DOI: 10.1111/j.1750-2659.2009.00114.x
www.influenzajournal.com

Original Article

FAO-OIE-WHO Joint Technical Consultation on Avian Influenza at the Human-Animal Interface

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Acknowledgements: Support for this meeting was provided by the European Commission, US Centers for Disease Control, Canadian International Development Agency, EU-funded project FluTrain, the Government of Italy, and the Comune of Verona. This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

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Accepted 30 March 2009.

For the past 10 years, animal health experts and human health experts have been gaining experience in the technical aspects of avian influenza in mostly separate fora. More recently, in 2006, in a meeting of the small WHO Working Group on Influenza Research at the Human Animal Interface (Meeting report available from: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_3/en/index.html) in Geneva allowed influenza experts from the animal and public health sectors to discuss together the most recent avian influenza research. Ad hoc bilateral discussions on specific technical issues as well as formal meetings such as the Technical Meeting on HPAI and Human H5N1 Infection (Rome, June, 2007; information available from: http://www.fao.org/avianflu/en/conferences/june2007/index.html) have increasingly brought the sectors together and broadened the understanding of the topics of concern to each sector. The sectors have also recently come together at the broad global level, and have developed a joint strategy document for working together on zoonotic diseases (Joint strategy available from: ftp://ftp.fao.org/docrep/fao/011/ajl37e/ajl37e00.pdf). The 2008 FAO-OIE-WHO Joint Technical Consultation on Avian Influenza at the Human Animal Interface described here was the first opportunity for a large group of influenza experts from the animal and public health sectors to gather and discuss purely technical topics of joint interest that exist at the human-animal interface.

During the consultation, three influenza-specific sessions aimed to (1) identify virological characteristics of avian influenza viruses (AIVs) important for zoonotic and pandemic disease, (2) evaluate the factors affecting evolution and emergence of a pandemic influenza strain and identify existing monitoring systems, and (3) identify modes of transmission and exposure sources for human zoonotic influenza infection (including discussion of specific exposure risks by affected countries). A final session was held to discuss broadening the use of tools and systems to other emerging zoonotic diseases. The meeting was structured as short technical presentations with substantial time available for facilitated discussion, to take advantage of the vast influenza knowledge and experience available from the invited expert participants. Particularly important was the identification of gaps in knowledge that have not yet been filled by either sector. Technical discussions focused on H5N1, but included other potentially zoonotic avian and animal influenza viruses whenever possible.

During the consultation, the significant threat posed by subtypes other than H5N1 was continually emphasized in a variety of contexts. It was stressed that epidemiological and virological surveillance for these other viruses should be broadening and strengthened. The important role of live bird markets (LBMs) in amplifying and sustaining AIVs in some countries was also a recurring topic, and the need for better understanding of the role of LBMs in human zoonotic exposure and infection was noted. Much is understood about the contribution of various virus mutations and gene combinations to transmissibility, infectivity, and pathogenicity, although it was agreed that the specific constellation of gene types and mutations that would characterize a potentially pandemic virus remains unclear.

The question of why only certain humans have become infected with H5N1 in the face of massive exposure in some communities was frequently raised during discussion of human exposure risks. It was suggested that individual-level factors may play a role. More research is needed to address this as well as questions of mode of transmission, behaviors associated with increased risk, virological and ecological aspects, and viral persistence in the environment in order to better elucidate specific human exposure risks.

It became clear that great strides have been made in recent years in collaboration between the animal health and public health sectors, especially at the global level. In some countries outbreaks of H5N1 are being investigated jointly. Even greater transparency, cooperation, and information and materials exchange would allow

more timely and effective responses in emergency situations, as well as in assessment and planning phases.
Ensuring sustainability was also frequently emphasized, e.g. in infrastructure and capacity development and in development of tools and systems for surveillance, assessment and response. It was suggested that one way for tools and systems built or planned to address avian influenza to become more sustainable would be to make them applicable for a broader array of existing and emerging zoonotic diseases.

Keywords Influenza, human-animal interface, zoonotic influenza, avian influenza, pandemic, H5N1.

Please cite this paper as: Writing Committee for the Joint Technical Consultation on Avian Influenza at the Human-Animal Interface. FAO-OIE-WHO Joint Technical Consultation on Avian Influenza at the Human-Animal Interface. 7–9 October, 2008, Verona, Italy. Consultation Summary, May 2010. Influenza and Other Respiratory Viruses. 4 (Suppl. 1): 1–29.

1 Introduction

Although much has been learned over the past years, many essential scientific questions about avian influenza, including questions about the risk to humans and emergence of a pandemic influenza strain, remain unanswered. Addressing these questions requires analysis of all available information on virological and epidemiological aspects of avian influenza in animals and people. The animal health and public health sectors have each generated data and expertise, yet mechanisms for timely sharing of this information and for collaborating more closely on generation and analysis of data are urgently needed.

This joint technical consultation was a milestone towards better global understanding of avian influenza risks at the human–animal interface and for moving forward collaboratively. As other pathogens besides avian influenza H5N1 are also potential zoonotic and pandemic threats, this meeting focused on H5N1 but included in the discussions other animal influenza viruses and other zoonotic pathogens at the human–animal interface. It offered a forum for sharing and discussing information and technical tools from both the animal health and public health sectors, and provided a valuable opportunity to discuss how tools and systems might be developed and adapted for broader application at the human–animal interface.

1.1 Objectives

The Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE) and the World Health Organization (WHO), in collaboration with the Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe), the European Commission (DG RTD) and the OIE/FAO Influenza Network of expertise (OFFLU), called this technical consultation to:

- Identify critical virological characteristics for zoonotic influenza and for the emergence of a potentially pandemic strain.
- Evaluate external factors affecting the evolution and emergence of a pandemic influenza strain, and identify monitoring mechanisms for pandemic strain emergence.
- Identify likely modes of transmission and exposure sources for zoonotic infection with avian influenza viruses.
- Maximize outcome of ongoing research and preparedness efforts and identify gaps in knowledge.
- Identify next steps for further collaborative data collection, data analysis and research.

1.2 Agenda and participants

The meeting was structured as a series of short presentations, with substantial time designated for moderated panel discussions and direct technical input from participants. Please see Appendix D for the complete consultation agenda. Approximately 80 participants, representing five continents, were invited as technical experts (Appendix E). At the end of the consultation, general conclusions, gaps (Appendix B), and proposed actions (Appendix A) were developed based on the data presented and the technical discussions.[1]

1.3 Opening remarks

In their opening remarks, Drs. Gaetana Ferri (Italian Ministry of Health), Isabel Minguez (European Commission), Joseph Domenech (FAO), Bernard Vallat (OIE) and Keiji Fukuda (WHO) stated their hopes that this joint technical consultation would represent a milestone event in technical collaboration between the animal and public health sectors, and emphasized that the meeting was the first opportunity for an international, multidisciplinary group of scientists to discuss purely technical questions regarding avian influenza viruses (AIVs) and their threat to animal and human health. They noted that the results of the consultation would provide a technical basis for governments, policy makers, and donors to build and strengthen programs to address avian influenza as well as other zoonotic, emerging, and re-emerging infectious diseases. The participants were charged to take stock of what is and is not known about avian influenza (AI), highlight what does and does not

[1]Available at http://www.fao.org/avianflu/en/conferences/verona_2008.html

work regarding its prevention and control, and identify key areas for future technical collaboration between the animal and public health sectors. It was emphasized that both sectors are jointly responsible for overcoming any barriers to such collaboration.

It was noted that the ongoing H5N1 HPAI crisis has presented both challenges and opportunities to the global community, and has resulted in an unprecedented response, both on the national and international levels. International organizations such as FAO, OIE, and WHO have established and improved tools and developed global strategies to respond better to these challenges, have supported countries and regions, and have strengthened links with each other. Member countries have increased their internal and regional collaborations, initiating integrated national preparedness programs, joint task forces, and interministerial committees. Achievements in AI prevention and control were noted, including improved disease awareness, elimination of outbreaks in most affected countries and control of the disease in many others, as well as better understanding of the importance of controlling pathogens at their source, of political commitment, of strong veterinary and public health systems, of multidisciplinary and multisectoral involvement, of public–private partnerships, of socio-economic analysis and advocacy, and of effective communication among all stakeholders.

Given the international realities of globalization, climate change, and other converging factors, it was further noted that the risk of infectious disease outbreaks will always remain and that the strategies and lessons learned from AI should serve as the foundation of systems designed to prevent and control other zoonotic diseases. It was stressed that we must invest in the improvement of general tools and methodologies related to early detection, active and passive surveillance, preparedness, emergency response, communication, and collaboration, including the funding of collaborative activities to study infectious diseases at the human–animal interface. It was also emphasized that steps already taken by animal health and public health organizations in confronting H5N1 in a collaborative and integrated manner must be made self-sustaining, so that progress can continue even after short term funding flows cease or are redirected to other areas of zoonotic disease.

2 Virological characteristics of influenza viruses (Session 1)

The objective of this session was to identify virological characteristics important for zoonotic and pandemic disease. Speakers presented data on the distribution and phylogeny of H5N1 and other zoonotic AIVs; the effects of single mutations and virus-level factors on influenza transmissibility, infectivity, and pathogenicity in humans; receptors and host specificity; the zoonotic potential of other AIVs; which specific virus characteristics are of interest for public health; and the occurrence of these characteristics in circulating animal viruses.

2.1 Epidemiology, distribution, and phylogeny of currently circulating animal influenza viruses

H5N1 avian influenza in poultry and humans

The currently circulating H5N1 AIV was first identified in animals in 1996 and first caused disease in humans in 1997. Since 2003, it has caused widespread animal outbreaks and associated human cases, as it has spread in poultry and wild birds across Asia, Africa, and Europe and affected domestic poultry, wild birds, and several mammalian species in more than 60 nations. The virus is now endemic in poultry in several countries. The disease can be effectively controlled in poultry when appropriate measures are correctly applied,[2] but such application requires a strong veterinary infrastructure, investment of significant resources, and cooperation among all stakeholders.

Introduction of H5N1 into a country may occur through importation of captive birds, movement of infected poultry and products, indirect mechanical transmission via contaminated equipment and materials, and/or movement of wild birds. It was generally agreed that in developed countries, legal movement of poultry (e.g., eggs and day old chicks) poses negligible risk due to extensive industry regulation, but illegal movement of poultry poses great risks. While the role of wild birds has remained controversial, it was agreed that wild bird migration has been responsible for some instances of long distance virus spread (e.g., into some European countries) but that the maintenance of virus in poultry in many endemic regions is the result of local poultry trade rather than re-introduction of viruses via wild birds. It was agreed that the exact method of specific introductions into individual countries generally remains undetermined.

From 2003 through October, 2008, 387 human cases of H5N1 have been confirmed in 15 countries in Asia, Africa, and Europe. Of these, 245 were fatal, giving a case fatality rate (CFR) that ranges from 44 to 81% depending on the country. Human CFR is likely influenced by time to presentation at a health care facility, appropriateness of clinical management, surveillance bias in case detection, and population characteristics. Most human H5N1 cases have occurred where the disease is entrenched in the poultry populations, and exposures have been to avian (rather than human) virus sources, re-emphasizing the importance of disease control in the avian reservoir. To date, virus clades

[2]Guidelines are available from OIE (http://www.oie.int/eng/normes/mcode/en_sommaire.htm) and FAO (http://www.fao.org/avianflu/en/animalhealthdocs.html)

identified in human cases reflect those circulating locally in animals.

Participants discussed the likelihood that all human cases are being detected. Clearly, some human cases have likely gone unrecognized because of logistical and diagnostic constraints and limited access to health care, as well as differences in surveillance systems (i.e., influenza like illness/ILI surveillance versus pneumonia surveillance), outbreak investigation capabilities, and political willingness to investigate and report suspects. In some cases, H5N1 infection may not be considered a differential diagnosis due to lack of clinical experience or because no poultry exposure was reported. It was mentioned that the number of ''official'' WHO-reported cases is likely low for the above reasons, and because samples from some true cases (especially subclinical, mild, or acutely fatal cases) may not be submitted for laboratory confirmation at a WHO-approved laboratory.[3] It is unknown what proportion of H5N1 cases may be subclinical or mild. Some seroprevalence studies have indicated that these cases do occur but at a low frequency (see section 4.2 exposure).

The public health sector is frequently asked whether the pandemic risk is increasing or decreasing, especially given the decreased number of reported human H5N1 cases since 2006. To date, the H5N1 virus genes are entirely of avian origin, human cases are sporadic, and there is no evidence of sustained human-to-human transmission. The many possible reasons for the decreasing number of reported human cases were discussed, but there was general consensus that the animal and public health sectors must remain vigilant, because whenever AIVs (H5N1 or other subtypes) are circulating and evolving, and whenever humans are potentially exposed, a pandemic threat will remain.

Risks from other subtypes and co- circulation

Numerically, the majority of human infections with AIVs since 1959 have been caused by the H5N1 subtype (due to the current outbreak). It was noted that AIVs such as H9N2 and H7 viruses have also infected humans, and it was agreed that it is likely that both animal and human infections with AIVs are underreported (for humans, particularly those causing milder infections such as H9N2 and H7). As a variety of AIVs are both animal and public health threats, knowledge of where these viruses are circulating is critical to minimizing risk. However, very little is known about the overall circulation of AIVs globally. To increase data on the geographic distribution and prevalence of other subtypes, it was discussed that H9, and possibly additional AI subtypes, be made OIE-notifiable for animals (as H5 and H7 AIVs are currently). However, it must be considered that a lack of surveillance mechanisms for such viruses in many countries could penalize those exporting countries with good surveillance systems.

Whether different clades within a subtype or different AI subtypes can outcompete each other was discussed. It was noted that multiple viruses within the same subtype generally do not co-circulate in poultry. It is unclear whether this is due to competition between different viruses of the same subtype or because viruses have not been introduced in poultry populations at the time when another virus of the same subtype is circulating. It was agreed that the mechanisms underlying the generation of clade diversity and clade replacement within subtypes are not well understood.

It was further suggested that the identification of multiple subtypes in live bird markets (LBMs), some poultry populations, and wild birds may indicate that virus subtypes circulate in separate compartments within these populations, rather than indicating true co-circulation. It was commented that viruses will circulate most efficiently in species to which they are adapted, and such adaptation could affect host range and therefore limit spread. The effects of immunity among clades within a subtype and among subtypes on circulation and co-circulation in the field were also discussed, but these effects, including the effects of other mechanisms on virus circulation, require further investigation. It was noted that, overall, there is insufficient data to make conclusions on co-circulation of AIVs in poultry.

2.2 Viral determinants of zoonotic infectivity and pathogenicity in humans

Effects of virus mutations

The four critical steps of the viral life cycle for influenza viruses are (i) virus binding, fusion, and entry (mediated by the hemagglutinin/HA protein), (ii) transcription and replication (mediated by the PB1, PB2, PA, and NP proteins); (iii) modulation of innate immune responses (mediated by the NS1 protein); and (iv) virus particle release (mediated by the neuraminidase/NA protein) and transmission. Changes to these proteins therefore affect the infectivity, pathogenicity, and transmissibility of AIVs in animals and people. Although extensive and detailed data exist describing specific genomic mutations and protein changes which influence characteristics of avian and human influenza viruses, it is currently not possible to predict what specific combination or ''constellation'' of mutations would be required to transform an AIV into a pandemic virus. It is also not possible to predict whether H5N1 would retain its high mortality if it were to become easily transmissible among humans.

[3]List of WHO approved laboratories for human H5 diagnosis is available at: http://www.who.int/csr/disease/avian_influenza/guidelines/h5_labs/en/index.html

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Receptor specificity is considered a key factor that affects infectivity, pathogenicity, and pandemic potential of avian influenza viruses, and that influences the species barrier. The viral HA protein specifically binds either Neu5Ac-α2,3-Gal (2,3) or Neu5Ac-α2,6-Gal (2,6) sialic acid (SA) receptors on host cells. Birds, horses, sea mammals, dogs, cats, mice, and monkeys express predominantly SA2,3 receptors, while humans, pigs, and ferrets express predominantly SA2,6 receptors. In general, viruses tend to preferentially bind the type of receptor predominantly expressed in the upper airways of their typical host, so that avian viruses typically bind SA2,3 receptors and human viruses typically bind SA2,6 receptors. However, this association is not exclusive and recent studies (e.g., experimental infections in airway epithelial cell cultures and animal models, lectin-binding studies) show that the distribution of receptor type also varies by tissue location, including in different levels of the respiratory tract, as well as by cell type and species. Data are not yet available on differential receptor distribution among races/breeds or individuals within a host species.

Despite these uncertainties, a SA2,6 receptor binding preference is considered essential for an influenza virus to be easily transmissible to or among humans. Although some H5N1 viruses have acquired the capacity to bind to some SA2,6 receptors, clearly these changes have so far been insufficient to allow easy transmission to or among humans.

The HA protein also plays a role in AIV pathogenicity. Systemic infections may develop when the HA contains a polybasic cleavage site (as seen in the currently circulating H5N1 viruses) which may be cleaved by ubiquitous proteases present in virtually every cell of the body. This is a key feature of increased pathogenicity in birds.[4] Systemic infections may also develop when HA receptors that are able to bind a specific virus are present in a wide variety of host tissues. It has been suggested that although the presence of few SA2,3 receptors in the human upper respiratory tract may limit zoonotic transmission of AIVs (as mentioned above), the higher concentration of SA2,3 type receptors in the human lower respiratory tract may increase AIVs' pathogenicity in human lungs. Furthermore, it was noted that cats and dogs differ in receptor expression from pigs and ferrets in a pattern that is not consistent with the pathophysiology of their respective H5N1 infections, indicating that susceptibility and pathogenicity are not just due to receptor specificity of the HA protein and the role of other viral components (such as the NA) should be further studied.

[4]OIE definition of highly pathogenic avian influenza, Article 10.4.1., Provision 1.a., http://www.oie.int/eng/normes/mcode/en_chapitre_1.10.4.htm

It was agreed that receptor physiology is an area in great need of future research. Further studies using natural glycan arrays and mass spectroscopy in various species would help to unravel the complicated questions of receptor specificity of viruses, receptor structure and distribution in different tissues and species, and how receptors modulate virus transmissibility and pathogenicity. The importance of collecting appropriate specimens from human H5N1 cases for evaluation of receptors was also stressed.

Mutations in the other seven influenza genes also influence host range and other characteristics of AIVs. Mutations in the PB2 gene (including E627K and D701N) may influence the optimal temperature of polymerase activity and interaction with host cell factors, and thus replication rate in the mammalian upper airway. Changes in the NS1 and PB1-F2 genes are thought to influence the host immune response to AIVs. A 19–25 amino acid stalk deletion in the NA protein may allow more efficient virus release, and may be required for adaptation of viruses from wild aquatic birds to domestic chickens. Moreover, it has been postulated that the severe human infections seen with H5N1 may be associated with cytokine dysregulation (i.e., severe pneumonia and multiple organ failure), also potentially modulated by the NS1 and PB1-F2 genes.

Changes in the genetic structure of influenza viruses, especially in the M and NA genes, may also indicate decreased sensitivity or resistance to antiviral drugs. Resistance to the adamatane group of antiviral drugs has been widespread in H5N1 clade 1 and 2.1 viruses but is less commonly seen in other H5N1 clades. Resistance to the neuraminidase inhibitor group of antiviral drugs (e.g., oseltamivir) has also been found in some influenza viruses. Recent experience with oseltamivir-resistant H1N1 human seasonal influenza viruses has shown that such resistance in the N1 subtype may occur without causing any loss of virus infectivity or pathogenicity, raising the concern that a similar situation could arise with H5N1. Certainly, more research on antiviral drugs and their limitations is needed.

Species differences

Pathogenesis and transmissibility of AIVs have been studied in animal models. In experimental H5N1 infections, respiratory and systemic pathology and pathogenicity vary by host species, and virus strain and dose-dependent differences exist in transmissibility, infectivity, pathogenicity, and mode of transmission. Pathogenicity is linked to efficient replication; however acute respiratory distress syndrome and multiple organ dysfunction syndrome have been seen in some animal models even when replication is limited to the lungs, indicating that systemic pathogenicity does not necessarily depend on systemic replication. Concerns were raised about the applicability of results from animal models in relation to human disease. The importance of obtaining

data from humans and identifying the appropriate animal model for addressing different research questions was stressed (see also section 4.1, models, below).

The complicated epidemiology of swine influenza was presented. Currently, H1N1, H3N2, and H1N2 subtypes are endemic in some regions, and swine influenza viruses (SIVs) in North America differ from those in Europe. Modern SIVs are usually derived through reassortment of human, avian, and swine viruses. Swine influenza viruses have occasionally transmitted to humans, with at least 40 documented cases representing all SIV subtypes. The main risk factor for humans is exposure to infected pigs, with little evidence of human-to-human transmission, though the total number of human SIV cases is small given the number of swine workers worldwide. Many SIV infections in people likely go undetected; however, it is difficult to determine seroprevalence due to cross-reactivity between human and swine viruses in the hemagglutination inhibition (HI) assay and the fact that recent human seasonal influenza exposure or vaccination can boost antibody titers to SIVs.

3 Evolution and emergence of a pandemic virus strain (Session 2)

The objective of session 2 was to evaluate the factors affecting evolution and emergence of a pandemic strain and discuss monitoring systems. The speakers presented data on the evolution of human pandemic viruses; the evolution of H5N1 in birds; characteristics of H5N1 influencing mutation and reassortment; WHO and OFFLU monitoring activities; and the role of antigenic cartography. Much discussion focused on surveillance, thus a separate surveillance section was added to this summary.

3.1 Viral determinants and ecological conditions affecting mutation rate and probability of reassortment

Emergence of a pandemic strain

To date, only influenza subtypes H1, H2, and H3 have met the three requirements for causing human pandemics, namely, they (i) contained an HA to which the human population was immunologically naïve, (ii) were able to replicate and cause disease in humans, and (iii) were able to efficiently transmit between people. The role of pigs in the past three pandemics is unclear and may have been overestimated and that of domestic poultry underestimated. However, no precursor avian/animal viruses to the previous H1, H2, and H3 pandemic strains are available, thus we do not know the series of mutations that occurred during their emergence and so can not learn from the past to predict the course of emergence of the next pandemic. However, it is likely that once AIVs have mutated sufficiently to circulate widely in humans, they will no longer circulate in poultry. They may, however, transmit to and circulate in pigs.

In discussion, it was noted that the last three pandemic subtypes arose from AIVs that had low pathogenicity in poultry, thus the next pandemic virus may evolve from either a low or high pathogenicity AIV. It also may evolve from an influenza subtype other than H5N1. The current concern about H5N1 reflects primarily the potential severity of an H5N1 pandemic, because even if acquisition of pandemicity is associated with some loss of virulence for humans, the multifactorial virulence properties of H5N1 suggest that it would likely still remain a formidable cause of human morbidity and mortality.

Co-circulation of viruses was discussed again in the context of influenza pandemics (it was previously discussed in the Risks from other subtypes and co-circulation subsection of section 2.1). It was suggested that more influenza circulation in human populations leads to more cross-protection and increased overall immunity (perhaps through internal genes) and reduces the risk for a pandemic. However, competition among subtypes in humans was seen as unlikely to decrease risk of emergence of a pandemic strain, as two seasonal influenza A subtypes (H1 and H3) already co-circulate in humans on an ongoing basis.

There was much discussion on how to prioritize potentially pandemic subtypes and strains. The question of the risk of avian H1s and H3s was raised, as both avian H1 and H3 viruses are circulating in avian populations, especially in LBMs. Current avian H3s are still cross-reacting antigenically to some extent with human seasonal strains, so that seasonal influenza infection and vaccination may have boosted immunity to avian H3s in people. Thus, participants agreed that H3 may be a minimal threat. However, seasonal H1s may not be boosting immunity to avian H1 strains, as avian and human H1s are antigenically distinct. Both H1 and H3 diversity in avian populations and their antigenic cross-reactivity should be further assessed using neutralization and HI test serology studies of human sera from different sub populations against avian strains to evaluate the risk from these subtypes. As H2s are not included in human seasonal vaccines and those born after 1968 have no immunological memory to these viruses, and because this subtype has proven pandemic potential, it was suggested that H2 viruses still pose a pandemic risk. H9N2 viruses and H7 viruses have repeatedly infected humans and H9N2 viruses in particular are geographically widespread. Thus, they both remain pandemic candidates. It was suggested that organizations prepare a repository of vaccine seed strains for a variety of different subtypes, based on viral surveillance in animal populations and zoonotic risk.

Mutation and reassortment

The original low pathogenic virus progenitor of the currently circulating H5N1 is thought to have emerged from the natural gene pool in wild ducks, then started to circulate in domestic ducks and geese, then moved to other domestic poultry. The current virus emerged when reassortant viruses were generated locally in domestic ducks (due to the frequent gene flow from the wild bird reservoir), and then, in 1997, spread through domestic ducks and other poultry in farms and LBMs. Rapid HA evolution occurred in 1999–2000, when most clades were generated, perhaps due to circulation of virus among large, immunologically naïve populations of diverse species. This may have allowed selection of H5N1 viruses adapted to multiple hosts, accounting for the ecological success of this virus strain.

In general, populations of influenza viruses are highly diverse, and evolve rapidly. Substitution rates are generally high for all influenza viruses (including this H5N1 and human viruses) regardless of their host. The rates are significantly higher in HA and NA genes compared with internal genes, and there is negative selection for mutation in genes other than HA and NA. Selection forces are site-specific within the HA, generally affecting antigenic receptor binding and glycosylation sites. Mechanisms for evolution include neutral and selection-driven mutation, reassortment, and possibly compensatory mutations that maintain fitness of reassortant viruses. Forces that influence the direction of viral evolution were discussed; the diversity currently seen in H5 viruses in birds is probably due to spatial heterogeneity and adaptation to a variety of avian hosts.

Many inherent virus characteristics predispose influenza viruses to mutation and reassortment. The influenza RNA polymerase is not capable of proofreading the progeny genomic RNA and therefore, nucleotide substitutions occur with high frequency. The short viral generation time further expands the supply of substitution mutants available for selection. Genome partitioning into eight RNA molecules allows easy reassortment, as demonstrated by frequent field isolations of reassortant AIVs. In addition, avian–human reassortant viruses have already emerged and currently circulate in swine. The 16 HA and 9 NA AIV subtypes currently known offers a broad array of host range, viral tropism, viral shedding, and immune evasion phenotypic characteristics that may confer selective advantages under a variety of pressures. Reassortant genotypes show that certain gene linkages do seem to occur based on functional interactions, but these are not yet well understood. Because influenza viruses are established in multiple avian and mammalian hosts, including humans, dual infections are possible and can allow reassortment in a co-infected individual, especially species expressing both SA2,3 and SA2,6 receptors in the upper airway (e.g., swine). Influenza viruses cause a mucosal infection therefore limited immunologic memory favors immune evasion, repeated infections, co-infection, reassortment, and mutation. These characteristics contribute to the plasticity and overall evolutionary success of influenza viruses.

Interestingly, in contrast to human and avian viruses, there was almost no antigenic change in classical SIV strains between the time of their introduction at the beginning of the previous century until the emergence of human-avian-swine triple reassortant H3N2 viruses in the late 1990s.

3.2 Monitoring for important viral changes

Monitoring by WHO and OFFLU

The WHO Global Influenza Surveillance Network (GISN) was established in 1952 to monitor antigenic and genetic evolution and mutations and spread of human seasonal influenza virus variants, to decide on the composition of human influenza virus vaccines. Resistance to antiviral pharmaceuticals is also monitored. This information is important for biannually recommending virus strains for human seasonal and H5 vaccines, and for assessing changes influencing the reliability of current diagnostic reagents, increasing human zoonotic or pandemic risk, changing clinical outcomes, or resulting in drug resistance. Some laboratories in the network are monitoring swine and avian viruses as well.

The OIE/FAO Network of Expertise on Avian Influenza (OFFLU; now entitled 'OIE/FAO Network of Expertise on Animal Influenza') was created in 2005 to facilitate exchange of scientific data and biological materials, offer technical advice and expertise, collaborate with the WHO influenza network, and support AI research. Active collection and analysis of AIV strains allows the OFFLU network to share information and material in support of global AI prevention and control. Technical activities address gaps in influenza diagnostic and epidemiological knowledge.

OFFLU and WHO are working to formalize communications and build upon current collaborations including information sharing and technical projects. Activities to improve virological and epidemiological monitoring and joint analysis will be crucial to early detection and risk assessment of public health-relevant AIVs circulating in animal populations.

The example of Africa and the Middle East was used to demonstrate how animal sector virological surveillance might be used to identify public health-relevant viral mutations. In these regions, H5N1 has been identified in both poultry and wild birds since 2006, and the sequence data from many isolated viruses has been made available to the scientific community. The data (which suggest multiple

introductions in some areas and ongoing circulation in others) can be used to inform specific animal sector prevention and control measures. As well, data can be used to inform public health risk assessment. For example, mutations associated with previous human pandemic isolates have been identified in these viruses, and adamantane resistance has also been identified. These findings were communicated to the international public health sector immediately after determination. Improved two-way communication between the animal and public health sectors regarding which specific mutations are of public health interest, and which of those mutations are circulating in animal populations, would optimize early detection of emerging viruses with increased zoonotic or pandemic potential.

The importance of systematic monitoring of AIVs for antiviral resistance was stressed. When current antivirals are no longer useful against circulating strains, new antivirals need to be developed. Laboratories need to investigate new resistance mutations by genotypic and phenotypic screening, flag resistant viruses for tracking, and communicate these findings readily between the animal and public health sectors.

Development of a standard H5N1 nomenclature by the joint WHO/OIE/FAO H5N1 evolution working group has provided both the animal and public health sectors with a phylogenetic classification system based on the HA gene.[5] This system improves interpretation of sequence data from different laboratories, removes subjective geographical references, allows for expansion as new clades emerge, and provides a basis for a more extensive system including antigenic variation and genotyping. Expansion of the system to H9 and SIVs is being planned. It was mentioned that the unified nomenclature further strengthens pandemic preparedness activities related to vaccine, antiviral, and diagnostic test development and stockpiling by focusing efforts on the most relevant emerging viruses.

Antigenic cartography

Antigenic cartography provides a way to visualize the antigenic evolution of influenza viruses using HI assay data. In antigenic maps, antigenically similar viruses appear closer together, allowing visualization of antigenic changes through time and geographical space. The technique was first applied to human H3 virus evolution, using ferret-serum generated HI data from human seasonal viruses, and since 2004 has been effectively used by WHO for selection of human influenza vaccine strains. H5 antigenic cartography is in the early stages of development for human vaccine strain selection, but is also being used for evaluating avian viruses for animal health sector use. Different patterns are being seen using the animal health sector HI data, which may be due to creation of HI sera in chickens (rather than ferrets) or to using sera raised with adjuvanted (rather than non-adjuvanted) antigens. It was suggested that, ideally, the antigenic analyses of circulating strains by the animal health and public health sectors should be integrated.

Epidemiological and virological surveillance and information sharing

In discussion, the importance of strengthening global virological and epidemiological surveillance for H5N1 and other animal influenza viruses to ensure early detection of both disease and virological changes was strongly emphasized.

It was agreed that both the animal and public heath sectors would benefit from improved knowledge of the properties of H5N1 (or other AIVs) that are circulating in animals to adequately assess which strains should be recommended for veterinary and human vaccines and to update diagnostic reagents according to genetic and antigenic evolution. Having a full and broad picture of the distribution and prevalence of viruses and disease globally would allow better assessments of animal and public health risks, as well as the identification of mutations of public health significance.

Surveillance in poultry and wild birds in Europe, North America, Hong Kong, and other selected locations is intensive, but in many areas of AI risk, surveillance is weak or lacking and needs to be supported and improved in a sustainable way. It was noted that in Europe, existing surveillance has led to early detection of H5N1 on several occasions. Currently, the extensive European data is maintained in the DG-SANCO database,[6] and partly (for wild bird isolates) in the EU-funded research project New-Flubird.[7] A common global platform and linking of surveillance systems would be ideal, with one constraint being the differences in types of surveillance among countries. Improved communication between existing platforms would already be a positive step forward.

It was recognized that when effective passive and active surveillance leads to early disease detection, then disease control is improved. However, effective animal sector surveillance requires a complete and functional veterinary infrastructure and supporting diagnostic laboratory capacity. As well, effective use of resources requires appropriate targeting (e.g., by species, sector) and implementation according to differing disease patterns (e.g., for sporadic versus endemic disease situations). It was recognized that

[5]http://www.who.int/csr/disease/avian_influenza/guidelines/nomenclature/en/index.html

[6]DG Sanco data available at http://ec.europa.eu/food/animal/diseases/controlmeasures/avian/eu_resp_surveillance_en.htm

[7]New Flubird data available at http://www.new-flubird.eu/

surveillance may not be implemented properly, even if the system is appropriately written in the national legislation. Surveillance systems in humans should also vary by the disease situation. For example, where AIVs are endemic and sporadic human cases are occurring, it was suggested that it would be most efficient to focus on the early identification of clusters of human cases.

The social aspects of surveillance were discussed, for example that passive surveillance fails when people feel threatened by the consequences or when tools and systems are impractical for the targeted community (e.g., broad case definitions for AI in areas where poultry deaths are common), and thus, that surveillance should be community-based and customized for each setting. The use of community-level incentives and disincentives was discussed, and it was agreed that the differences between what may by considered incentives and disincentives by the key players in the human and animal health sectors may not be appreciated.

It was agreed that overall, surveillance in human and animal populations should be better coordinated. Coordination is working well in Indonesia, where there is active human surveillance in areas of animal outbreaks and *vice versa*. This has, for example, reduced average time to human antiviral treatment from 4 to 2 days. It was suggested that it would be more sustainable to coordinate AI surveillance with surveillance for other zoonotic diseases. It was agreed that any coordination requires good communication between the animal and public health sectors, which may vary on the local level and may be influenced politically.

There was a generalized call for OIE, FAO, and WHO to formalize the sharing of virus samples and associated information for all AIVs. The importance of whole genome sequencing of an appropriate virus subset and ensuring timely availability of information was also stressed. The problem of information sharing with and among countries who may have technological difficulties in ''connecting'' was discussed (as these are often the countries at risk). It was noted that timely information sharing can also allow individual countries to decrease their risk of exposure.

4 Human transmission risks and exposure source (Session 3)

The objective of session three was to identify likely modes of transmission and exposure sources for zoonotic infection with AIVs. During this session, speakers presented data on possible modes of seasonal and zoonotic influenza transmission; sources of exposure for human cases of H5N1 (including the potential roles of exposure to poultry products and by-products, of culturally relevant poultry/human interactions, of poultry management systems, of LBMs and of contaminated environments); food safety issues; and evidence to explain the low incidence of H5N1 cases in humans. The country representatives briefly outlined what they considered the successes and challenges of their national H5N1 experience, which are also summarized here.

4.1 Modes of transmission for human infection with avian influenza viruses

Modes of transmission

The modes of human seasonal influenza transmission have not been completely elucidated. People shed influenza virus from the respiratory tract, and potential modes of transmission include contact spread, aerosol spread, and droplet exposure. Influenza virus survives on hands for 5 minutes but on other surfaces for 12–48 hours. It was suggested that hand hygiene is important to decreasing risk. Viability of virus in aerosols depends on initial concentration, temperature, and humidity. Inhalable particles account for <10% of the volume of a cough, but despite some animal experiments and studies in humans the role of long distance aerosols is uncertain. It is unknown whether droplet induced infection is the result of direct deposition of droplets onto facial mucous membranes, deposition onto hands with transfer to the face, or inhalation. Additional seasonal influenza transmission studies, evaluating the effects of masks, respirators, and hand hygiene on transmission, are pending.

Potential modes of zoonotic AIV transmission to humans also include contact (with oral or nasal mucus membranes or conjunctiva) and inhalation (of contaminated dust from rearing or slaughter, or fine water droplets generated during household or live bird market slaughter). Mouse, non-human primate, domestic cat, guinea pig, ferret, and pig models each has its specific applications for the study of influenza virus virulence and transmission (also discussed in the species differences subsection of section 2.2, above). For example mice are susceptible to field strains of H5N1 avian viruses, but H3N2 human viruses require adaptation to the mouse host through repeated passages. Ferrets are the best animal model for studying both virulence and transmissibility of influenza viruses to humans, due at least partly to similar respiratory tract distribution of SA2,6 receptors. Guinea pigs may be a suitable model to study human influenza virus transmission, but their use for other influenza viruses remains unknown. Pigs are also susceptible to infection with some avian and human viruses, but have not shown clinical disease or systemic infection in experimental studies with H5N1 to date.

Ferret studies suggest that contact and droplet transmission of H5N1 and other AIVs to mammals are generally inefficient, although H5N1 has been transmitted to ferrets housed in a room where asymptomatic infected chickens were slaughtered. Overall, studies show that transmission (as well as pathogenicity and virulence) depend not only on animal host species but also on virus subtype and virus strain, dose, and exposure route.

4.2 Exposure risk for human infection with avian influenza viruses

Exposure data on human cases

Specific exposure risks for AI H5N1 infection in humans are not well understood, and likely differ greatly by country. Along with direct contact with sick or infected poultry, indirect contact with poultry, environmental contamination, and contact with healthy infected poultry are also likely to be risks. Most humans infected to date were not in ''traditional'' occupational risk groups, while subpopulations such as children and housewives seem to be at greater risk in some countries. As well, the risks posed by different types of poultry, and household animals such as cats, are not yet understood. It was agreed that it is not currently possible to globally disentangle data and determine specific risk activities, and that epidemiological data collection and analysis should be improved. It was suggested that ecological aspects, the species of birds or other animals, the vaccination status of domestic poultry, and the type of poultry production system[8] associated with human cases should also be recorded and considered in analysis. It was stressed that, although it is clear that control of AI in poultry is the most important step in reducing zoonotic risk and pandemic threat, understanding specific zoonotic risks is important to enable development of practical risk reduction measures for humans.

Representatives from affected countries reported that human cases are usually located in areas of poultry cases, and that exposure history has included household poultry raising (especially poultry living inside the house), poor poultry vaccination coverage, exposure to sick or dead poultry, lack of an indoor water source, visiting LBMs, having an underlying medical condition, and in some cases occupational poultry exposure. In many cases, a specific exposure was inconclusive or unknown despite in-depth investigation.

The question of why human H5N1 cases seem to be occurring only in certain countries and communities was discussed. It was agreed that this reflects primarily the presence of infected poultry and the amount of virus present, but might also reflect the surveillance system or other as yet unidentified local ecologic, cultural, genetic, virological, or management factors.

Most studies have indicated a very low seroprevalence of antibodies to AIVs among people in high risk occupations, such as poultry cullers and LBM workers, in affected countries. The many difficulties with the serological tests were mentioned, and it was noted that more sensitive and discriminating subtype-specific tests need to be developed. It was agreed that more seroprevalence studies for AIVs in humans need to be done and the results from completed studies need to be shared with the wider scientific community in a more timely manner. It was noted that solutions must be found to improve timely publishing and sharing of study results with the animal and public health communities, to improve the availability of seroprevalence, case control and attack rate data for zoonotic AIVs.

Consumption and inactivation

Avian influenza is not generally considered a food safety issue, as complete cooking inactivates the virus and the risk of infection from foods cross contaminated with virus is negligible.

Virus is contained in meat, viscera, blood and eggs from poultry infected with highly pathogenic AIVs. Consumption studies of raw infected chicken meat in ferret and pig models suggest that H5N1 viruses initiate infection via the tonsil or pharynx with spread to the upper and lower respiratory tract. However, experimental data in pigs and ferrets suggest that foodborne infection by consumption of raw infected meat would require higher viral doses than would infection through respiratory tract exposure. Thus, risk reduction measures for humans include pasteurization or thorough cooking of meat and eggs, basic kitchen hygiene, and consuming products derived from vaccinated poultry (as poultry vaccination prevents viremia and localization of virus in muscle tissue).

Freezing at −70°C preserves the virus, while inactivation at −20°C is inconsistent and unpredictable, and refrigeration (4°C) allows slow virus inactivation in meat due to decreasing pH and enzymatic action. Infectious virus has been detected in frozen raw poultry stored in a household freezer.

Risk from live bird markets and virus in the environment

Multiple AIV subtypes, including H5N1, H9N2 and H6N1, have been obtained from birds in LBMs in Asia. Interestingly, H7 subtype viruses are not commonly found in LBMs. Isolation rates and virus subtypes differ by species of poultry and location, with more frequent virus recovery from aquatic poultry (ducks and geese) than chickens, and higher isolation rates during the winter. Studies show that LBMs can maintain, amplify, and allow dissemination of

[8]Poultry production sectors described in: FAO Recommendations on the Prevention, Control and Eradication of Highly Pathogenic Avian Influenza in Asia, Sept. 2004, available at http://www.fao.org/docs/eims/upload/165186/FAOrecommendationsonHPAI.pdf

AIVs to farms and are a source for human infection, and are therefore a useful site for targeted surveillance. It was noted that, in an affected country, virus concentration is generally low at the farm or household level, increases at wholesale markets, and is further amplified and sustained at LBMs from where virus may be disseminated back to farms and households.

Data from different countries was presented. Risk factors for LBM contamination included housing of unsold poultry overnight, presence of Muscovy ducks, presence of a large duck population, and slaughtering in multipurpose areas and in stalls. Human risk at LBMs was associated with the presence of restaurants and food stalls in markets, having family members in the market, and the use of traditional slaughtering processes. Viral burden in LBMs was shown to be decreased by implementing a rest day, removal of particular species (e.g., quail), improving market hygiene, and not allowing live poultry to remain overnight. However, LBMs must be specifically assessed as they vary greatly among and within countries and therefore do not all have the same risk factors.

It was discussed that in many countries LBMs play an important role in people's cultural and economic lives, and thus appropriate and culturally sensitive ways to decrease associated AI risks must be sought. Specific targeted assessments of LBMs would allow understanding of the environmental contamination of different areas within LBMs and among LBMs in different settings, communities, and countries. Having decisive political support would allow the animal and public health sectors to develop appropriate strategies, regulatory frameworks and guidance. Measures to decrease risks could then be integrated into national systems to improve the general hygiene of LBMs and reduce risks for AIV and other animal and zoonotic pathogens.

Contamination of environments can be heavy during poultry outbreaks, with virus being isolated from households, wet feces, pond water, mud under animal cages, soil (including that beneath houses on stilts), in poultry ranging places, and on the feathers of dead poultry. In environments, AIVs survive in water, in feces, and on surfaces. Temperature, porosity of the surface and water salinity all affect survival time. More recent H5N1 viruses have been shown to survive longer in chicken feces than those viruses from 1997, but studies suggest this is due to longer decay times because of higher virus titers within feces and is not an intrinsic resistance of the virus strains to inactivation.

Cultural practices associated with risk

Some key cultural practices may increase risk to humans. For example, traditional poultry production and people sharing their living areas with poultry put humans in close and prolonged contact with infected animals and contaminated environments, and cock fighting involves direct contact with avian blood and respiratory secretions. Often these practices are linked with economics (household poultry turning household waste into inexpensive protein, duck farmers paying rice farmers to allow ducks to feed on left over rice); practicality (food stalls and family members helping in LBMs; eggs and poultry available in household or village); necessity (LBM and household slaughter required when no available cold chain; workers staying in poultry house to protect poultry); cultures and beliefs (entertainment and prestige of cock fighting; believing in bad luck or karma as cause of outbreaks). It was suggested that extensive public awareness campaigns and communication may improve public knowledge but not change practices due to the considerations described above. It was emphasized that cultural issues are complicated and take time to change, requiring an integrated package of interventions, education, and work within the community.

Poultry systems and management practices associated with risk

Much more is known about risk of spread of the virus in animal populations than is known about human zoonotic risk. Because exposure of humans mainly occurs directly or indirectly through infected poultry, it is important to understand the risk posed by different poultry populations. As well, poultry raising and marketing systems differ among countries and therefore pose different risks. In general, risk of spread among birds is increased in countries that have large poultry populations, and that produce a variety of avian species in all four FAO-defined poultry sectors,[8] especially when much of the production is in small scale farms or in households. The H5N1 endemic countries tend to have large domestic waterfowl and wild bird populations, although the limited available field data on the role of wild birds in virus spread is difficult to interpret in the context of reservoirs and infection dynamics. The disease often has seasonal occurrence, with outbreaks generally occurring in the winter, due to many factors including rice harvests and holiday festivals as well as weather.

Risk of incursion onto a farm is determined by the amount of outside contact and whether it involves possibly infected or contaminated material, the local level of infection, and biosecurity measures taken. It was noted that even in endemic countries most poultry and locations will not be infected or contaminated (with the exception of some LBMs), though each flock will have its own risk profile based on multiple factors, especially biosecurity level. Increasing human populations, food prices, and concerns about ethical rearing could lead to more poultry raised outdoors, which would increase risk for exposure and virus spread.

There was some discussion on the effects of naturally acquired influenza immunity on infection dynamics in

poultry and wild birds. Some birds probably have immunity to a variety of AIV strains, and this may influence what subtypes are seen in the populations season to season.

Public health aspects of poultry vaccination

The topic of poultry vaccination in was raised several times during the meeting, and the national vaccination programs of China, Egypt, Indonesia, and Viet Nam were described by representatives of the respective Ministries of Agriculture. Countries consider vaccination of poultry important for protecting public health as well as animal health. The vaccination coverage varies among countries, among locations in a country, and among poultry sectors and avian species. Constraints to effective implementation may include inability to achieve adequate coverage of large, dispersed poultry populations, insufficient manpower, inadequate post-vaccination monitoring, use of different vaccines, variable vaccine quality and lack of quality assurance, as well as weak regulatory support and insufficient infrastructure of veterinary services in some cases. Strategically targeting vaccination by species or sector may increase efficiency of national programs. It was recognized that comprehensive recommendations for effective poultry vaccination are already available from OIE and FAO.[9]

The possibility of harmonizing the selection of virus strains for avian and human vaccines was raised, as the updating processes are currently different. However, the needs, processes, and vaccine development systems are also different. Given the importance of poultry vaccination for the protection of animal and public health, the need for continued vaccine research was stressed, including working towards developing a poultry vaccination platform that elicits neutralizing antibody, works in multiple species, can be given orally or is otherwise easy to administer, and provides good duration of protection. Monitoring of AIV strains in the field, especially in the commercial production sectors, is also important.

Other variables affecting risk of human disease

Discussions of human risk variables invariably raises the question of why the number of human cases is relatively small given the massive potential exposure of humans in areas where H5N1 is circulating. It was suggested that there are likely other inherent virus-related or individual host-related variables that influence transmission to and infection of humans.

Virus-specific factors (described in depth in previous sections) do not seem to explain the observed pattern of human infections. Differences in virus dose and exposure intensity also do not explain the infection pattern, because there are very few cases in cullers and others potentially exposed to very large virus doses and 25% of negative controls report high levels of exposure to poultry, while 25–30% of H5N1 cases do not report any poultry exposure. The mode of transmission also does not explain the observed epidemiology as case control studies have not identified unusual exposures (like swimming in rivers and lakes, or eating raw duck blood) as explanations for the majority of cases. It was therefore suggested that increased risk must be associated with host factors, including immunity or genetic or phenotypic susceptibility. Evidence for some clustering of cases among blood relatives supports the potential role of genetic susceptibility, although shared environmental exposures must also be considered when investigating human clusters.

How to evaluate these factors was discussed. It was agreed that a more full assessment of the potential individual variables (e.g., analyses of ILI/health history, co-infection with other influenza viruses, assessment of antibody and cell mediated immunity (CMI), glycan arrays for receptors, genetic evaluation, epidemiological studies of families where some individuals are highly exposed and some are not), as well as more extensive and consistent data on exposures as described above (e.g., behavioral factors, seasonality, climate, links with poultry outbreaks, gender, age, occupation; behaviors/activities including level of skill, species of animals present, virus clade, and cultural aspects) would provide not only clues to the true exposure risks but practical information for more effective surveillance and monitoring and for development of more effective control and prevention strategies.

National-level successes and challenges:

Invited representatives of selected Ministries of Health and Ministries of Agriculture identified their national successes and challenges regarding H5N1 at the human-poultry interface, including:

Successes:

- Increased political commitment and coordination with local authorities
- Increased cooperation between animal health and public health sectors
- Increased collaboration with international reference laboratories, and with international partners (FAO/OIE/WHO) and funding agencies
- Increased public and professional awareness and availability of community-based information, education, and communication activities
- Vaccination campaigns preventing disease spread among poultry and reducing viral load

[9]HPAI Manual chapter, HPAI code chapter, output from Vaccination meeting 2007 (http://www.oie.int/eng/info_ev/Other%20Files/A_Guidelines%20on%20AI%20vaccination.pdf)

- Implementation of government compensation promoting rapid disease reporting and transparency
- Upgraded national laboratory diagnostic capacity and infrastructure

Challenges:

- Inadequate virological and epidemiological surveillance in domestic poultry including waterfowl, and in wild birds
- Understanding the linkage between poultry outbreaks and disease in humans, including understanding occurrence of human cases where no cases were reported in poultry
- Risks from extensive backyard, household, and rooftop poultry production
- Risks from LBMs
- Large populations of poultry to vaccinate and risks posed by unvaccinated poultry in LBMs and household flocks
- Cultural practices such as cock fighting
- Ineffective (or unfunded) compensation programs for culled poultry during outbreak control
- Ongoing tensions between levels of governments and among sectors

5 Broadening the use of tools and systems (Session 5)

During this session speakers briefly discussed emerging infectious diseases (EIDs) at the human–animal interface, tools and methods used to evaluate emergence of other zoonotic diseases, and the OIE/FAO/WHO Global Early Warning System for transboundary animal diseases (GLEWS). There was recognition that some tools and systems were developed for, or strengthened by, the H5N1 situation over the past 10 years, but that these systems have also been used effectively to address many other zoonotic or emerging diseases.

Presenters emphasized that EIDs are the ''new reality'' as up to 34 new EIDs are expected worldwide by 2015, and noted that 61% of EIDs are zoonoses. Speakers reviewed the factors influencing emergence including genetic, biological, physical, environmental, ecological, social, political, and economic factors, as well as the role of animal and public health systems. Changes in host–pathogen ecology were considered the most important single driver for emergence. The convergence of these human, animal, and environmental health factors requires working collaboratively, in a multidisciplinary way, and at local, national, and global levels to attain optimal health of humans, animals, and the environment. In discussion, it became clear that this concept was not new, however the roles and strategies of all the players globally are not fully understood nor effectively integrated.

''Wicked problems'' (those that have no solution through traditional processes) were discussed in the context of EIDs, and it was noted that managing these problems requires linking together separate problem-solving activities into integrated strategies and systems. For example, all countries have a stake in everyone else's disease surveillance, however it is not necessarily in a country's best interest to share surveillance information with their neighbors or the international community. Managing such dilemmas requires working across disciplines, professions, and animal and public health communities and factoring in social, economical, and political forces, as well as ensuring political will, prioritizing research to support evidence-based policies and decisions, adding value gained from avian influenza H5N1 experience by applying it to other zoonoses, determining the potential application of ''big science'' (e.g., global technology and bioinformatics) and creating concurrent planning scenarios of improving what exists and creating what doesn't.

The animal and public health sectors have vast experience in addressing EIDs, and recognize the importance of rapid response, global collaboration, and multidisciplinary teams. In the past, these activities have consistently been done separately, but now the continuum between animal and human pathogens, the need for integrated (meaning linked not necessarily single) strategies, and the need for improved animal and public health infrastructures is increasingly apparent. Health is now recognized as an outcome shaped by a broad range of social, economic, natural, ecological and political environments that form an ever-changing dynamic. Thus, new ways of working together need to be identified that reflect this reality. Our work on avian influenza H5N1 has given us valuable experience in how to effectively do risk communication and messaging, and how to evaluate social and cultural determinants of disease; however, we must build on these experiences and become even better as we appreciate the need to incorporate the social sciences into our strategies to confront new emerging zoonoses.

Today's technologies can help to better detect, manage, and contain the international spread of EIDs. There have been great improvements in global tools and systems, such as surveillance and forecasting of emerging diseases through intersectoral (animal, human, and environment) collaboration such as GLEWS, formal collaboration with wildlife disease experts, support of EID vectorborne network, and WHO global outbreak alert and response network (GOARN), global public health information network (GPHIN), and connection of different laboratory networks. Technology and successful collaborations have allowed risk mapping, forecasting and early detection of EID events [e.g., Rift valley fever (RVF) and Ebola]. Working together on each of the steps from forecasting through response at the country-level builds trust, and therefore facilitates a more efficient and coordinated response and improved prevention and control. It was noted that standardization of risk analysis and forecasting needs to be addressed, includ-

ing identifying standard procedures, methodologies, and/or platforms and training personnel in their use. It was further emphasized that animal and public health authorities should have a common and coordinated strategy to forecast, detect, and control EID outbreaks, as well as common Standard operating procedure (SOPs) for district surveillance officers and veterinarians to control selected EIDs using an FAO/OIE/WHO agreed strategy, as well as preparedness and occupational health guidelines.

Issues around early detection of EIDs were discussed. The current and future activities of the GLEWS early warning system were reviewed, and include bringing together animal and public health systems to share information on zoonotic disease outbreaks, conduct epidemiological and risk analyses, and to deliver early warning messages to the international community. The goal is to develop holistic approaches to pathogen and disease understanding which include ecological and socioeconomic factors, pursue outbreak probability modeling, and examine disease presence or absence in relation to a variety of external factors. It is also planned to expand the use of this system to share many kinds of data (e.g., laboratory diagnostic capacities of countries or regions, veterinary infrastructure, and training available) and to provide a common platform for other collaborative work (such as identifying risk factors for endemic diseases). It was suggested that international agencies could place interns in countries to conduct GLEWS surveillance and build internal commitment for programs.

It was noted that to ensure early detection, surveillance needs to be improved in wildlife, especially in situations where wildlife come into contact with humans (e.g., via the pet trade, bush-meat or live game markets), as well as in domestic livestock. However, experience with the WHO event management system has shown that, with increased surveillance, it becomes challenging to determine which identified events require a response. Work is ongoing to boost the real signals against the background, look at more reliable sources of information, and develop a gold standard for a positive predictive value of information. It was mentioned that another large area of work is to link other tools for information gathering and analysis (e.g., Google). Using ''big science'' technologies to solve the surveillance question was discussed, such as using deep amplicon sequencing to pick up subclinical pathogens. Broad geographical sampling would also decrease concerns about transparency by ''evening out the playing field.'' It was mentioned that, in 2008, we have the technology to not be surprised by every new outbreak, and should be applying it more appropriately.

6 General conclusions

The world faces continued threats from avian influenza and other zoonotic diseases, which can only be effectively minimized through new strategies of collaboration focused at the human–animal interface.

Collaboration and coordination

Much has been learned about controlling avian influenza in animals and people, and the world is better prepared to confront influenza threats. However, important gaps remain both in scientific knowledge (e.g., modes of transmission, occupational risk, baseline exposure rates, role of live bird markets) and in the rational and sustainable implementation of control measures. The animal and public health sectors need to coordinate and complement their research as well as their disease control and prevention activities in a more formalized manner and to the fullest extent possible.

Surveillance and use of data

The circulation and continuous evolution of potentially zoonotic animal influenza viruses in birds, humans, and other hosts poses an ongoing public and animal health threat. Along with H5N1, other animal influenza viruses also have or could develop the characteristics necessary to infect humans and potentially become a pandemic strain. The prevalence and distribution of all animal influenza viruses have been insufficiently characterized on a global level, and is likely to be underestimated. Some systems and tools for virological and epidemiological surveillance and monitoring of animal influenza viruses in animal and human populations exist. However, influenza surveillance needs to be expanded to integrate other relevant private and public institutions so that circulation, evolution, dynamics, and risks can be fully understood and analyzed, sustainably and in real time.

Transdisciplinary research on zoonotic risk

Controlling avian influenza in poultry is the primary method to reduce human risk from zoonotic infections. Understanding the measures aimed at preventing and controlling HPAI H5N1 in poultry has improved greatly over the past 4 years. In many countries measures have been effectively applied, decreasing the number of human cases being reported. However, the specific human activities and behaviors, as well as host, virus and ecologic and country-level factors (e.g., the role of live bird markets), associated with human zoonotic influenza have not been identified sufficiently to support strategies to eliminate public health risk. Further data collection, analysis, and research both within and between the human and animal health sectors are critical to fully understand the scientific basis for zoonotic risk.

Sharing of information and technical tools

There has been a dramatic improvement over the past few years in both the collaboration between the animal and

public health sectors and the availability of technical tools for monitoring and understanding influenza (e.g., antigenic cartography, shared databases). However, mechanisms for facilitating broad and timely access to information and tools are not adequately developed to ensure early detection of, rapid assessment of, and response to threats from influenza viruses. The implementation of more effective prevention and control tools and strategies can only be achieved through a more effective and timely exchange of genetic, antigenic, and epidemiological data on these viruses.

Moving towards sustainability

Ensuring sustainability is crucial to maintaining infrastructure and capacity development and development of tools and systems for assessment and response. One way for tools and systems built or planned to address AI to become more sustainable would be to make them applicable for a broader array of existing and emerging diseases.

Addressing other emerging zoonoses

It is clear that avian influenza H5N1 is just one of a number of emerging zoonoses, and that experience with H5N1 at the human–animal interface can be enormously instructive and insightful in meeting the challenges of future emerging diseases. The development of effective best practices, tools, and systems to control and prevent H5N1 can be leveraged and applied to other zoonoses.

Conflict of interest

The authors and contributors have not declared any conflicts of interest.

Appendix A: Recommended short to medium term actions

Collaboration and coordination

1. Promote and strengthen ongoing collaboration (e.g., joint evolution working group, technical exchange of scientific information, national coordination of sectors) and identify novel areas for additional technical collaboration.
2. Identify new strategic partners to better address gaps in knowledge at the human–animal interface.

Surveillance and use of data

1. Broaden the timely collection of both HPAI and LPAI influenza viruses and associated epidemiological data to ensure that the full scope of hosts, ecologies, and geographic areas are represented (e.g., including environmental monitoring in markets, rice paddies, households, and other areas of increased risk).
2. Expand partnerships with the private sector and improve capacity where necessary to ensure adequate influenza surveillance.
3. Support research on diagnostic tests for influenza in poultry and humans aimed at improving consistency, sensitivity, rapidity, and cost-effectiveness.
4. Use virological surveillance data to inform continual reassessment of diagnostic reagents and vaccines, monitor virus evolution and antiviral resistance, and assess risks of emergence of potential zoonotic and pandemic strains.

Transdisciplinary research on zoonotic risk

1. Increase and improve data on zoonotic influenza in humans through standardized data collection, and additional case control and serological studies in the field.
2. Develop tools and conduct integrated analysis of zoonotic risks from animal influenza viruses, and translate technical knowledge gained into practical strategies and recommendations at the interface.
3. Determine the public health risks from live poultry markets and assess the impact of interventions at different levels of the market chain.
4. Improve understanding of the pathogenesis and modes of intra- and inter- species transmission of zoonotic influenza viruses through more detailed studies in humans and better animal models, including improving understanding of the tissue distributions of virus receptors and their role as barriers to transmission, and use knowledge to enhance animal and public health risk mitigation strategies.
5. Improve understanding of the factors that drive the evolution of animal influenza viruses in poultry, other birds, and mammals.
6. Promote full genome sequencing of isolates and ensure continual updating of information on all relevant influenza virus mutations and reassortments.
7. Determine the zoonotic potential of swine and other animal influenza viruses of various subtypes.
8. Develop and validate more sensitive and specific tests for detecting antibodies to avian influenza viruses in avian and non-avian species including humans.
9. Incorporate experts in social sciences and communication to ensure that interventions and recommendations to decrease public health risks take into account cultural and socioeconomic aspects that will improve the efficacy of implementation.
10. Monitor the impact on public health of measures to reduce infections in poultry, such as poultry vaccination, and strive to continually improve such measures.

Sharing of technical tools and information

1. Continue to strengthen and improve existing mechanisms and systems for information collection, sharing, and analysis maintained by OIE and FAO (including OFFLU) and WHO (such as GLEWS) and facilitate and promote interagency collaboration wherever possible.
2. Establish real-time communication systems to widely share and discuss technical information among all global, regional, and national partners and stakeholders.
3. Find innovative solutions to improve technical collaboration and effective information and material sharing.

Actions for broadening

1. Promote a more holistic and collaborative approach to improve both human and animal health and build more effective teams and partnerships, especially through strengthening of existing institutions.
2. Promote study of the ecology of emerging zoonoses and construct new interventions and prevention strategies based on scientific understanding of the effects of ecology on diseases at the interface.
3. Encourage the further expansion and refinement of the GLEWS system and the GLEWS platform for sharing information among the organizations (e.g., consider including laboratory and outbreak investigation team training and developing internships).
4. Move towards coordinated development of diagnostics and reagents for use across animal and public health laboratories wherever appropriate, to ensure improved standardization, comparability, and accuracy of results.

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5. Recognizing the fact that many infectious diseases of humans have emerged from previously unrecognized pathogens in wildlife, leverage the concept of ''Big Science'' by using novel approaches to pathogen discovery, the use of new informatics tools, and open sharing of information.
6. Devise and apply tools to monitor the efficacy of implemented strategies towards a better response capability for emerging diseases of importance.

Appendix B: Gaps at the human–animal interface

Surveillance

1. Enhanced and sustainable epidemiological and virological surveillance in animals and humans (with improved scope and quality of data collected) for H5N1, H9N2, and H7 viruses as well as other potentially zoonotic animal influenza viruses, including swine influenza viruses (leading to closer estimates of the global prevalence and distribution of these viruses).
2. Solution to achieve better reporting of potentially zoonotic non-H5 and H7 subtypes.
3. Enhanced surveillance specifically among ducks, other silent reservoirs of avian influenza, and wild birds to evaluate prevalence and persistence.
4. Improved surveillance in human populations potentially exposed to animal influenza viruses, including sero-surveillance and serological studies.
5. Increased support of virological surveillance, especially the use of screening tests, with confirmatory testing and more frequent and representative genetic characterization, antigenic characterization, and full genome sequencing of selected strains.

Virology

1. Phylogenetic information on other potentially zoonotic influenza subtypes.
2. Understanding the contribution of avian virus reassortment to host range expansion, virulence, and transmissibility.
3. Understanding determinants of fitness, and of the fitness loss/gain by reassortment among influenza viruses.
4. Efficient and reliable methods for virus isolation from environmental samples, including air.
5. Understanding of factors affecting cross-protection of poultry and human vaccines.
6. Understanding of the effect of vaccination on influenza virus evolution.

Epidemiology

1. Expanded and consistent capture of epidemiological data on human zoonotic influenza infections (including use of standard data collection tools and standard definitions).
2. Estimate of the baseline level of potential risk variables for populations in general.
3. Estimate of the true incidence and numbers exposed for H5N1 and other potentially zoonotic influenza subtypes in humans (e.g., by systematic review and meta-analysis).
4. Valid baseline data, including serosurvey data, for exposure to H5N1 and other potentially zoonotic influenza subtypes, including serological investigation of people living near poultry outbreaks, working in high risk populations, and in contact with confirmed human cases.
5. Determination of risk factors for human zoonotic influenza infections within and among countries, including virus, host, and ecological factors (including understanding of risk associated with indirect contact with poultry and contaminated environments and posed by different avian and mammalian species).
6. Further investigations of the link between poultry outbreaks and human cases (especially when no apparent link exists), including joint investigations and analysis of national/community level factors contributing to risk.
7. Understanding which production and slaughter practices or procedures have increased risk for human exposure and infection.
8. Analysis of role of case definition (e.g., contact with sick and poultry) in identification of human cases.
9. Comparative analysis of the epidemiology of different zoonotic influenza viruses in humans.
10. Expanded knowledge of host range of animal influenza subtypes and strains.
11. Understanding of competition among and within circulating virus subtypes.
12. Understanding of viral persistence in the environment.
13. Availability of rationales for developing practical public health measures and messages to optimize impact.

Live bird markets

1. Understanding of virus prevalence and transmission in LBMs, including impact of market interventions on virus circulation.
2. Understanding LBMs as a risk factor for human disease.

Virus transmission/infectivity/pathogenesis

1. Understanding of receptor structural diversity, distribution, and binding, including virus, host species and individual binding differences, using new technologies such as glycan arrays and virus histochemistry, and including hypothesis testing using virus infectivity studies in various species.
2. Understanding of the HA mutations required to change the binding affinity of H5N1 and other potentially zoonotic animal influenza viruses to allow the virus to pass more easily to/among humans, and of selection forces affecting binding affinity.
3. Understanding of the species barrier, including determinants of species barriers strength for different viruses.

4. Understanding the transmission/infectivity/pathogenesis of human seasonal and potentially zoonotic animal influenza viruses in various animal species, as well as humans, including understanding of viral determinants of these characteristics and identification of appropriate animal models for associated research.
5. Comparison of characteristics of avian viruses that remain in the avian reservoir to those that spill over to the mammalian host.
6. Understanding of host-specific factors that affect the polymerase complex, and therefore replication.
7. Understanding homosubtypic and heterosubtypic immunity to human seasonal and potentially zoonotic animal influenza viruses and its effect on transmission/infectivity/pathogenesis and serological responses, including understanding of non-HA gene immunity.
8. Better understanding of role of heterogeneity in shedding and thus transmission from infected hosts.
9. Additional assessment of the impacts of virus genotype on phenotype.

Analysis and sharing

1. Mechanisms for timely and open sharing of information, viruses, reagents, sequence information, technology, and tools within and among sectors.
2. Mechanisms for joint data collection and analysis among sectors.
3. Mechanisms for timely sharing of information from international or regional epidemiological and virological analyses back to countries from which the data came and neighboring countries at risk.
4. More complete analysis on available virus isolates (e.g., genetic, antigenic, and genotypic).
5. Better understanding of antiviral resistance, including how it is acquired, and its effects on fitness.
6. Solutions to maximize use of the available information.
7. Expanded use of new technologies (e.g., antigenic cartography) to analyze other virus subtypes.

Pandemic potential

1. Determination of the pandemic potential of various influenza subtypes and strains, including receptor repertoire, geographical distribution, and human exposure/seroprevalence/immunity.
2. Model to assess human infection/transmission potential of viruses.
3. Understanding of pathways if virus adaptation to humans, including investigations using reverse adaptation of human strains.
4. System to track mutations and evolution to ensure understanding of development of a pandemic strain (retrospectively, if necessary).

Behavior change and assessment

1. Determination of costs and benefits of household, village, and community poultry management practices, including cultural relevance.
2. Behavior change communication that is targeted at stakeholders at each critical point along the chain.
3. Risk reduction measures focused at the community level, and implemented by the community.
4. Impact assessments for proposed and implemented measures.
5. Focus on biosecurity at all levels of the human–animal interface.

Diagnostics

1. Standardization/harmonization of laboratory testing/diagnostic procedures with respect to reference antigens and antisera for human sera, poultry sera, wild bird sera, and reference materials.
2. Antigen detection tests that are as sensitive and specific but not as expensive as RT-PCR.
3. Serological tests that show significant difference between homologous and heterologous local strain antigens, and a better understanding of what is the protective HI titer.
4. Sensitive and specific serologic tests to identify previous human infection with AIVs.
5. Updated best-practice assay manuals, implementation of proficiency testing in laboratories, and training of diagnosticians and epidemiologists.

Optimizing the human health–animal health interface

1. Optimized, coordinated surveillance and disease reporting system for influenza and other zoonotic diseases.
2. Joint meta-leadership training and skill development.
3. Better understanding of the difference between incentives and disincentives of animal and public health to create win–win situations and build trust and respect between sectors.
4. Shift from capacity building to capacity effectiveness and sustainability.
5. Optimized roles and responsibilities of PPP and Non-governmental organization (NGOs).
6. Research and development centers to work holistically and ecologically for emerging zoonoses, beginning with H5N1.
7. Participation of business communities as effective and equitable players in controlling, responding, and preventing EIDs.
8. An integrated collaborative mindset and action plan to better understand infectious disease ecology and ensure applicability for other zoonotic diseases.
9. Global agenda for action.

10. More surveillance of animal outbreaks that precede human cases in collaboration with Ministries of Agriculture, Veterinary Services, and NGOs working in conservation.
11. Improved technologies for forecasting and outbreak prediction.
12. More ecological studies.
13. Mechanism for joint analysis of gaps and research priorities.

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Appendix C: Abbreviations and acronyms

AI	Avian influenza
AIV	Avian influenza virus
ARDS	Acute respiratory distress syndrome
CFR	Case fatality rate
DG-SANCO	EU Directorate General for Health and Consumer Affairs
EC	European Commission
EU	European Union
EID	Emerging infectious disease
FAO	Food and Agriculture Organization
GIS	Geographic information system
GLEWS	Global Early Warning System
HA	Hemagglutinin (gene or protein)
HI	Hemagglutinin-inhibition testing
ILI	Influenza-like illness
HPAI	Highly pathogenic avian influenza
IZSVe	Istituto Zooprofilattico Sperimentale delle Venezie
LBM	Live bird market
LPAI	Low pathogenic avian influenza
MODS	Multiple organ dysfunction syndrome
NA	Neuraminidase (gene or protein)
NGO	Non-governmental organization
NS	Non-structural (gene or protein)
OIE	World Organization for Animal Health
OFFLU	The OIE/FAO Network of Expertise on Avian Influenza*
RVF	Rift valley fever
SA	Sialic acid
SARS	Severe acute respiratory syndrome
SIV	Swine influenza virus
SOP	Standard operating procedure
WHO	World Health Organization

*OFFLU has recently changed its name to *The OIE/FAO Network of Expertise on Animal Influenza* to reflect its broader scope.

Appendix D: Agenda

ORGANIZED BY OIE FAO WHO

FAO - OIE - WHO Joint Technical Consultation on Avian Influenza at the human-animal interface

Palazzo Verità Poeta, Verona, Italy | 7 - 9 October 2008

The Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO), with support from the Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe) and the EC funded project FLUTRAIN, have called this technical consultation to

- identify critical virological characteristics for the emergence of zoonotic and pandemic viruses
- evaluate external factors affecting the evolution and emergence of a pandemic strain, and identify monitoring mechanisms for pandemic strain emergence
- identify likely modes of transmission and exposure sources for zoonotic infection with avian influenza viruses
- maximise outcome of ongoing research and preparedness efforts and identify gaps in knowledge
- identify next steps for further integrated data collection, analysis and research

IN COLLABORATION WITH IZSVe offlu

PATRONAGE AND FINANCIAL CONTRIBUTION CDC FLUTRAIN Comune di Verona

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FAO/OIE/WHO JOINT TECHNICAL CONSULTATION ON
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Tuesday **7 October**

WELCOMES AND MEETING OBJECTIVES/METHODS OF WORK

MODERATOR: ILARIA CAPUA

Welcomes

9.00–9.10 *Romano Marabelli*
9.10–9.15 *Isabel Minguez*
9.15–9.35 *Joseph Domenech*
9.35–9.55 *Bernard Vallat*
9.55–10.15 *Keiji Fukuda*

Objectives of the meeting and methods of work

10.15–10.25 *Ilaria Capua*

10.25–10.50 Coffee

SESSION 1: VIROLOGICAL CHARACTERISTICS OF INFLUENZA VIRUSES

OBJECTIVE: TO IDENTIFY VIROLOGICAL CHARACTERISTICS IMPORTANT FOR ZOONOTIC AND PANDEMIC DISEASE

MODERATORS: RUBEN DONIS, GIOVANNI CATTOLI
RAPPORTEUR: TARA ANDERSON

Session 1.a: Epidemiology, distribution, and phylogeny of currently circulating animal influenza viruses

10.50–11.10 Overview of human cases of AI H5N1 since 1997
Sylvie Briand
11.10–11.30 Overview of animal outbreaks of AI H5N1 globally since 1997
Ian Brown
11.30–11.45 Phylogeny of avian H5N1 viruses infecting humans
Mike Perdue
11.45–12.00 Circulation of other zoonotic avian influenza viruses
Ilaria Capua

Session 1.b: Viral determinants of zoonotic infectivity and pathogenicity in humans

12.00–12.30 Effects of single mutations and virus-level factors on influenza transmissibility/infectivity/pathogenicity in humans
Ron Fouchier

12.30–13.30 Lunch

13.30–13.45 Receptors and host specificity
Mikhail Matrosovich
13.45–14.00 Zoonotic potential of other animal influenza viruses
Kristien Van Reeth
14.00–14.15 Specific characteristics of interest for public health
Masato Tashiro
14.15–14.30 Occurrence in animal viruses of mutations with potential human health implications in Africa
Giovanni Cattoli

14.30–15.30 Panel discussion for Session 1
Thread leaders: *Ron Fouchier, Malik Peiris*
Panel: speakers and moderators from session 1

15.30–16.00 Coffee

16.00–16.30 Panel discussion for Session 1 (continued)
16.30–17.00 Major points for inclusion in final recommendations

17.30–20.00 Welcome cocktail (at venue)

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Wednesday **8 October**

SESSION 2: EVOLUTION AND EMERGENCE OF A PANDEMIC STRAIN

OBJECTIVE: TO EVALUATE THE FACTORS AFFECTING EVOLUTION AND EMERGENCE OF A PANDEMIC STRAIN AND IDENTIFY MONITORING FOR EMERGENCE OF A PANDEMIC STRAIN

MODERATORS: ILARIA CAPUA, MIKE PERDUE
RAPPORTEUR: TARA ANDERSON

Session 2.a: Viral determinants and ecological conditions affecting mutation rate/probability of reassortment

08.30–08.45	Evolution of human pandemic viruses *Richard Webby*
08.45–9.00	Evolution of H5N1 in birds *Gavin Smith*
09.00–09.15	Viral characteristics of H5N1 influencing mutation/reassortment events with pandemic potential *Ruben Donis*
09.15–09.30	External factors influencing H5N1 mutation/reassortment events with pandemic potential *Ab Osterhaus*

Session 2.b: Monitoring for important viral changes

09.30–09.45	The WHO process for monitoring of novel influenza strains *Alan Hay*
09.45–10.00	Role of antigenic cartography in monitoring *Derek Smith*
10.00–10.15	OFFLU activities at the Human-Animal interface *Gwenaelle Dauphin*
10.15–10.45	**Coffee (30 min)**
10.45–11.45	Panel discussion for Session 2 Thread leaders: *Ab Osterhaus, Alan Hay* Panel: speakers and moderators from session 2
11.45–12.15	Major points for inclusion in final recommendations (30 minutes)
12.15–13.15	**Lunch (60 min)**

SESSION 3: HUMAN TRANSMISSION RISKS & EXPOSURE SOURCE

OBJECTIVE: TO IDENTIFY LIKELY MODES OF TRANSMISSION AND EXPOSURE SOURCES FOR ZOONOTIC INFECTION WITH AVIAN INFLUENZA VIRUSES

MODERATORS: MALIK PEIRIS, STEFANO MARANGON
RAPPORTEUR: TARA ANDERSON

Session 3.a: Modes of transmission for human infection with avian influenza viruses

13.15–13.30	Modes of transmission for human seasonal influenza virus *Allison McGeer*
13.30–13.45	Possible modes of transmission of avian viruses to people *David Swayne*

Session 3.b: Exposure risk for human infection with avian influenza viruses

13.45–14.00	Potential sources of exposure to H5N1 for WHO confirmed human cases *Liz Mumford*
14.00–14.15	Potential role of exposure to poultry products and by-products in human H5N1 infections *David Swayne*
14.15–14.30	Potential role of live animal markets and the environment in human exposure to avian influenza viruses *Malik Peiris*
14.30–14.45	Indonesian's Healthy Food Markets Program and Food Safety *Gina Samaan*
14.45–15.00	Effects of poultry management on risk of human exposure (at the community level) *Les Sims*
15.00–15.30	**Coffee (30 min)**

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15.30–15.45 Review of culturally-relevant poultry/human interactions
Wantanee Kalpravidh
15.45–16.00 Evidence to explain the low incidence in the face of large population-level exposure
Peter Horby

Session 3.c: Summaries of national data on human exposure from selected affected countries
16.00–16.10 National data: Summary of animal health information relevant to human exposure to H5N1 in China
Hualan Chen
16.10–16.20 National data: Summary of exposure data in Chinese human cases of H5N1
Zhou Lei
16.20–16.30 National data: Summary of animal health information relevant to human exposure to H5N1 in Egypt
Mona Ali
16.30–16.40 National data: Summary of exposure in Egyptian human cases
*(TBA)**
16.40–16.50 National data: Summary of animal health information relevant to human exposure to H5N1 in Indonesia
Elly Sawitri
16.50–17.00 National data: Summary of exposure data in Indonesian human case
Wilfried Purba
17.00–17.10 National data: Summary of animal health information relevant to human exposure to H5N1 in Viet Nam
Tung Nguyen
17.10–17.20 National data: Summary of exposure data in Vietnamese human cases
Hien Nguyen
17.20–17.30 Clarifications from this session (discussion to be held on 9/10)

Thursday **9 October**

8.30–10.00 Panel discussion for Session 3
Thread leaders: *David Swayne, Keiji Fukuda*
Panel: speakers and moderators from session 3

10.00–10.30 Major points for inclusion in final recommendations

10.30–11.00 Coffee (30 min)

SESSION 4: DEVELOPMENT OF MEETING OUTPUT
MODERATORS: ALEX THIERMANN
PANEL: ILARIA CAPUA, KEIJI FUKUDA, JUAN LUBROTH
RAPPORTEUR: TARA ANDERSON

11.00–13.00 Development of technical meeting output

13.00 Close of technical consultation on Avian Influenza

13.00–14.00 Lunch (60 min)

SESSION 5: BROADENING THE USE OF TOOLS AND SYSTEMS
MODERATOR: LONNIE KING

14.00–14.30 Importance of the HAI in the broader sense
Lonnie King
14.30–14.45 Tools and methods used to evaluate emergence of other zoonotic diseases
Pierre Formenty
14.45–15.00 GLEWS
Juan Lubroth

15.00–16.00 Discussion and development of recommendations
Chair: *Lonnie King*
Overview Committee: *Pierre Formenty, Wantanee Kalpravidh, Juan Lubroth, JC Manuguerra, Stefano Marangon, Vincent Martin, Angela Merianos, Marguerite Pappianou, Alex Thiermann, Boubacar Seck*

16.00–16.10 Closing remark

16.10 End of the meeting

*Presentation given by Mona Ali.

Appendix E: Participants

ORGANIZED BY

FAO - OIE - WHO Joint Technical Consultation on Avian Influenza at the human-animal interface

Palazzo Verità Poeta, Verona, Italy | 7 - 9 October 2008

List of participants

IN COLLABORATION WITH

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© 2010 FAO, OIE and WHO, *Influenza and Other Respiratory Viruses*, **4** (Suppl. 1), 1–29

FAO/OIE/WHO JOINT TECHNICAL CONSULTATION ON
AVIAN INFLUENZA AT THE HUMAN-ANIMAL INTERFACE
VERONA, ITALY | 7-9 OCTOBER 2008

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