards are compared with the International Standard Bovine Tuberculin in eight guinea-pigs by applying eight intradermal injections per animal and employing a balanced complete Latin square design. The reading of the results and the statistical evaluation are identical to the potency test. The response to bovine PPD in guinea-pigs sensitised with *M. avium* should be 10% or less in comparison with avian PPD.

This will require eight albino guinea-pigs per laboratory (16 in total).

3. International collaborative study

The study will be co-ordinated by MHRA-NIBSC under the guidance of the study expert panel and under the supervision of the OIE Biological Standards Commission. A questionnaire will be sent by MHRA-NIBSC to potential participants, including questions such as which potency assay they can perform using guinea-pigs or cattle, live or inactivated *M. bovis* sensitisation, and in the case of cattle with experimentally infected or natural reactors. Participants will also be asked their ability and willingness to perform the required assays using a common study protocol within a certain timeframe. The participation will be chosen by the study expert panel on the basis of the responses. The target number of participating laboratories would be as follows: 10 for guinea-pigs sensitised with live *M. bovis*, 10 for guinea-pigs sensitised with heat-killed *M. bovis* strain AN5, five for naturally sensitised reactor cattle and four for cattle sensitised by experimental infection. If these numbers are not achieved, the study expert panel will reconsider the study design.

3.1 Guinea-pig inactivated *M. bovis* sensitisation

Each participant will be asked to test each of the candidate preparations in three separate experiments. For each candidate preparation, sensitise not fewer than nine albino guinea-pigs, each weighing 300 g to 500 g, by the deep intramuscular injection of a suitable dose of heat-inactivated *M. bovis* strain AN5 suspended in buffer and made into an emulsion with Freund's incomplete adjuvant. A standard stock of inactivated AN5 will be distributed to participants in order to ensure conformity. Not less than 4 weeks after the sensitisation of the guinea-pigs, shave their flanks to provide space for not more than four injection sites on each side. Prepare dilutions of the preparation to be examined and of the reference preparation using isotonic phosphate-buffered saline (pH 6.5–7.5) containing 0.005 g/litre of polysorbate 80. Use not fewer than three doses of the reference preparation and not fewer than three doses of the preparation to be examined. Choose the doses such that the lesions produced have a diameter of not less than 8 mm and not more than 25 mm. Allocate the dilutions randomly to the sites using a Latin square design. Inject each dose intradermally in a constant volume of 0.1 ml or 0.2 ml. Measure the diameters of the lesions after 24 to 28 hours and calculate the result of the test using the usual statistical methods and assuming that the diameters of the lesions are directly proportional to the logarithm of the concentration of the tuberculins.

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5 The proposed numbers of animals include spares for contingencies.

The results and raw data will be submitted to MHRA-NIBSC for analysis and evaluated by the study expert panel.

This will require a total of 60 guinea-pigs per laboratory.

3.2 Guinea-pig live *M. bovis* sensitisation

As above, but instead of inactivated *M. bovis* AN5 sensitisation use deep intramuscular injection of 0.0001 mg of wet mass of living *M. bovis* AN5 suspended in 0.5 ml of a 9 g/litre solution of sodium chloride. Each participant will be asked to test each of the candidate preparations in three separate experiments.

The results and raw data will be submitted to MHRA-NIBSC for analysis and evaluated by the study expert panel.

This will require a total of 60 guinea-pigs per laboratory.

3.3 Reactor cattle

Cattle should be procured from field cases from infected herds that have reacted positively between 3 mm and 15 mm in the tuberculin skin test and positively in the interferon gamma release assay. They should be held in isolation for at least 8 weeks. The candidate preparations are assayed against the International Standard Bovine Tuberculin by a four-point assay using two dilutions at five-fold intervals of each candidate tuberculin. For the standard, 0.1 and 0.02 mg of PPD tuberculin are injected as these volumes correspond with about 3250 and 650 IU. The candidate preparations are diluted in such a way that the same weights of protein are applied. The injection volume is 0.1 ml, and the distance between the middle cervical area injection sites is 15–20 cm. In one assay, the candidate preparations are compared with the International Standard Bovine Tuberculin in ten reactor cattle, applying eight intradermal injections per animal in both sides of the neck, and employing a balanced complete Latin square design. The thickness of the skin at the site of each injection is measured with callipers in tenths of a millimetre, as accurately as possible before and 72 hours after injection.

The results are statistically evaluated using the same standard methods for parallel-line assays as employed in the potency tests in guinea-pigs. The results and raw data will be submitted to MHRA-NIBSC for analysis and evaluated by the study expert panel.

Each participant will be asked to test each of the candidate preparations in three separate experiments. This will require at least 30 reactor cattle of at least 6 months of age.

3.4 Experimentally infected cattle

Participants will be asked to propose their method of experimental infection, including the dose and strain of *M. bovis* to be used for sensitisation. At least 6 weeks post-inoculation, the tuberculin test is carried out as above. This will require at least 8 animals of at least 6 months of age.

The results and raw data will be submitted to MHRA-NIBSC for analysis and evaluated by the study expert panel.

Each participant will be asked to test each of the candidate preparations in three separate experiments. This will require at least 24 cattle of at least 6 months of age.

3.5 Stability testing

MHRA-NIBSC will prepare samples for the accelerated thermal stability test. Ampoules from final definitive fill preparations will be incubated at various temperatures (i.e. –20°C, 4°C, 37°C) for different durations (i.e. 3, 6, 12, 24 months). These samples will only require testing once by one Reference Laboratory using guinea-pig sensitised with heat-killed AN5. Depending on progress with the

international collaborative study, the longest duration of stability test may not be complete by the time that all other data in support of the adoption of the new standard are ready. In this case, samples from further time points can be tested after the adoption (this is a common practice for other standards).

A stability test on two candidate preparations, using three temperatures and four time points will require a total of 144 guinea-pigs, comparing samples of two incubation temperatures (4°C or 37°C) with the sample stored at –20°C.

4. Report of the international collaborative study

A draft report will be prepared by the study expert panel. A copy of the draft report is sent to each participant together with the code used to identify their own laboratory. The participants should confirm that:

i) Their data have been correctly interpreted in the analysis;

ii) The proposed material is suitable to serve as a reference standard for the purpose defined; and

iii) The proposed unitage is appropriate.

The final report will be submitted to the OIE Biological Standards Commission.

Annex 6

Original: English
December 2015

AD HOC GROUP ON HIGH THROUGHPUT SEQUENCING, BIOINFORMATICS AND COMPUTATIONAL GENOMICS (HTS-BCG)

Paris, 7–9 December 2015

The Third meeting of the OIE *ad hoc* Group (AHG) on High Throughput Sequencing, Bioinformatics and Computational Genomics (HTS-BCG) was convened at the OIE Headquarters from 7 to 9 December 2015.

The Agenda and List of Participants are given at Appendices I and II, respectively.

1. Opening

Dr Elisabeth Erlacher-Vindel, Deputy Head of the Scientific and Technical Department, welcomed the participants on behalf of Dr Bernard Vallat, Director General of the OIE, and of Dr Monique Eloit, Director General elect who would begin her 5-year term of office in January 2016. Dr Erlacher-Vindel explained that the specific task of the Group was to develop a clear and detailed plan on how the OIE Platform Project could be implemented: *Creation of an OIE platform for the collection and management of genomic sequences in animal health* to complement the epidemiological database within WAHIS[1].

2. Appointment of chairperson and rapporteur

The meeting was chaired by Prof. Massimo Palmarini, and Dr Antonino Caminiti was designated as rapporteur.

3. Update on actions taken since the last *ad hoc* Group meeting

At its last meeting in November 2014, the Group agreed that it would be worth developing specific standards for HTS-BCG for inclusion in the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*) to give guidance to potential users of the technology for purposes relevant to animal health. To this end an introductory chapter entitled *Standards for high throughput sequencing, bioinformatics and computational genomics* had been drafted and sent to OIE Member Countries in October 2015 for first-round comment. If the chapter is well received it could be proposed for adoption by the Assembly in May 2016.

The Group had also previously provided input on the programme for the 1-day OIE Seminar on *New Diagnostic Technologies and International Standard Stetting* that was held on 17 June 2015 in Saskatoon, Canada during the WAVLD[2] Symposium. The eleven presentations highlighted a spectrum of new tools, including HTS-BCG, along with their potential problems and challenges. These new technologies become even more robust when linked to epidemiological information. Participants found the seminar to be interesting, practical, timely and of scientific importance. The PowerPoint presentations and abstracts of the OIE seminar are available on the OIE Website at: http://www.oie.int/eng/WAVLD2015/presentations.htm.

1 WAHIS: World Animal Health Information System
2 WAVLD: World Association of Veterinary Laboratory Diagnosticians

4. Review draft work plan and assess what has been done and what steps are needed for implementation of the platform project

The Group took note of Recommendation 2 of Resolution No. 33, adopted by the OIE World Assembly in May 2015, which states: "The OIE establish a platform for the collection and management of partial and complete genomic sequences (including genotype assignment) with the aim to integrate the reporting of genomic sequence data into the OIE World Animal Health Information System (WAHIS), with the collective support of OIE Reference Centres, and involving all OIE Member Countries."

In accordance with this recommendation, the Group proposed that the initial model for the OIE platform be the creation of a centralised rather than a decentralised system.

The purpose of the OIE sequence database maintained within WAHIS is to provide a permanent and official record of the genetic sequences (preferably whole genome sequences) of the pathogens/infectious agents that have been the subject of Member Country reports to WAHIS, whether immediate notification or 6-monthly reports. (NB. The purpose of the OIE sequence database is NOT to be a full and complete record of the sequences of infectious agents detected in animal populations, but rather the record of the pathogens/infectious agents involved in animal health events reported by Member Countries.)

The Group suggested that the priority for the OIE be to establish this genomic platform managed by the OIE itself. The establishment of linked institutional databases and broader pathogen-specific databases connected to the platform would be a desirable objective to be left for a later stage once the platform has been established. These would require the full involvement of OIE Reference Centres and other communities of experts.

Modules with analysis tools will also be useful but are not essential for the initial stage of the project. However, modules to facilitate the upload of curated sequences at the local level might need to be considered within this project and will have to be considered for the implementation stage.

This approach best fulfils Resolution No. 33 and would also result in a focused and feasible project.

5. Assess the pilot project and detail the steps needed for implementation

Based on the Terms of Reference, the Group determined that the OIE platform project has two main goals:

1. Establishment of a pathogen genomic platform
   a) Refine the vision for the platform;
   b) Suggest next steps for its implementation.

2. Definition of standards to be used for the sequence information to be uploaded in the platform.

The Group agreed that the principal output of this meeting would be a revision of the draft pilot project. This document (see Appendix III) details the objectives, strategy and architecture of the OIE platform. The second output would be consensus comments on the draft *Terrestrial Manual* chapter. These comments, together with those submitted by OIE Member Countries, would be considered by the OIE Biological Standards Commission (BSC).

The practical recommendations for the establishment of the genomic platform are the following:

1. The appointment of a full-time Project Manager to work within the framework of the next version of WAHIS. The role of the Project Manager is to define the technical specifications of the genomic platform, including the system connectivity in the first instance. The Project Manager should be based at the OIE Headquarters working in close collaboration with the Information, Administration, Logistics and Publications Dept, World Animal Health Information and Analysis Dept and the Scientific and Technical Dept.

2. The *ad hoc* Group could provide guidance and support to the Project Manager and meet on a regular basis to follow up the project implementation. This would ensure close links with the BSC and transparency for the Member Countries.

3. Once the technical specifications of the project have been finalised, it should be put to tender within the WAHIS project.

Members of the Group discussed the draft *Terrestrial Manual* chapter and helped to identify steps in the process that were not yet fully covered in the text. The Group made appropriate recommendations, which will be considered in the process of overall review of the chapter. These included the necessity to clearly identify the purpose of the application of the technology, the appropriateness of the specimens for that purpose and the corresponding preparations of the samples for testing and the preparation and quality control of sequence data. A consolidated version of the chapter will be forwarded to the BSC for consideration along with Member Country comments.

6. Any other matters

None

7. Finalisation and adoption of the draft report

The AHG finalised and adopted the draft report.

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…/Appendices

Appendix I

AD HOC GROUP ON HIGH THROUGHPUT SEQUENCING, BIOINFORMATICS AND COMPUTATIONAL GENOMICS (HTS-BCG)

Paris, 7–9 December 2015

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Agenda

1. Opening
2. Appointment of chairperson and rapporteur
3. Update on actions taken since the last *ad hoc* Group meeting
4. Review draft work plan and assess what has been done and what steps are needed for implementation of the platform project
5. Assess the pilot project and detail the steps needed for implementation
6. Any other matters
7. Finalisation and adoption of the draft report

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Appendix II

AD HOC GROUP ON HIGH THROUGHPUT SEQUENCING, BIOINFORMATICS AND COMPUTATIONAL GENOMICS (HTS-BCG)

Paris, 7–9 December 2015

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List of participants

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Appendix III

AD HOC GROUP ON HIGH THROUGHPUT SEQUENCING, BIOINFORMATICS AND COMPUTATIONAL GENOMICS (HTS-BCG)

Paris, 7–9 December 2015

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Terms of Reference

1. Review draft work plan and assess what has been done and what steps are needed for implementation

2. Assess the pilot project and detail the steps needed for implementation

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Appendix IV

OIE PATHOGEN GENOMICS PLATFORM

CREATION OF AN OIE PLATFORM FOR THE COLLECTION AND MANAGEMENT OF GENOMIC SEQUENCES IN ANIMAL HEALTH

1. INTRODUCTION

The use of high throughput sequencing (HTS), bioinformatics, computational genomics (BCG) and metagenomics in the veterinary field is increasing. Sequence information is, therefore, increasingly playing a role in the diagnosis and management of microbial infections, in the characterisation of infectious agents, and the traceability of their spread over time.

The growing reliance on generating and using sequence information and the concurrent ever-increasing trend toward global open information systems will have crucial and far-reaching implications for veterinary laboratories, including the traditional notification and management of infectious diseases and food-borne infections.

The OIE has a leading and central role in the management, interpretation and use of information in animal health. The OIE also develops standards for the generation of data during investigations of animal infections on the farm and at any point along the "value chain" linking animals to consumers.

The OIE considers that pathogen genomic sequences and the associated sequence analysis data should be an integral and necessary part of the reporting of cases and outbreaks of disease at the international level. New technological tools, including HTS-BCG and metagenomics, should therefore be introduced and used in the context of accepted practices in animal disease diagnostic and control processes, including laboratory quality assurance systems.

Sequence data, in particular those referring to whole pathogen genomes, are very relevant not only in the epidemiological context but also in improving the understanding of disease pathogenesis and host responses. It can thus be envisaged that sequence databases of major veterinary pathogens will have an ever-increasing role in animal health especially if enriched by related metadata.

Strategies, policies and practices for analysing and managing genomic sequences and related metadata are, therefore, a priority on the OIE agenda. The primary objective is to develop a comprehensive approach and an *open access* database within the OIE World Animal Health Information System (WAHIS) to collect, store and share sequence information relating to animal disease events and their control. Additionally, it will be necessary to develop standards for the generation, storage, management and interpretation of sequences and their related epidemiological data.

The OIE intends to make full use of the competence and expertise of its worldwide Reference Centre network in the development of policies and practices for the management and use of sequence information. To this end, the OIE is developing standards for the management of HTS-BCG for inclusion in the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*). In the future, sequence data will be included in WAHIS and the OIE Reference Centre network will play a key role in this project.

2. DEFINITION OF THE OIE STRATEGY

The strategy of the OIE is to provide a permanent and official record of the genetic sequences (preferably whole genome sequences) of pathogens that have been the subject of country reports to the OIE (whether immediate notifications or 6-monthly reports). The OIE does not intend to provide a sequence database to be a full and complete record of the sequences of infectious agents detected in animal populations, but rather to provide a record of the pathogens/infectious agents involved in animal health events reported to the OIE by Member Countries.

The sequence information should be stored within WAHIS, which would then include two components: (i) the epidemiological database and (ii) the OIE pathogen genomics platform (hereafter referred to as the OIE platform). Each sequence will be systematically linked to the corresponding epidemiological information within WAHIS.

The overall strategy should include a process of defining standards for production, assembly and storage of genomic sequences to be integrated into the OIE *Terrestrial Manual* and the OIE *Manual of Diagnostic Tests for Aquatic Animals* (*Aquatic Manual*).

3. OVERVIEW OF THE OIE PLATFORM

The OIE platform will provide an open and transparent centralised system with the OIE Reference Laboratories or national reference laboratories generating and providing the genetic sequence information (hub–spoke model) under the responsibility of the OIE Delegate (Figure 1).

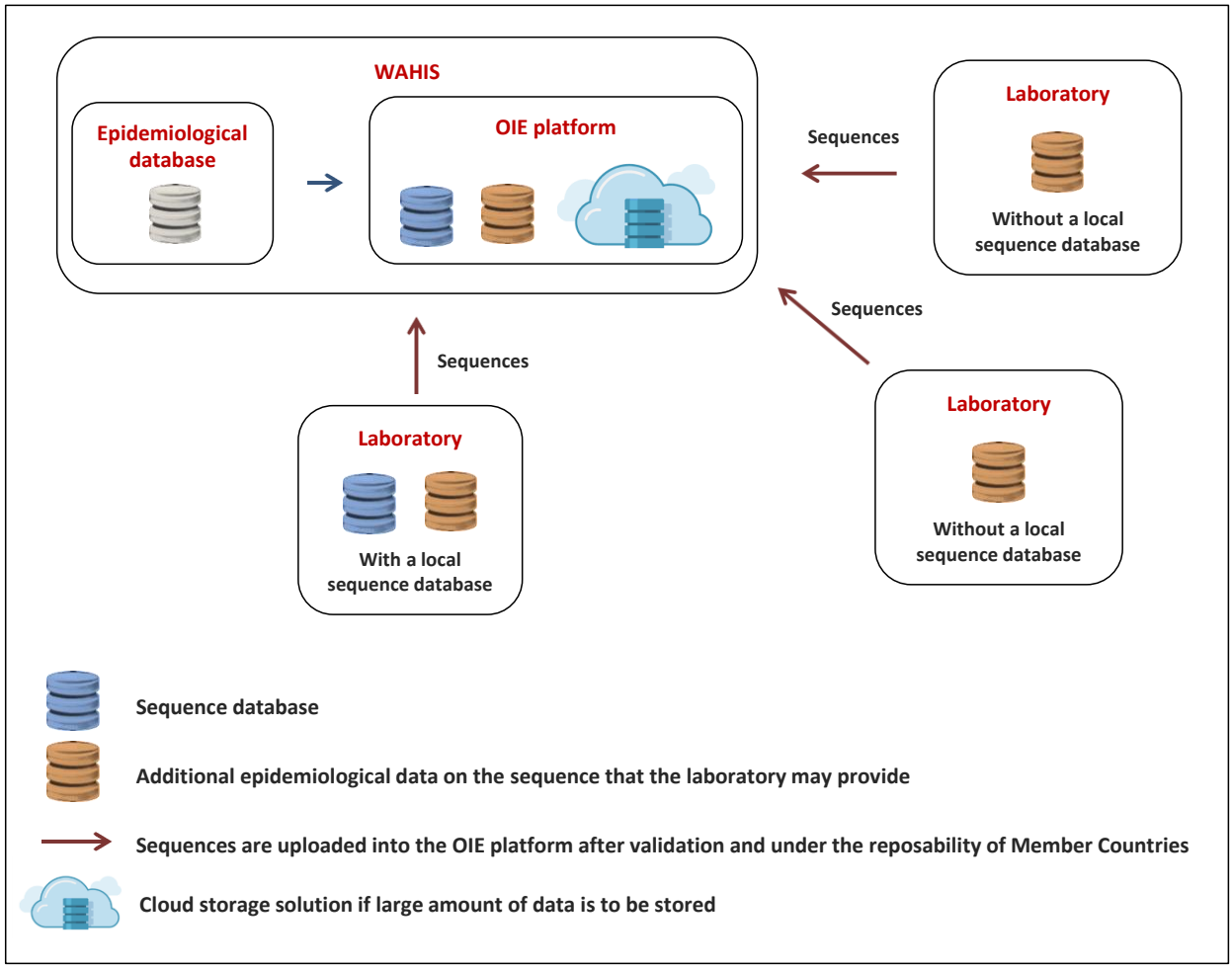


Figure 1. Overview of the OIE platform.

According to this model, laboratories may or may not host local databases and may or may not have the infrastructure to upload sequences to the OIE platform. Consequently, the OIE will provide web interfaces to upload sequences to the OIE platform, which is intended to be flexible and allow sequence submission in several ways.

WAHIS will link the epidemiological data with the corresponding pathogen sequences. However, from a structural point of view, the epidemiological database and the OIE platform will be separated to add flexibility to the overall system.

Member Countries will be responsible for the sequence submission to the OIE platform.

In compliance with the objective of the OIE to ensure transparency in animal health and the open access nature of data stored in WAHIS, sequence data stored in the OIE platform should be equally accessible.

The adoption of this model for the OIE platform does not preclude:

i) the establishment of separated local databases or pathogen-based databases maintained by the OIE Reference Centres. Indeed, the OIE encourages OIE Reference Centres to engage in networking activities and this would equally apply to such databases;

ii) the possibility that the OIE platform could provide services of different nature in the future (e.g. modules for data analysis provided by OIE Reference Centres or links to other resources of the OIE network).

The system design should be stable and robust but adaptable to evolving methodologies and technologies.

4. ARCHITECTURE OF THE OIE PLATFORM

The structure of the OIE platform (Figure 2) will consist of the following components:

i) Genomic sequence database linked, but structurally separated, to the epidemiological component of WAHIS;

ii) Interface module for uploading the sequence data;

iii) Connection module to link the genomic sequences to the corresponding epidemiological data stored in WAHIS;

iv) Administration module for data management, user access control and data workflow.

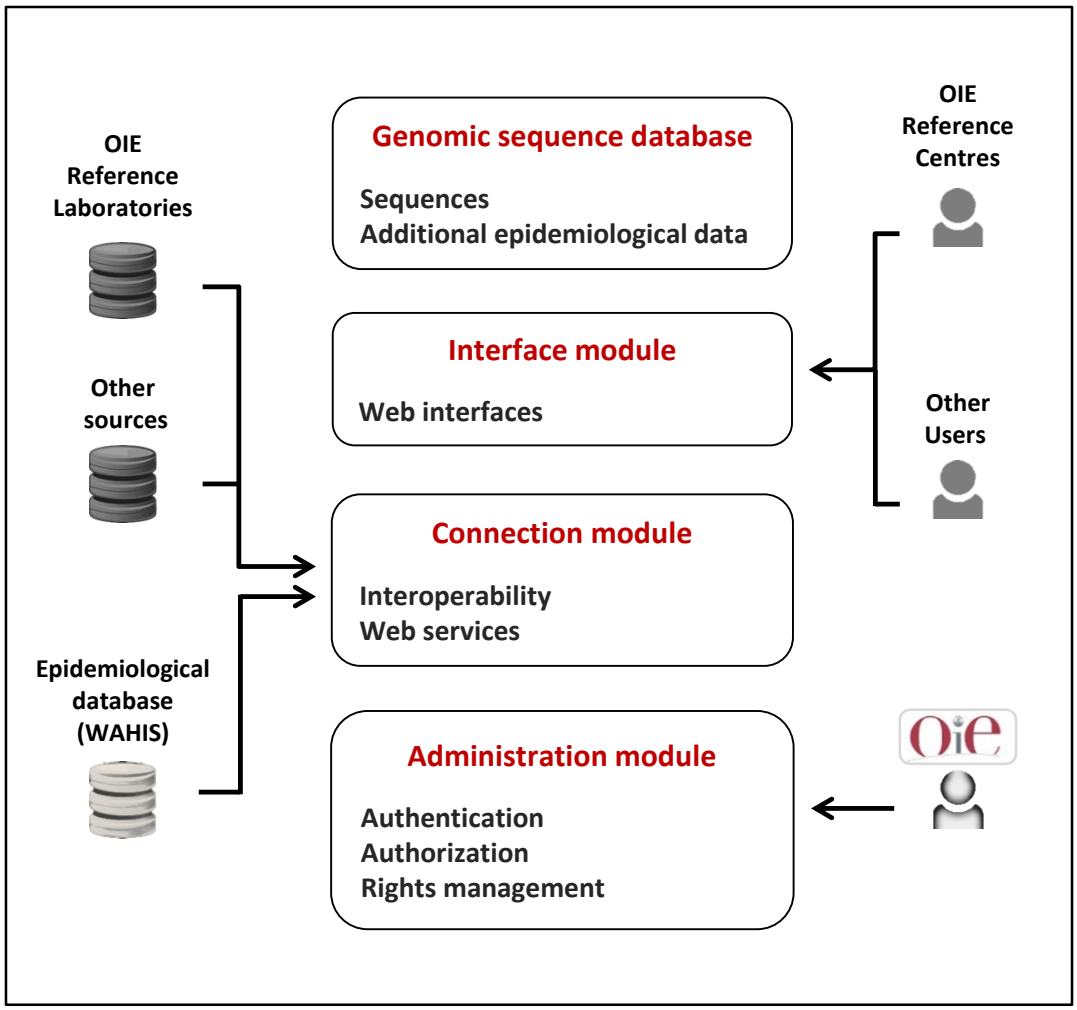


Figure 2. Architecture of the OIE platform.

5. COMPONENTS

5.1. Genomic sequence database

The genomic sequence database is the core component of the OIE platform. This database will allow genomic sequences to be stored, indexed, searched and available.

The database must support the complex and evolving set of data associated with the sequence and the sequence information itself. Sequence files are most naturally stored in a flat file format.

For each genomic sequence, the database will collect and store metadata on the technology and methodology used to generate the sequence data, and any additional epidemiological data that the submitting laboratory may decide to provide.

Data should be collected and stored in accordance with the standards outlined in chapter 1.1.11 of the *Terrestrial Manual* entitled *Standards for high throughput sequencing, bioinformatics and computational genomics*.

5.2. Interface module

The interface module will enable the laboratory to upload sequence data. Two prerequisites to upload a sequence to the platform are i) the creation of a link between the platform and the WAHIS, and ii) the meeting of standards set out by the OIE.

5.3. Connection module

The connection module is an interoperability module that assures the connectivity between the genomic sequence database with the epidemiological data stored in WAHIS.

5.4. Administration module

Similarly to the epidemiological component of WAHIS, the OIE platform will collect and store potentially sensitive information. This poses security challenges for the OIE platform. For this reason, it is important to implement an administration module and appropriate standards to manage the data at different levels and for different activities such as the uploading and access of the genomic sequences.

This module will guarantee compliance with quality requirements outlined in chapter 1.1.11 of the *Terrestrial Manual* during the uploading of the sequences, it will manage visibility and access of data, and it will trace information on the use of data. Issues surrounding intellectual property rights need to be addressed by the OIE and a common policy needs to be agreed.

Because the amount of sequence information will increase over time, the OIE platform must be extensible.

6. DATA FLOWS

The OIE requires that Member Countries notify any event of epidemiological significance (immediate notifications and follow-ups) and transmit periodic reports on the presence or absence of OIE listed diseases (6-monthly reports). Official communications between Member Countries and the OIE are subject to strict procedures, and the publication of data follows a series of steps before information is made public.

Figure 3 shows the current data flow of an immediate notification.

Following an immediate notification, OIE Member Countries will be required to upload to the platform the sequences of pathogens isolated in the outbreak (or in the group of outbreaks) reported in that notification. The requirement to provide sequence information should not delay the initial immediate reporting.

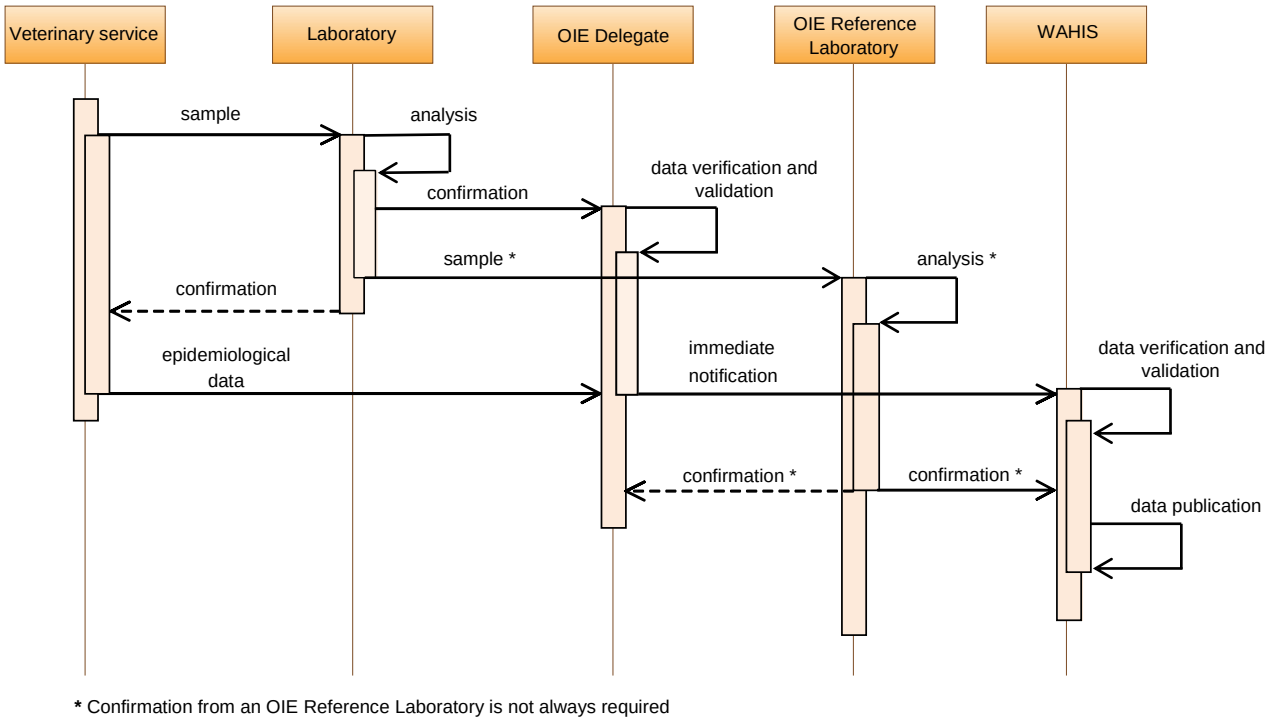
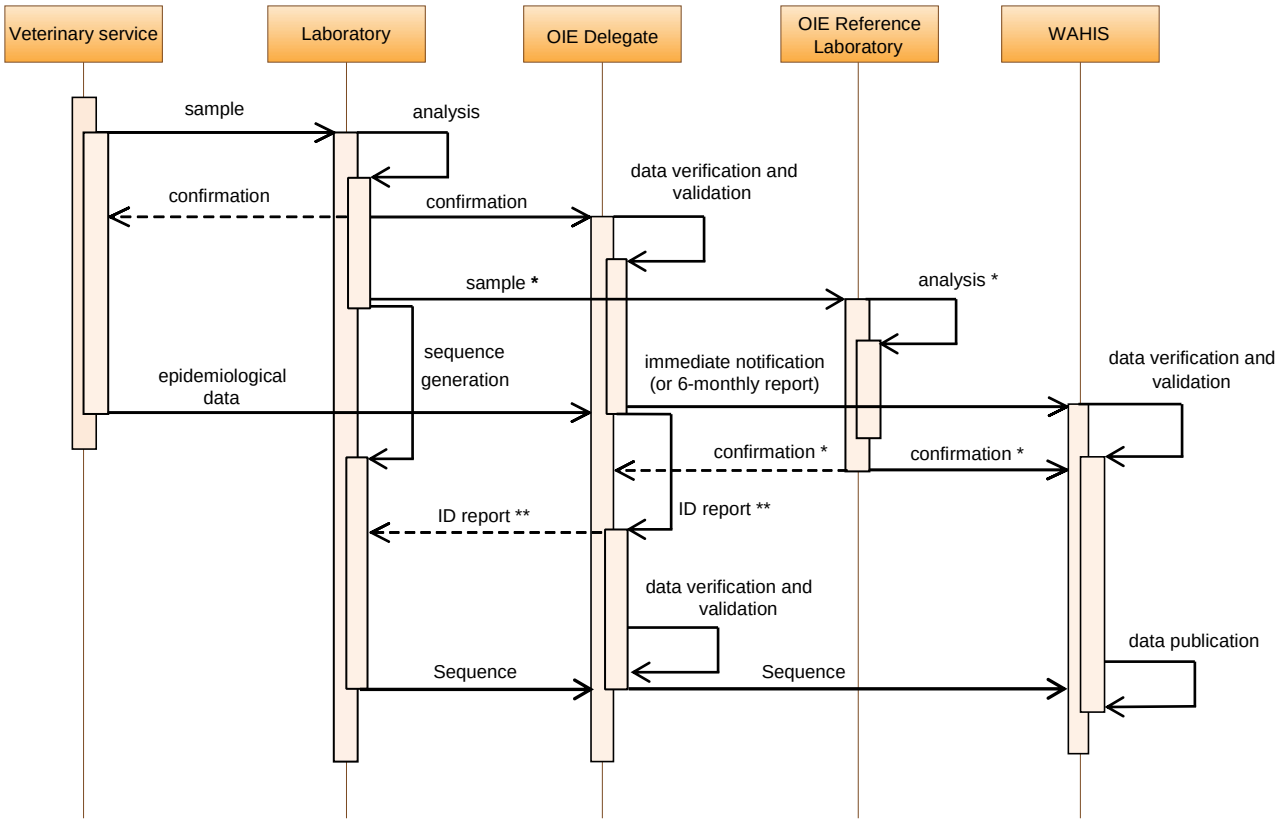


Figure 3. Current data flow of an immediate notification to OIE.

Figure 4 shows the possible data flow for the upload of the sequences following an immediate notification or related to the 6-monthly report. The sequence information should be transmitted through the OIE platform and linked to the corresponding epidemiological data in WAHIS (in the diagram, the box WAHIS includes the new OIE platform).



***** Confirmation from an OIE Reference Laboratory is not always required

** Or any other way to establish a link between the sequence and the corresponding epidemiological data stored in WAHIS

Figure 4. Suggested data flow in the proposed system for the upload of pathogen genomic sequences following an immediate notification (or related to a 6-monthly report)

Annex 7

OIE Procedure for Registration of Diagnostic Kits

Abstract sheet

Name of the diagnostic kit: BIONOTE® Rapid MERS-CoV Ag Test Kit
Manufacturer: BioNote, Inc.
OIE Approval number: xxxxx
Date of Registration: xxxxxx

Disease: Middle East Respiratory Syndrome

Pathogen Agent: Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Type of Assay: Immunochromatographic assay

Purpose of Assay: Certified by the OIE fit for the qualitative detection of Middle East Respiratory Syndrome Coronavirus antigens from nasal swabs in dromedary camels for the following purposes:

- Detection of MERS CoV infected herds (herd test) with acutely infected animals with high virus loads;
- When used as a supplemental test, to estimate prevalence of infection to facilitate risk analysis s, e.g. surveys, herd health schemes and disease control programs

Species and Specimen: Nasal swabs in dromedary camels

1. Information on the kit

Please refer to the kit insert available on the OIE Registry web page or contact manufacturer at:

Website link: www.bionote.co.kr

Email address: bionote@bionote.co.kr

2. Summary of validation studies

Analytical characteristics

Analytical sensitivity

BIONOTE® Rapid MERS-CoV Ag Test Kit detected up to 3.125 ng/ml of recombinant nucleocapsid antigen of MERS CoV.

Analytical specificity

Other coronaviruses such as bovine corona virus (vaccine and field strain), canine corona virus and feline corona virus did not react with this kit.

Repeatability data

Within run variation was assessed using quadruplicates of 5 inhouse samples (one strong, one medium, one weak and two negative samples) in four runs by one operator. Between run variation was assessed using triplicates of 5 inhouse samples in 30 runs by 3 operators on separate days. Batch-to-batch variation was assessed using 5 inhouse samples by 1 operator on one day. CV values were all below 5%.

Diagnostic Characteristics

Threshold determination

BIONOTE® Rapid MERS-CoV Ag Test Kit is a qualitative test. The presence of the purple line on both the control (C) and test (T) position is considered to be the threshold determination. The test sample is positive when two lines (C line and T line both) appear and negative when only the C lineappears. Lines consist of immuneo-reaction of the gold conjugate and target analytes. Gold conjugate consist of colloidal gold and MERS CoV antibody. The threshold is determined by the analytical sensitivity as 10^5 $TCID_{50}$ (50% Tissue Culture Infective Dose).

Diagnostic sensitivity (DSn) and specificity (DSp) estimates

Test method under evaluation		Target Species
Diagnostic sensitivity	N DSn CI	*(66)* *(93.9%)* *(85.20-98.32%)*
Diagnostic specificity	N DSp CI	*(523)* *(99.6%)* *(98.63-99.95%)*

Comparative performance

Summary		***UpE and Orf1A rRT-PCR***		***Total***
		POS	***NEG***	
BIONOTE Rapid MERS-CoV Ag Test Kit	*POS*	*62*	*2*	*64*
	NEG	*4*	*521*	*525*
Total		*66*	*523*	*589*

Reproducibility

The scope of this interlaboratory comparison was to determine the proficiency of the Real-Time PCR and the BIONOTE® Rapid MERS-CoV Ag Test Kit (BRM Kit) to detect MERS-CoV in real nasal swab samples collected in transport media in three participating laboratories.

[Test Date]: October 2015

[Test site]

Three laboratories participated in the International Inter-laboratory Comparison on the BIONOTE Rapid MERS CoV Ag Test Kit . (Participants also tested samples by Real Time PCR and results are shown for information only.)

1. Abu Dhabi Food Control Authority (ADFCA)
Location: United Arab Emirates
Status: Abu Dhabi
Level of expertise : highly trained technician
Accreditation status : ISO 17025

2. King Faisal University Laboratory (KFU)
Location: Kingdom of Saudi Arabia
Status: Al-Hasa
Level of expertise : highly trained technician
Accreditation status : ISO 17025

3. Molecular Biology & Genetics labortories (MBG)
Location: United Arab Emirates
Status: Dubai
Level of expertise : highly trained technician
Accreditation status : ISO 17025

[Materials]

Test panel information
The panel consisted of 6 positive and 4 negative samples. Samples were prepared from samples with known history. Samples were aliquoted in portions of 300µl and stored in 2ml vials. Test samples were prepared from nasal swabs from MERS positive and negative camels.

Shipping conditions
The samples were dispatched to the participants on the month of October 2015. Each participant received one box containing the test materials (Ten 2ml vials containing 300µl of each sample).

Samples were frozen and shipped with dry ice to the laboratories.

[Result]

BIONOTE® Rapid MERS-CoV Ag Test Kit

Samples were analyzed by each lab using BRM Kit and Real-Time PCR. BRM Kit results of three participants are illustrated in table 1 below.

Table 1. BRM Kit results of three participants

Sample No.	Targeted results (original)	KFU, Saudi Arabia	MBG LAB	VLD-ADFCA
1	Positive	Positive	Positive	Positive
2	Positive	Positive	Positive	Positive
3	Negative	Negative	Negative	Negative
4	Positive	Positive	Weak Positive	Positive
5	Positive	Positive	Weak Positive	Positive
6	Negative	Negative	Negative	Negative
7	Positive	Positive	Positive	Positive
8	Negative	Negative	Negative	Negative
9	Negative	Negative	Negative	Negative
10	Positive	Positive	Positive	Positive

Real-Time PCR test

Samples were also analyzed by the 3 participants using real time PCR. ADFCA (Abu Dhabi, UAE) real-time PCR results are based on UPE and Roche MERS-CoV qPCR kit in which the Orf la gene is targeted. KFU, (Saudi Arabia) real-time PCR results are based on UPE and CDC MERS-Co V qPCR kit in which the N2 gene is targeted. MBG, (Dubai, UAE) real-time PCR results are based on 2nd Derivative Max Analysis. Qualitative and quantitative Real-Time PCR results of each participant are given in table 2 below.

Table 2. Real-Time PCR result

Sample No.	KFU, Saudi Arabia			MBG LAB		VLD-ADFCA		
	Real-Time PCR-Result	CT Value UPE	CT Value N2	Real-Time PCR-Result	2nd Derivative Max Analysis	PCR-Result	CT Value UPE	CT Value ORF1a
1	Positive	21.33	16.65	Positive	19.59	Positive	23.65	24.1
2	Positive	16.01	15.97	Positive	19.61	Positive	23.34	23.84
3	Negative	No Ct	No Ct	Uncertain**	>35	Negative	No Ct	No Ct
4	Positive	19.95	18.16	Positive	21.2	Positive	24.8	24.68
5	Positive	25.9	19.03	Positive	21.15	Positive	24.89	24.51
6	Negative	No Ct	No Ct	Uncertain**	>35	Negtive	No Ct	No Ct
7	Positive	20.06	19.86	Positive	19.22	Positive	23.16	23.26
8	Negative	No Ct	No Ct	Uncertain**	>35	Negative	No Ct	No Ct
9	Negative	No Ct	39.95*	Unertain**	>35	Negative	No Ct	No Ct
10	Positive	22.16	18.95	Positive	20.84	Positive	24	23.87

* *Sample 9 gave an inconclusive Ct value of 39.95 in N2 qPCR, but no Ct in upE and therefore, it was considered as negative by KFU.*

** *For MGB lab the Ct value cut off is 35; any amplification beyond 35 is reported as inconclusive*

Application

Laboratory in which the kit is in current use.

Laboratory name: Veterinary Laboratories Division, Abu Dhabi Food Control Authority
Location: Abu Dhabi
Status: National Laboratory
Accreditation status: ISO 17025 accredited
Purpose of test: Screening (see also the purpose of assay)
Status of test: Supplementary

References

Song D, Ha G, Serhan W, Eltahir Y, Yusof M, Hashem F, Elsayed E, Marzoug B, Abdelazim A, Al Muhairi S. 2015. Development and validation of a rapid immunochromatographic assay for detection of Middle East respiratory syndrome coronavirus antigen in dromedary camels. *J. Clin. Microbiol.*, **53**:1178 –1182. doi:10.1128/JCM.03096-14.

Acknowledgement

Most of the validation studies were organised and performed by the Veterinary Laboratories Division of Abu Dhabi Food Control Authority (ADFCA), United Arab Emirates. BioNote thanks Dr. Salama, the director of Veterinary Laboratories Division, Animal Wealth Sector, ADFCA, UAE for continous support for this work.

Annex 8

BSC Work Plan: from February 2016

Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
Circulate the chapters approved by the BSC to Member Countries for second-round comment
Remind authors of the chapters identified previously for adoption in 2017 but not yet received
Commission the chapters for proposal for adoption in 2017 or 2018
Change title of Part 2 and Part 3
Review and update disease-specific chapter titles where necessary
Review guidelines (now chapters) in Part 3 and identify which should be moved to Part 1
Activities
Laboratories: guidelines for applicants, SOPs for approval and maintenance of Reference Centre status; evaluation criteria for on-site visits
Guidelines for the preparation and validation of reagents for molecular tests
Guidelines for the preparation and validation of antigen standards
Project to develop Replacement International Standard Bovine Tuberculin
OIE Platform for the Collection and Management of Genomic Sequences in Animal Health
***Ad hoc* Groups**
Virtual OIE Biobank
High throughput sequencing and bioinformatics and computational genomics (HTS-BCG)
Meetings
WAVLD, June 2017, Serronto, Italy