Summary of OFFLU TECHNICAL MEETING
Royal Holloway, University of London, UK
4 – 5 April 2012

List of participants:

Experts – Ann Cullinane (Ireland), Celia Abolnik (South Africa), Charlotte Houlsager (Denmark), Chris Morrissy (Australia), Christian Mathieu (Chile), David Suarez (USA), David Swayne (USA), Erica Spackman (USA), Frank Wong (Australia), Gaelle Simon (France), Giovanni Cattoli (Italy), Guus Koch (Netherlands), Hiroshi Kida (Japan), Hoang Dang Nguyen (Vietnam), Ian Brown (UK), Irit Davidson (Israel), Ilaria Capua (Italy), Jenny McKimm Breschkin (Australia), John Pasick (Canada), Les Sims (Australia), Lars Erik Larsen (Denmark), Marek Slomka (UK), Marisa Peyre (France), Mary Pantin Jackwood (USA), Magdy Hassa (Egypt), Nestor Alfonso Mosos Campos (Colombia), Nguyen Tung (Vietnam), Nichole Hines (USA), Nicola Lewis (UK), Nining Hartaningsih (Indonesia), Pastor Alfonso (Cuba), Paul Selleck (Australia), Richard Webby (USA), Ron Fouchier (Netherlands), Sasan Fereidouni (Germany), Sujira Parchariyanon (Thailand), Susan Trock (USA), Subhash Morzaria (FAO), Thierry van den Berg (Belgium), Thunai Obaid Al-Shekaili (UK), Tom Chambers (USA), Timm Harder (Germany), Veronique Jestin (France), Yashihiro Sakoda (Japan)

OFFLU Steering Committee - Steve Edwards (Chairman)
OFFLU Executive Committee - Peter Daniels (Chairman), Keith Hamilton (OIE) and Gwenaelle Dauphin (FAO)
OFFLU Scientist – Filip Claes (FAO)
OFFLU Secretariat – Gounalan Pavade (OIE)
WHO – Liz Mumford

Summary of main points:

Day 4 April 2012

Steve Edwards, Chairman of the OFFLU Steering Committee (SC), welcomed all the participants. Then Peter Daniels, Chairman of the OFFLU Executive Committee (EC), gave an overall introduction to OFFLU's technical activities, and experts leading each of these small working groups provided an update on progress.

Vaccination (David Swayne):

- Several activities have been completed, including:

    - OFFLU field projects in Indonesia and Egypt to provide recommendations on appropriate seed viruses for avian influenza (AI) poultry vaccines.
    - OFFLU review of AI control measures used during the past 10 years with a focus on vaccination – 2 papers have been published (Swayne and Pavade) and one is in the pipeline.
- On-going activities include a Vaccination Handbook (Marisa Peyre) which is currently a concept. It was agreed that the handbook would be of most value by focusing on practical principles rather than going into exhaustive details. The International Federation of Animal Health (IFAH) has agreed to take part of the preparation of the handbook.
- Proposals for future activities included:
    - A standing technical group to provide recommendations and assistance to countries on selection of seed viruses for AI poultry vaccines (subtypes H5, H7 and others). The group would be analogous to the OIE Equine Influenza Expert Surveillance Panel and the WHO GISRS network. Further work is needed to flesh out this proposal.
    - An OFFLU Vaccination meeting, as follow-up to the 2007 Verona Vaccination meeting. The meeting would focus on practical aspects (field application, vaccinating young birds, evaluation of field immunity), lessons learned, and on-going activities (Vaccine Handbook and seed virus selection group).

Action (DS and GD): To propose when and how OFFLU can hold an AI vaccination meeting and put forward a detailed proposal at the next OFFLU EC meeting.

Action (DS): To further scope the possibility of establishing a standing technical group to advice on seed viruses for AI poultry vaccines and put forward a proposal to the EC.

Action (MP): To finalise the table of content of the Vaccination Handbook and start receiving contributions from authors followed by feedback from reviewers.

Standard H5 antisera (Ian Brown):

- The technical activity works towards developing global reference standard sera for H5 influenza A virus through collaboration between OFFLU partners. This involves selecting broadly cross reactive and sensitive sera for a diverse panel of virus strains representative of all geographical regions. From this a reference standard antisera will be chosen for production and supply.
- Current status - antigens have been selected for raising large batches of standard H5 antisera, a small number of aliquots of the selected antisera have been received by the originating laboratories along with the homologous viruses.

Actions (IB):
1) Reference Antigens and proposed sera to be distributed to partners to test against panel of H5 antigens and sera held by partner laboratories, including new emerging clades of H5
2) Report to the OIE Biological Standards Commission
3) To determine those laboratories prepared to produce the reference sera and start production.
4) Global distribution of reference sera and antigens

RNA standard (Timm Harder):

- This OFFLU technical activity has been exploring the possibility of developing a universally usable RNA standard, initially for H5 avian influenza virus targeted PCR assays.
- Copy based standards are generally not required for diagnostic applications since most research groups have their own RNA standard. A switch of standards would require methodological adaptations and might challenge comparability.

Action (TH): The activity has concluded its mission to explore the possibilities of developing an RNA standard and has therefore achieved its objective. No further work is needed.

Action (GP): Post on website necessary information on how to obtain the RNA standard from Friedrich-Loeffler-Institute, creating visibility to the outputs of this work.

AI diagnostic ring trial (Nichole Hines/Timm Harder):

- Nichole Hines presented results from the first world-wide OFFLU AI ring trial for eight OIE AI Reference Laboratories and Collaborating Centres.
- Being the first such ring trial this was considered as a pilot.
- It was agreed that this was a most useful exercise and results highlighted several areas where improvements in diagnostic services may be achieved.
- Some refinements to the ring trial itself will be made based on experiences with this first pilot.
- Nichole Hines and Timm Harder were happy to continue to coordinate this activity.
- AAHL (Chris Morrissy, Peter Daniels) are willing to contribute to preparation of next ring trial (SE Asia materials).
- Results of regional proficiency testing coordinated by four Reference labs (AHVLA, USDA, IZSVe, AAHL) on PCR diagnosis were presented by Filip Claes.

Action (NH/TH): The AI ring trial activity to continue as a regular annual activity with on-going refinement to account for experiences and feedback from this first pilot.

Action (GP): Organize a teleconference with participants from the ring trial to clarify objectives and results, and to organize and plan next trial.

Code of conduct including PIP framework (Peter Daniels):

- The aim of the OFFLU Code of Conduct Group is to develop a an OFFLU code of conduct to facilitate, through a reliance on professionalism and trust, timely sharing of biological material and information whilst ensuring that all contributors are acknowledged in the benefits derived from that material or information.

Action (PD): OFFLU to progress further in developing an OFFLU recommended code of conduct for sharing of biological material and information.

The same OFFLU technical group to consider the implications of the WHO Pandemic Influenza Preparedness (PIP) framework on sharing of influenza biological material between animal health OFFLU laboratories and WHO GISRS laboratories through dialogue with WHO.

Update on Swine influenza virus (SIV) group activities (Richard Webby):

- Influenza surveillance in swine is important to better understand animal health and public health threats.
- Currently, SIV surveillance is patchy and underfunded. There are challenges to developing sustainable SIV surveillance.
- This OFFLU technical activity is working towards making a significant contribution to coordinating global SIV surveillance and to strengthening links between the animal health and public health sectors.
- At the latest SIV group meeting (March 2012), leading experts who are currently generating surveillance data shared this information to generate a global overview of the current swine influenza situation and surveillance activities.
- The group also proposed terms of reference and a work plan for the coming year to be submitted to EC and SC for review and approval. These documents, together with the report of the March 2012 meeting will be available on the OFFLU website soon.
- The group is currently drafting a review paper for publication titled 'A review of influenza A virus in swine worldwide and global coordination of swine influenza surveillance and research'. They hope to submit this to a peer reviewed journal very soon.

Action: The SIV expert group to continue after reviews of ToRs (including membership) by the EC/SC. Updates will be presented to the larger OFFLU network in the OFFLU technical meetings and through the website. Review paper to be published soon.

Update from Equine expert surveillance panel (ESP) (Ann Cullinane):

- The equine surveillance panel meets annually at OIE. The panel reviews influenza activity and virus strains each year and gives recommendations on vaccine composition. The recommendations are published in the OIE bulletin and on the OIE website to guide industry in preparation of commercial vaccines.
- Equine influenza surveillance is patchy worldwide and efforts are being made to improve global coverage, through OIE laboratory twinning projects and by developing links with stakeholder bodies such as the FEI (International Equine Federation).
- There is a need to ensure that vaccine manufacturers follow the recommendations of the ESP – industry compliance has been less than ideal. The ESP has been engaging with vaccine industry to encourage better compliance with the recommendation.

Action: To update equine influenza chapter of the OIE manual (OIE).

Influenza across mammalian species and links with avian influenza (John Pasick):

- Influenza viruses of varying subtypes have been reported in a wide range of mammalian species. Although highly pathogenic avian influenza (HPAI) H5N1 does not appear to have adapted to any class of animals other than birds its occurrence is reported in a range of mammalian species.
- The role of various factors including environmental and ecological conditions, receptor mediated host range, viral determinants, gene constellations and subsequent genetic

changes should be further explored to study interspecies transmission of avian influenza virus.

Influenza in mink (Lars Erik Larsen):

- A new human-swine reassorted H3N2 influenza A virus has been identified as a cause of respiratory problems in at least 25 Danish mink farms in 2009. It is not known whether this virus evolved in pigs or in minks, but based on the phylogenetic analysis it may have been circulating since 2005/6. Introduction into the minks probably occurred through feeding uncooked pork tissues to minks but there is also the possibility of horizontal spread. This virus induced severe clinical signs in mink. Since the H and N genes are of human origin this virus may be - or may develop into - a zoonotic strain with pandemic potential (current vaccines do not protect). There is no indication that this virus is circulating in swine or humans but if the virus is low virulent in pigs the virus may circulate without being noticed due to the lack of active surveillance of influenza A virus in pigs.

Capacity building (Giovanni Cattoli):

- Achievements of this group include:
    - Development of videos on laboratory techniques for AI in English and French by FAO and IZSVe.
    - An e-learning course on AI has been developed (under the EU-funded FLUTRAIN project) and will be posted on the training section of the OFFLU website.
    - Interaction with the WHO-GIP Digital Library for Influenza Training website for training material on influenza at the animal-human interface: contributions are expected from the OFFLU community, with training materials. (http://influenzatraining.org/en/)

Action (GC):

1) Development of additional training materials requested by scientists/laboratory technicians including on sequencing protocols, phylogeny, and bioinformatics.
2) Development of recommendations on AI training including selection and certification of the participants.
3) Development of a 'train the trainers' programme.

Action (GP): Keep website up to date and post training materials as soon as they become available.

Update on LAMP (Loop mediated isothermal Amplification) project (Sasan Fereidouni):

- This OFFLU technical project, supported by OIE, follows a call to OFFLU laboratories to submit proposal for technical projects which aim to improve global detection and preparedness for AI.
- LAMP is a technique which may offer options for accurate and rapid detection of AI in developing countries. Its development may also have an application for detection of other animal pathogens.
- The project aims to validate and optimize use of an H5-LAMP

- Tested with a panel of low and high pathogenic avian influenza H5 viruses (sensitivity evaluation).
- Tested with a panel of low pathogenic non-H5 viruses (specificity evaluation)
- IAEA H5 LAMP showed high sensitivity, but needs further modification to achieve high specificity.
- The project has been further extended until July 2013.

Action (SF/AG): Further validation, and training to the laboratories, on this technique.

Genetic module update for discussion (Filip Claes):

- An FAO Empres-i genetic module linking epidemiological data with genetic data was introduced to the participants by FAO. Several maps were presented.
- FAO asked experts for advice on how the module could be used.
- The experts acknowledge that there was a need for such a tool.

Action: Experts to provide feedback to FAO on potential uses for the Empres-i genetic module

OFFLU contribution to WHO Vaccine Composition Meeting (VCM) (Giovanni Cattoli):

- OFFLU contributes to the WHO VCM to provide data from the animal sector which is important to select potential vaccine candidate viruses for human vaccines, should H5 or H9 AI viruses in animals emerge to become pandemic threats. OFFLU representative regularly attend WHO VCM.
- At the February 2012 meeting OFFLU contributed 39 H5 sequences and 39 H9 sequences. In addition, to generate valuable antigenic data, panels of ferret sera from St Jude's Children's Hospital (WHO Collaborating Centre) were distributed and tested against a panel of avian influenza viruses in three OFFLU laboratories using the standard WHO protocol HI test.

Action (FC/MK): For the next VCM preparation, request for submission of genetic data from OFFLU laboratories to be started three months in advance.

OFFLU contribution to WHO research agenda (Les Sims):

- The WHO organized a global consultation to develop a public health research agenda for influenza. OFFLU provided contributions to one of the five key research streams on reducing the risk of emergence of pandemic influenza.
- Les Sims presented the Animal intervention strategies under different epidemiological and field conditions that can reduce risk of zoonotic infection which contributed to the WHO research agenda.

Variant influenza in humans (Susan Trock):

- 35 human cases of variant influenzas were reported between Dec 2005 and Nov 2011; this included 13 H1N1v, 2 H1N2v, 20 H3N2v
- 14 cases were reported between July 2011 – November 2011 including 12 H3N2v, 1 H1N1v, 1 H1N2v

Equine influenza at the human animal interface (Ann Cullinane):

- There are historical accounts linking respiratory disease episodes in horses in time and space to respiratory disease in humans. There is some suggestion that these disease outbreaks may have been caused by influenza, but there is no hard evidence to support influenza being the cause because the virus was not isolated until many years later.
- Current equine influenza viruses are subtypes H3N8. These viruses have also become established in canine populations (USA) and have also been isolated from pigs on sporadic occasions in China.
- Although humans have been experimentally infected with H3N8 equine influenza viruses, currently there is no evidence that H3N8 equine influenza can lead to sustained human to human transmission in the field setting. Enhanced surveillance at the human animal interface is necessary to determine if exchange of viruses between horses and people occasionally occurs.

Risk assessment tools:

- Susan Trock presented the CDC risk assessment tool for influenza viruses for pandemic preparedness which aims to identify gaps in information/knowledge, documentation of the process and focus risk management efforts.
- Ilaria Capua also presented the EFSA risk assessment tool on "Development and validation of a methodological risk assessment framework capable of assessing the pandemic potential of new influenza viruses or viral subtypes emerging in animals" which aims to provide an open, documented and systemic approach for identifying and evaluating influenza viruses with pandemic potential by considering all known relevant risk factors.

Action (IC/ST): Keep OFFLU updated on further developments. OFFLU to provide technical assistance where possible.

Open discussion on H5N1 transmission studies, research moratorium and surveillance

Main points:

- The recent public debate about whether to publish the findings of H5N1 transmission studies in ferrets and the associated moratorium on research studies has had a negative impact on animal influenza research. There are also concerns that this has led to barriers for day to day activities such as transfer of influenza material between laboratories and approval of research proposals. In addition to the risk of increased regulation hampering research activities, there is a risk that funding agencies may divert resources away from transmission studies.
- Transmission studies are very important for developing a better understanding of the risks posed by influenza viruses to animal health and public health. The outputs from these studies are also important for informing risk assessments. OFFLU has identified the need for such research and highlights this in the OFFLU Research Agenda. OIE has also issued a press release in support of research to better understand health risks from influenza viruses.
- Responsible and well managed communication of research findings and activities from the outset is critical in avoiding undue alarm and public debate.

- To limit the impact on research activities and funding, international organizations should continue to promote the importance of research to determine health risks from influenza viruses.
- Experts felt that OFFLU should develop a position paper on this subject and circulate.
- It is important to continue scientific research studies in the context of capacity building, improving agricultural productivity and ensuring food security.
- Generally there is a need to improve surveillance for influenza viruses in animals and to strengthen national, regional and global surveillance systems.
- Animal influenza surveillance is needed to support OFFLU's contribution to the WHO influenza vaccine strain selection process and ensure pandemic preparedness.
- In endemic countries surveillance and reporting is weakening. This may also be linked to a lack of adequate compensation for poultry owners on positive findings. There is a need to reinvigorate and maintain vigilance. H5N1 remains a risk to public and animal health.
- Experts called for OIE and FAO to continue to promote the importance of surveillance for influenza viruses in animals and for continued research in line with the OFFLU research agenda.

Action: OFFLU to come with a position and talking points on necessity of research at the HAI; support to scientists from OFFLU network when they engage in dual use research of concern (DURC) that was previously approved by donors or called for in OFFLU research agenda or other research calls. PD to write first draft and circulate within OFFLU EC/SC. (OIE press release "Research is key for pandemic preparedness" has been published to this effect in March 2012).