

WHO/FAO/OIE TRIPARTITE COORDINATION FOR THE CONTROL
AND PREVENTION OF ZONOTIC INFLUENZA VIRUSES. EXAMPLE OF
OFFLU, GLOBAL NETWORK OF VETERINARY EXPERTISE

COORDINATION TRIPARTITE OMS/FAO/OIE POUR LE CONTRÔLE ET LA
PRÉVENTION DES VIRUS INFLUENZA ZONOTIQUES.
ILLUSTRATION AVEC OFFLU, RÉSEAU MONDIAL D'EXPERTISE VÉTÉRINAIRE

Par Gwenaëlle DAUPHIN¹

(Communication présentée le 22 octobre 2015

Manuscrit accepté le 29 Octobre 2015)

ABSTRACT

During the last decade a heightened awareness has developed on the potential of influenza infections in animals to cause serious disease in people. This is the result of increased reporting of zoonotic influenza in humans as well as the intense circulation of influenza strains with pandemic potential within the animal reservoir. OFFLU (OIE/FAO Network of expertise on animal influenza) was created in 2004 as a response to the large spread of the zoonotic avian influenza of H5N1 subtype. OFFLU is a formal partnership between the World Animal Health Organization (OIE) and the Animal Production and Health Division of the Food and Agriculture Organization of the United Nations (FAO) to maintain an active network of expertise on animal influenza. One of its four objectives is specifically to collaborate with the WHO (World Health Organization) influenza network on issues relating to the animal-human interface, including early preparation of human vaccines. Stronger technical collaboration, both institutionally and nationally, among scientists in the animal health and public health sectors has been established through joint technical discussion, information sharing and development and use of common tools.

Key-Words: *influenza, zoonotic, tripartite, network.*

RÉSUMÉ

Au cours des dix dernières années, on a de plus en plus pris conscience du potentiel qu'ont les infections animales par l'influenza à causer une maladie sérieuse chez l'homme. Ceci a été à la fois le résultat d'observations plus fréquentes d'infections par des influenza zoonotiques chez l'homme et de la circulation intense de souches influenza avec un potentiel pandémique dans le réservoir animal. OFFLU (Réseau OIE/FAO d'expertise sur l'influenza animal) a été créé comme une réponse à la dissémination majeure du sous-type H5N1 du virus influenza aviaire à caractère zoonotique. OFFLU est un partenariat formel entre l'OIE (Organisation Mondiale de la Santé Animale) et la division de santé et production animales de la FAO (Organisation de l'Alimentation et de l'Agriculture des Nations Unies) afin de maintenir un réseau actif d'expertise sur l'influenza animal. L'un des quatre objectifs d'OFFLU est spécifiquement de collaborer avec le réseau influenza de l'OMS (Organisation Mondiale de la Santé) sur les problèmes relatifs à l'interface animal-homme, y compris la préparation des vaccins humains. Une collaboration technique plus forte, à la fois institutionnelle et nationale, parmi les scientifiques des secteurs de la santé animale et de la santé publique a été établie au travers de discussions techniques conjointes, de partage de l'information et du développement et de l'utilisation d'outils communs.

Mots-Clés : *influenza, zoonotique, tripartite, réseau.*

(1) DVM, FAO-Animal Health Service. Viale delle terme di Caracalla. 00153 Rome. Italy.
e-mail : gwenaëlle.dauphin@fao.org3

Glossary/Glossaire

APHL: Association of Public Health Laboratories
CDC: Center for Disease Control
FAO: Food and Agriculture Organization of the United Nations
GISRS: Global Influenza Surveillance and Response System
GLEWS : Global Early Warning System for Major Animal Diseases Including Zoonosis
HPAI: Highly Pathogenic Avian Influenza
IRAT: Influenza Risk Assessment Tool
MERS-Co: Middle East Respiratory Syndrome-Coronavirus
NAMRU-3: Naval Medical Research Unit 3

OFFLU: OIE/FAO Network of expertise on animal influenza
OIE: World Animal Health Organisation
PIP: Pandemic Influenza Preparedness
SIV: Swine Influenza Virus
SARS: Severe Acute Respiratory Syndrome
UNICEF: United Nations Children's Fund
VCM: Vaccine Composition Meeting
WHO: World Health Organization
4WLplatform: Four-Way Linking Platform

INTRODUCTION

Influenza viruses belong to the Orthomyxoviridae family characterized by segmented, single-stranded linear RNA-based genome. Such genome features provide high potential for reassortment between strains by exchange of segments and also evolution by gene mutation, which provides influenza viruses with high level of adaptive change, for example for infection of new host species. Two of the eight gene segments code for the hemagglutinin (H) and neuraminidase (N) proteins, instrumental in host-cell entry. At present, 16 H and 9 N subtypes are known -with potentially represents 144 possible subtypes- with different host susceptibility. Animals are only infected with type A influenza virus. All known influenza A subtypes are found in wild birds, especially water birds, their natural reservoir, among which a subset have been reported in poultry and only a few in mammals.

Among naturally occurring diseases, pandemic influenza is widely considered to pose the greatest threat to global health security. Previous pandemic influenza viruses are believed to have either emerged from animal populations or had components originating from animal populations. Human seasonal influenza viruses harbour molecular determinants of adaptation to humans and mostly infect humans, while zoonotic influenza directly originate from animal species (avian or mammal). The public health threat posed by influenza at the human-animal interface continues to be of concern for WHO (World Health Organization), OIE (Animal Health Organisation) and FAO (Food and Agriculture Organization of the United Nations), other animal and public health partners, and the world. New avian influenza virus strains, of which some have a zoonotic potential, frequently emerge and may spread for years in countries and regions. The trends in emergence and spread of zoonotic influenza have been growing in terms of frequency of events, impact and affected countries. This observed trend is the result of both better detection and a real increase in dynamics of avian influenza strains, mostly due to increased poultry production around the world, and especially in China, as well as intensified movements of poultry and poultry products.

The three recent highly visible global zoonotic influenza events have been: the on-going circulation of avian H5N1 virus and derived strains, the 2009 H1N1 pandemic, and the emergence of avian influenza H7N9. Since 2003 an H5N1 strain of highly pathogenic avian influenza (HPAI) has spread around the world and has since then been responsible for almost 19,337 animal outbreaks (*source EMPRES-i, FAO, as of 15th October 2015*)² and a total of 844 reported human cases, among which 449 human deaths (*source WHO- as of 15th October 2015*)³. Then the pandemic H1N1 2009 strain showed human infections globally. It spread rapidly and in many countries became the predominant H1 strain infecting people. The study of the eight gene segments revealed that this strain derived from a reassortment of North American triple reassortant (from human-avian-swine viruses reassortment) and Eurasian avian-like swine influenza viruses. Lastly, in 2013, a new zoonotic strain with pandemic potential, subtype H7N9, emerged in China in poultry and caused 678 confirmed human cases and 271 deaths (since February 2013). Moreover the 2014-2015 winter has witnessed the emergence of avian H5N8 HPAI in a few EU countries, and avian H5N2 HPAI in the US, both derived from the Eurasian H5N1. More than 250 poultry outbreaks with H5N2 were reported in the US from December 2014 to June 2015, causing the death of 50 million poultry. No human cases have been reported in these two regions despite the zoonotic potential of these viruses. In March 2015, HPAI H5N1 hit West Africa again with more than 230 outbreaks reported between December 2014 and August 2015 after 8 years with no outbreak (186 outbreaks had been reported between 2006 and 2008). The main response to these major influenza events has been for human and animal health authorities to work much more closely to monitor influenza infections in animals and to analyze these viruses for their potential threat to human health. Furthermore less visible events posing unknown risks to health continue to be identified, with increasing reports of sporadic human infections from a variety of influenza subtypes associated with animal infections, such as H1N1v, H1N2v, H3N2v (v standing for "variant"), and avian influenza H7N2.

(2) FAO. EMPRES Global Animal Disease Information System (EMPRES-i). <http://empres-i.fao.org>

(3) WHO. Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO http://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/

The ecology of these zoonotic influenza viruses is still partially unknown, in particular the determinants of transmissibility from wild birds to domestic birds, from animals to humans, and among humans, as well as reassortment events among virus strains. It is however obvious that the on-going circulation of such viruses in the animal reservoir, along with the on-going exposure of humans are responsible for human infections with zoonotic influenza viruses and pose a continued threat of emergence of a pandemic strain. Any strategy that reduces the risk of human exposure therefore reduces the probability that a pandemic virus might emerge. A continuous surveillance, with assessment of the pandemic risk, is required with animal influenza. This is a great challenge, given the high level of activity, wide spread of influenza viruses and the hardly predictable features of influenza ecology. The size of the poultry production sector and level of trade also represents a great challenge for proper surveillance. The veterinary sphere is responsible for the surveillance of the emergence and circulation of these influenza strains in animals. A good level of surveillance is required in both domestic and wild animal species, and implies a good detection and sharing of results within the veterinary sector and with the human health sector. The issue of influenza surveillance, detection, prevention and control at the human-animal interface has to be conducted in a well coordinated manner, to have a global geographical coverage and to involve various stakeholders.

One of the drivers of the “One health” approach has been the H5N1 panzootic, with its attendant human and animal suffering and its impact on food security and economies. Influenza activities at the human-animal interface are part of a huge, complex and interrelated scope of work requiring coordination of global, regional and country aspects as well as of a spectrum of diverse players and a dedication to maintaining momentum over a long duration to ensure sustainability. The need for, and benefits of, having such collaboration at the human-animal interface is continually re-emphasized with the occurrence of

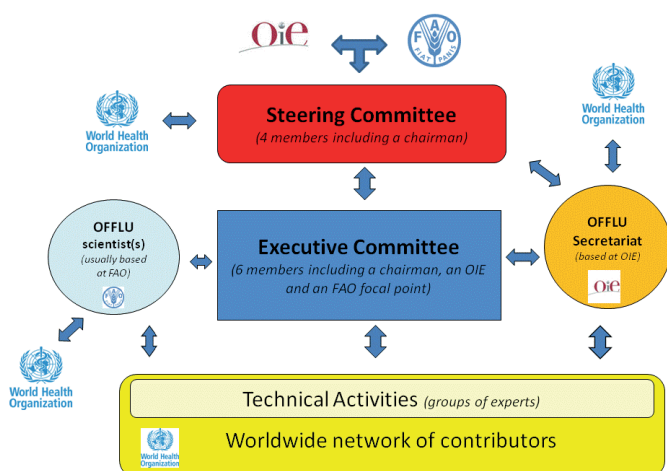
new influenza events. The OIE/FAO joint network of expertise on animal influenza (OFFLU) network was founded in 2004 by OIE and FAO, during the peak of HPAI H5N1 crisis, as a network of avian influenza expertise with the aim to ensure a good coordination within the veterinary world as well as a good interface with the human health world (Dauphin *et al.* 2010a; www.offlu.net). Since its foundation, this global network has matured and has made a few key achievements at the human-animal interface, including the establishment of mechanisms under the “OFFLU-WHO Collaboration” that will be described in this paper. A few other achievements at the national level will also be described.

INSTITUTIONAL TRIPARTITE COORDINATION, ESPECIALLY THROUGH OFFLU, THE OIE/FAO NETWORK OF EXPERTISE ON ANIMAL INFLUENZA

The OFFLU vision is that the animal health community will provide early recognition and characterisation of emerging influenza viral strains in animal populations, and effective management of known infections, thereby better managing the risk to human health and supporting global food security, animal health and welfare, and other community benefits derived from domestic animals and wildlife. OFFLU has four objectives:

- (1) to share and offer technical advice, training and veterinary expertise to international organisations and Member Countries to assist in the prevention, diagnosis, surveillance and control of animal influenza;
- (2) to exchange scientific data and biological materials (including virus strains) within the network, to analyse such data, and to share such information with the wider scientific community;
- (3) to collaborate with the WHO on issues relating to the animal-human interface, including pandemic preparedness for early preparation of human vaccine;
- (4) to highlight influenza surveillance and research needs, promote their development and co-ordination. One objective out of four is therefore fully dedicated to the interface with the human health sphere.

The core membership of OFFLU is composed of all 10 OIE/FAO Reference Centres for animal influenza along with around 20 other diagnostic laboratories, research and academic institutes. A total of about 60 experts in the fields of virology, epidemiology, vaccinology, and molecular biology from 29 countries and from international organizations are OFFLU contributors. Decisions and actions regarding OFFLU are taken by a Steering Committee and an Executive Committee. Strategic decisions are cleared by the two parent organizations. OFFLU is supported by a secretariat, technical working groups and OFFLU scientists (based on available funding) that may be based at the FAO or the OIE (*figure 1*). OFFLU gathers animal influenza expertise from all species susceptible to influenza



www.offlu.net

Figure 1: OFFLU's structure.

infections: pigs, poultry, wildlife, horses, other mammals and humans. OFFLU established a specific group of experts in swine influenza after the H1N1 influenza pandemic.

An effective and strong working relationship between OFFLU and WHO has been built over the last years. WHO has been present as an observer in OFFLU Steering Committee meetings and human health experts have been members of some OFFLU groups and activities. WHO has also contributed to all OFFLU strategic and technical meetings. Vice-versa OFFLU has participated in most WHO strategic and technical meetings related to influenza at the human-animal interface (e.g. vaccine composition meetings and strain selection process consultations, PCR working group meetings, research agenda). WHO participation in OFFLU meetings has ensured aligned strategies and technical decisions and improved exchange of information between the animal and human health sectors.

However it should be noted that the WHO influenza network, called WHO's Global Influenza Surveillance and Response System (GISRS, formerly known as the Global Influenza Surveillance Network (GISN)), was created many years before OFFLU, namely in 1952. This network has broader terms than OFFLU. It serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential, monitors the evolution of influenza viruses, provides recommendations in areas including laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment. GISRS is also bigger in size than OFFLU, with around 150 public health laboratories from 112 countries in the network. It is therefore by far stronger and more sustainable than OFFLU in terms of membership, means and volume of activities. However it does not have veterinary laboratories among its members but a few institutions working at the human-animal interface, which makes the linkage with OFFLU a necessity for monitoring of influenza with zoonotic potential. The GISRS annual running budget is almost 30 million US dollars while OFFLU's annual budget, being subject to OIE and FAO funding support, may have been on average around 250,000 US dollars between 2005 and today, period where significant funding has been made available in the field of influenza.

Two other tripartite initiatives that support collaborative influenza work at the human-animal interface should also be mentioned. In 2006, in response to health threats such as H5N1 HPAI and the Severe Acute Respiratory Syndrome (SARS), the OIE, FAO and WHO established a Global Early Warning System for Major Animal Diseases Including Zoonosis (GLEWS). GLEWS became one of the mechanisms used by the three organizations together for monitoring data from existing event-based surveillance systems and to track and verify relevant animal and zoonotic events. The other initiative is the tripartite Concept Note issued in April 2010 and signed by the Directors General of the three International Organizations entitled "The WHO, OIE, FAO Collaboration – Sharing responsibilities and coordinating global activities to address health risks at the animal human-ecosystems

interface". Through this document, the three international health organizations have formally undertaken to work closely together, with joint strategies at the human-animal-environment interface, to support their Member Countries. Within the framework of this tripartite alliance, the three Organizations set themselves, the following year, three priority areas: zoonotic influenza, antimicrobial resistance and rabies. Under this framework, staff of the three Organizations regularly exchange information on influenza.

Human and animal health systems do not only need to work together to address zoonotic influenza but they can also learn from each other and use their complementary. Human health systems have a lot to teach to animal health systems, for example on the relationship between public authorities and vaccine manufacturers, on the global laboratory network and derived activities. The veterinary sphere also has services to offer at the human-animal interface: it is smaller in size, which makes it easier when it comes to coordination, it has strong abilities in describing disease epidemiology in animal populations, it is able to conduct surveillance of influenza strains with pandemic potential in the animal reservoir, it collaborates with environment specialists to better understanding of influenza ecology and it applies new technology vaccines after shorter time after their development. Sharing of epidemiological and virological information on a real-time basis remains a challenge for both sectors and a critical issue for prevention of pandemics and epidemics and should be addressed jointly.

GLOBAL ACTIVITIES AND COLLABORATIONS AT THE HUMAN-ANIMAL INTERFACE

OFFLU and WHO have established and implemented various sets of collaborative activities, some of which have been particularly fruitful. They have also established joint technical working groups, or groups with members from both animal health and public health sides.

Collaborative OFFLU/WHO activities

Emergencies

When H1N1 was first reported in 2009, it was the first emergency for OFFLU to deal with (Food and Agriculture Organization, 2009). The collaborative relationships among FAO, OIE and WHO were sufficiently well established to be mobilized within hours for the discussion and sharing of available information. The OFFLU network was already strong and flexible enough to expand within a matter of days to swine expertise and changed its scope and name to the OIE-FAO Network of Expertise on Animal Influenza. OFFLU and WHO gathered international experts for a first WHO/OFFLU teleconference on H1N1 at the human animal interface only a few days after the first report. Three subsequent teleconferences on diagnosis, surveillance and diagnostic testing algorithms for the emergent virus in the animal health

sector were held the following two months. Reports from these discussions were made available on the OFFLU website, along with a variety of documents that were produced to assist animal health laboratories with identification of the emergent virus (i.e. list of laboratories for international shipment of H1N1-suspicious samples/isolates, guidance on the shipment of suspicious samples, algorithm for laboratory detection, guidance on sampling pigs for influenza diagnostic tests). The OFFLU network had also become established and respected enough to be asked by WHO to represent the animal health sector (in conjunction with OIE and FAO) in addressing two specific questions – the name of the virus, and specific issues regarding its origin – in high-level WHO teleconferences. A secondary benefit of these discussions was increased communication about swine influenza viruses in general among public and animal health experts and those new to the field. The Chairperson of OFFLU was interviewed by the journal *Nature* in 2009, which editorial stated: “OFFLU has also been outspoken on the need for countries to share virus samples and sequences for research and has built important bridges with the World Health Organization (WHO) and other public-health agencies. What is needed now is international support for a greatly expanded OFFLU-like network that has enough funding to do its own research and to coordinate global surveillance efforts on influenza and other diseases emerging from animals.” The other influenza emergencies that required urgent communication among scientists from animal and public health were for the emergence of H7N9 in 2013 in China and the introduction of H5N8/H5N2 in 2014 in Europe and the US. Teleconferences have been held between OFFLU laboratories and WHO Collaborating Centers to discuss testing protocols and results and try to coordinate efforts in filling some gaps in tests validation and challenge studies. OFFLU was also invited to take part to some WHO teleconferences organized by the GISRS network.

OFFLU/WHO conferences

Two joint conferences were held at the human-animal interface and reports published, i.e. the WHO/OIE/FAO joint technical Consultation on Avian Influenza at the Human-Animal Interface; (Verona, Italy, October 2008) and the WHO/OIE/FAO joint scientific consultation on influenza and other emerging zoonotic diseases at the human-animal interface, (April 2010, Verona, Italy) (Anderson *et al.* 2010; Dauphin *et al.* 2010b; World Health Organization/World Organisation for Animal Health/Food and Agriculture Organization, 2011). These meetings brought together top-level experts on influenza and other diseases from the animal and public health sectors to discuss virological and epidemiological priority issues, identify knowledge and technical gaps, and provide recommendations for further actions to address influenza and other emerging zoonotic diseases at the human-animal interface. Discussions emphasized that H5N1 was not the only animal influenza virus subtype posing an animal, zoonotic and pandemic threat, and that virological and epidemiological surveillance needed to be broadened to include other animal influenza viruses

with zoonotic potential. A major gap identified by experts at the second meeting was an overall lack of capacity and mechanisms to adequately collect and link virological and epidemiological information from humans and animals at the national and global levels. These linked data are required for valid animal and public health risk assessments to be made. A third influenza meeting called *One Flu Strategic Retreat* held in February 2011 (Treviso, Italy) aimed at promoting the timely sharing of surveillance data and viruses from swine, avian and human populations with the ultimate goal of improving both human and animal health. Given the convergence of influenza viruses, people, animals and the environment, the need for a novel, integrated approach was acknowledged. Five activities were identified to progress on the *One Flu* concept, that were (1) developing a manuscript on Repositioning Influenza; (2) developing an influenza risk assessment tool; (3) strengthening data management and data banks; (4) ensuring continued influenza data sharing; (5) building partnerships for better integration of public and animal health new way forward.

WHO consultation on the composition of influenza vaccines

This consultation process led by WHO GISRS aims to provide national public health authorities and vaccine manufacturers with guidance on the selection of candidate viruses for use in the development of human vaccines. Since January 2011, OFFLU's contribution to the biannual WHO Influenza Vaccine Composition meeting (VCM) has been formalized through an exchange of letters among the three organizations, including detailed terms of reference (Food and Agriculture Organization, 2011 ; 2012 ; 2013). This collaboration was formally extended for a new period of five years after the initial 3-year period. Under this collaboration, OFFLU provides before and during every VCM a summary of available epidemiological, virological and antigenic data on circulating HPAI H5N1 (and derived strains with zoonotic risk) and avian influenza H9N2 for each six-month reporting period. The data are collected from the FAO, the OIE and OFFLU institutions, and then compiled and analysed. The phylogenetic trees are built applying the same parameters as for the WHO Collaborating Centers, to enable data comparison. Furthermore since 2012 three OIE/FAO Reference Centres have been using ferret sera provided by WHO Collaborating Centers to test virus strains from the animal health sector for antigenic similarity to current human vaccine seed strains. In 2014, OFFLU was awarded an Association of Public Health Laboratories (APHL) - US Centers for Disease Control and Prevention (CDC) grant to improve the OFFLU contribution to the selection process for human vaccine candidate viruses for pre-pandemic preparedness purposes. The main outputs of this project include generation and distribution of ferret sera against animal viruses with pandemic potential, analysis of animal viruses with pandemic potential and data sharing within the OFFLU network and with WHO and its Collaborating Centers.

In addition to sharing a technical report before the VCM, two OFFLU representatives attend the meeting (one from FAO and one from an OIE/FAO Reference Centre) and contribute to the meeting's discussions and outputs. This OFFLU contribution to the VCM therefore relies on veterinary laboratories from several countries to share data (including unpublished data) with OFFLU for confidential use at the WHO VCM. This contribution allows crucial information from the animal health sector to be used by WHO for determining and updating strains of inter-pandemic human vaccines. As a result, a poultry strain was already selected as a candidate vaccine strain, based on OFFLU's reports and observed gaps in cross-protection. Although the means deployed in animal health are not comparable to those deployed in public health, OFFLU plans to develop a similar process for the selection of vaccine strains for poultry (to be conducted less frequently than the human one).

Risk assessment

Given the unpredictability of influenza viruses and the fact that human infections may occur whenever viruses are circulating in animals, vigilance and continual unisectoral and joint assessment of the health risks are crucial. One of the five activities that participants identified during the "One Flu Strategic Retreat" (February 2011, Treviso, Italy) was indeed the development of an Influenza Risk Assessment Tool that would provide the necessary signal to drive more specific pre-pandemic vaccine development. Later on, WHO and FAO and OIE through OFFLU, have technically and strategically supported and advised scientific institutions in the development of two influenza risk assessment tools for influenza strains with pandemic potential respectively developed by the U.S. Center for Disease Control (IRAT) and by a European consortium (FLURISK Tool). A collaboration goes on for the validation and application of these tools that requires common sets of data.

Sharing of influenza sequence data

OFFLU advocates for influenza data sharing and the use of any of the existing publicly available sequence databases. In May 2011, the Sixty-fourth World Health Assembly adopted at WHO the Pandemic Influenza Preparedness Framework (or 'PIP Framework') for the sharing of influenza viruses and access to vaccines and other benefits, after four years of negotiations (World Health Organization, 2011). This is an international arrangement that brings together Member States, industry, other key stakeholders and WHO to implement a global approach to strengthen preparedness for influenza pandemic and offer an equitable system to countries for access to pandemic vaccines. The PIP Framework is therefore an instrument established to ensure that countries share influenza viruses with human pandemic potential and also share the benefits derived from the sharing of those strains with all countries in need. A traceability system of "PIP material" (i.e. influenza viruses with

human pandemic potential) has been established. Even if this framework only covers influenza viruses with human pandemic potential, this may include influenza viruses of animal origin, if a given strain of animal origin is shown to have a link with human cases. Since the animal health sector was not part of these developments, OFFLU called for discussions with representatives of the PIP framework, after its resolution, to identify the possible implications of this legal framework on influenza activities in the veterinary sector. The sharing of benefits, if any, with the animal health sector derived from isolates originating from animals and becoming PIP material for human vaccine production is possible but terms would have to be discussed within beneficiary countries.

Such legal frameworks have to adapt to developments in technology. Companies and researchers can now develop influenza vaccines using only genetic sequence data. Like virus materials, sequences have therefore become essential for pandemic preparedness and response. They allow public health laboratories, research institutions and manufacturers to conduct risk assessments, carry out basic research in order to gain a better understanding of influenza and develop vaccines and other influenza-related products. However, in terms of sharing and traceability, sequence information is very different from physical viruses. Once sequences are placed in a public database, information sharing is facilitated, but traceability becomes challenging as well as protection of intellectual property rights. A Technical Expert Working Group was commissioned in 2013 by the PIP Advisory Group to assess the scientific, technical, operational and intellectual property implications of using genetic sequences rather than physical materials for influenza research and vaccine production, including how the transfer of such data could be monitored. FAO and OIE are members of this working group. The outcomes of this working group will have future consequences on the functioning modes of influenza sequence databases.

Research a gendas to guide research

In 2009, WHO developed an influenza research agenda in public health. OFFLU members actively participated to this effort. In 2010, an OFFLU Agenda for Influenza Research Priorities in Animal Species was developed by OFFLU scientists, presented at the OFFLU annual technical meeting and endorsed by the OFFLU Steering Committee (January 2011). The development of these two separate research influenza agendas were coordinated and aligned. In 2014, a new OFFLU strategic agenda was developed for animal influenza research. The contributors to this effort were from the field of influenza including animal health and public health scientists, representatives from animal production and trade (poultry, egg, and pork), the pharmaceutical sector, equine sports, policy advisers, and representatives from research funding bodies. In 2015, the European Commission, along with the European Food Safety Authority, developed a European influenza research agenda, based on the OFFLU one.

Joint working groups

Unified nomenclature for zoonotic influenza viruses

The WHO/OIE/FAO H5N1 Evolution Working Group, established in 2007, has selected three criteria for specific “clades” definition and grouped the circulating H5N1 viruses into numerous virus “clades” based on the phylogenetic characterization and sequence homology of the hemagglutinin gene of the influenza virus. This joint system for unified nomenclature has been updated three times since 2007 (World Health Organization/World Organisation for Animal Health/Food and Agriculture Organization, 2014). As of today, such unified nomenclature has only been established for H5N1. This nomenclature will have to be expanded to H5Nx and similar nomenclature would be useful also for other subtypes, in particular H9N2 (work under preparation at FAO, under the auspices of OFFLU). Moreover, FAO and OIE have been closely involved in the development by WHO of Best Practices for Naming New Human Infectious Diseases (in consultation with experts leading the International Classification of Diseases), issued in May 2015 (Fukuda *et al.* 2015). These best practices apply to new infections, syndromes, and diseases that have never been recognized or reported before in humans, that have potential public health impact, and for which there is no disease name in common usage. “(...) *The use of names such as ‘swine flu’ and ‘Middle East Respiratory Syndrome’ has had unintended negative impacts by stigmatizing certain communities or economic sectors. This can have serious consequences for peoples’ lives and livelihoods.*” (communication of Dr Keiji Fukuda, Assistant Director-General for Health Security, WHO).

The OFFLU swine influenza group

Historically surveillance for influenza viruses in pigs has been neglected. Swine Influenza Virus (SIV) infections are widely disseminated on most continents and are not associated with an estimated high economic cost; consequently influenza in swine has not been an OIE listed disease. The OFFLU SIV technical group was created in April 2011 to support improved coordination of global swine influenza surveillance and harmonization of SIV diagnostics and provide meaningful analyses of data from different regions. The group includes leading SIV experts and public health experts, including WHO. It published a review paper on SIV worldwide, with co-authors from both animal and public health sectors (Vincent *et al.* 2014). So far all SIV group meetings have been funded by human health projects.

Staff exchange

Staff exchange among sectors has happened, for example the WHO influenza Collaborating Center at the human-animal interface (Saint Jude’s children hospital, Memphis, USA) had a post-doc scientist loaned at FAO for a few weeks. CDC seconded staff at the OIE and at FAO to work at the human-animal interface. These exchanges are however still made on an exceptional basis.

NATIONAL ACTIVITIES AND COLLABORATIONS AT THE HUMAN-ANIMAL INTERFACE

Although OFFLU only conducted so far a limited number of actions at national level (e.g. OFFLU projects on vaccine efficacy in Egypt and Indonesia), a tripartite collaboration also exists on influenza at the human-animal interface at the national level. This paragraph provides two illustrations of such collaboration.

Four-way linking platforms

A tripartite work was initiated in 2010 through the development of WHO/OIE/FAO “four-way linking” framework (called 4WL). National-level linkages between the animal health and public health sectors, including linkages between the national epidemiology and virology units, were then strengthened through the establishment of this 4WL framework in Egypt, Bangladesh, Indonesia and Viet Nam (Food and Agriculture Organization, 2011; Forcella *et al.* 2015; Setiawaty *et al.* 2015). National task forces have been identified in all these four countries and 4WL meetings have been held. In Egypt, the designated task force met several times a year since its establishment, shared information, assessed the HPAI H5N1 situation, the Middle East Respiratory Syndrome- Coronavirus (MERS-CoV) risks, and planned national actions. These meetings have proved instrumental in facilitating the sharing of information between sectors and alerting public institutions of cases in humans and animals. The outcomes of a 4WL meeting held in January 2015 literally triggered an inter-agency emergency mission in Egypt, considering the change in epidemiological situation both in the human health and animal health sectors. These meetings, however, are still *ad hoc*, and the platform is not yet recognized as an official technical body. Technical recommendations made by the 4WL platform require high political support from decision makers, as most of the challenges are beyond the capacities of technical institutions of the ministries of health and agriculture. A legal framework is being discussed in Indonesia as a basis of collaboration between the ministries of health and agriculture. A paper was published in Indonesia on the successful 4WL approach for joint public health and animal health outbreak investigation (Setiawaty *et al.* 2015). The 4WL aims at improving institutional collaboration for smoother technical collaboration across sectors. In addition current efforts to develop a strong methodology for joint risk assessment are being made in Asia, initiated by FAO and WHO in Myanmar and should be expanded in the future.

Joint assessment missions of national situations

From November 2014, Egypt experienced a major upsurge in H5N1-related outbreaks in poultry and in human cases and reported the highest number of human cases ever reported by a country over a similar period of time. At the same time, poultry outbreaks of HPAI H5N1 were being detected in most

Egypt's governorates; the majority occurred in household poultry. In light of this surge of H5N1 cases, the Minister for Health and Population requested an urgent risk assessment to better understand the current situation of H5N1 infections in both animals and humans. A team of international experts was formed, with members from WHO, FAO, OIE, the US Centers for Disease Control and Prevention (CDC), the United States Naval Medical Research Unit 3 (NAMRU-3) and the United Nations Children's Fund (UNICEF), to ascertain the reasons behind the rapid increase of cases, and to provide concrete recommendations to curtail the rate of infection. The mission members were divided into two teams, focusing on either the veterinary or public health side and met a broad range of key stakeholders. The findings and recommendations were debated among the two teams. Some team members from WHO even joined the animal health team to better understand the animal health situation. They realized the complex and multi-dimensional situation (including poverty, livelihoods, marketing traditions and political context) in the animal health sector and admitted the difficult task for veterinary services and related stakeholders.

CONCLUSION

The concept of "One Flu" has been identified as a good example for the "One Health" approach. Significant improvements have indeed been made in terms of institutional collaborations, communication, joint work and analysis, common knowledge on zoonotic influenza viruses. However further collaboration between the public health and animal health sectors at global, regional and national levels, is critical for fully understanding and mitigating health threats. Mechanisms and systems built through work on influenza at the human-animal interface can be used by countries, regions and the international agencies to confront the emergence of new zoonotic or potentially zoonotic events. Such mechanisms have actually been used to facilitate cross-sectoral communication about the novel Coronavirus which has caused disease and deaths in humans in some countries in the Middle East from late 2012 and has an animal reservoir. But a wide variety of other existing and emerging threats such as rabies, antimicrobial resistance and food-borne zoonoses could also benefit from these mechanisms.

ACKNOWLEDGMENTS

All OFFLU members should be acknowledged for their contribution to the network, in sharing information and contributing to the technical or institutional life of OFFLU. Their contribution is made on a voluntary basis. The core OFFLU group is composed of members of the Executive and Steering committees and they should be specially thanked for their efforts and time. The collaboration between OFFLU and WHO has been mostly built by one WHO officer: Dr Liz Mumford who is a veterinarian. It is hoped that future WHO officers will continue the good work established by Dr Mumford.

REFERENCES

- Anderson T, Capua I, Dauphin G, Donis R, Fouchier R, Mumford E *et al.*. FAO-OIE-WHO Joint Technical Consultation on Avian Influenza at the Human-Animal Interface, Influenza Other Respir Viruses. 2010;4 (Suppl 1):1-29. doi: 10.1111/j.1750-2659.2009.00114.x.
- Dauphin G, Hamilton K, Kim LM, Choudhury B, Capua I, Edwards S. Main achievements of the World Organisation for Animal Health/United Nations Food and Agriculture Organization network on animal influenza. Avian Diseases. 2010a; 54:380-3.
- Dauphin G, Mumford L, Thiermann A, Capua I. Influenza Opening letter. Avian influenza at the human animal interface. Influenza Other Respiratory Viruses. 2010b; 4 (Suppl 1:i). doi: 10.1111/j.1750-2659.2010.4s1_prelim1.x.
- FAO. Progress in and around the Network of Reference Laboratories, epidemiological, Centres and Groups of Experts on Avian Influenza (OFFLU), EMPRES Transboundary Animal Diseases Bulletin. 2009; 34: 19-26. [en ligne]. Disponible sur : <ftp://ftp.fao.org/docrep/fao/012/i1215e/i1215e00.pdf>
- FAO. Four-way linking of epidemiological and virological information on human and animal influenza. EMPRES Transboundary Animal Diseases Bulletin. 2011; 39:36-9. [en ligne]. Disponible sur : <http://www.fao.org/docrep/015/i2530e/i2530e00.pdf>
- FAO. Contribution to the World Health Organization Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2012 (26 to 28 September 2011, Geneva, Switzerland. EMPRES Transboundary Animal Diseases Bulletin. 2011; 39:44-5. [en ligne]. Disponible sur : <http://www.fao.org/docrep/015/i2530s/i2530s00.pdf>
- FAO. OFFLU's contribution to the WHO consultation on the composition of influenza vaccines for the Northern Hemisphere 20 to 22 February 2012, Geneva, Switzerland. EMPRES Transboundary Animal Diseases Bulletin. 2012; 40: 36. [en ligne]. Disponible sur : <http://www.fao.org/docrep/015/i2811e/i2811e.pdf>
- FAO. OFFLU helps WHO with pandemic preparedness. EMPRES Animal Health 360. 2013; 42: 18. [en ligne]. Disponible sur : <http://www.fao.org/docrep/018/i3470e/i3470e.pdf>
- FAO/OIE/WHO Joint Scientific Consultation Writing Committee. Influenza and other emerging zoonotic diseases at the human-animal interface. Proceedings of the FAO/OIE/WHO Joint Scientific Consultation, 27-29 April 2010, Verona (Italy). FAO Animal Production and Health Proceedings. 2011; No. 13.
- Forcella S, El-din El Tantawy N, Yilma J, AbdelNabi A, Claes F, Dauphin G, Mumford E. The development of a four-way linking framework in Egypt: an example of the FAO, OIE and WHO joint activities to facilitate national risk assessment. Veterinaria Italiana. 2015; 51:45-50.

- Fukuda K, Wang R, Vallat B, Naming diseases: First do no harm. *Science* 2015; 348(6235): 643. DOI: 10.1126/science.348.6235.643.
- Setiawaty V, Dharmayanti NL, Misriyah, Pawestri HA, Azhar M, Tallis G *et al.* Avian Influenza A(H5N1) Virus Outbreak Investigation: Application of the FAO-OIE-WHO Four-way Linking Framework in Indonesia. *Zoonoses Public Health*. 2015; 62(5):381-7. doi: 10.1111/zph.12158.
- Vincent A, Awada L, Brown I, Chen H, Claes, F, Dauphin, G *et al.* Review of Influenza A Virus in Swine Worldwide: A Call for Increased Surveillance and Research. *Zoonoses Public Health*. 2014;61(1):4-17. doi: 10.1111/zph.12049.
- WHO. Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. 2011. ISBN 978 92 4 150308 2.
- WHO/World Organisation for Animal Health/Food and Agriculture Organization (WHO/OIE/FAO) H5N1 Evolution Working Group. Revised and updated nomenclature for highly pathogenic avian influenza A (H5N1) viruses. *Influenza Other Respir Viruses*. 2014; 8:384-8.