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27-29 April 2010, Verona (Italy)

World Health Organization

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Bernadette Abela-Ridder, Peter Daszak, Gwenaelle Dauphin, Ruben Donis, Stephane DeLaRocque, Pierre Formenty, M. Kathleen Glynn, Billy Karesh, Hans-Dieter Klenk, Vincent Martin, John MacKenzie, Elizabeth Mumford, Pierre Rollin, Alex Thiermann, and JoEllen Welter

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Executive summary

The Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO) held a Joint Scientific Consultation on Influenza and other Emerging Zoonotic Diseases at the Human-Animal Interface from 27 to 29 April 2010, in Verona, Italy. This meeting and the first technical meeting held in Verona in 2008 were part of a recent series of international policy and technical meetings, which also included the International Ministerial Conference on Animal and Pandemic Influenza (IMCAPI) meetings, and the "One Health" meetings held in Winnipeg, Canada and Stone Mountain, United States of America. Initially the focus was on pandemic and avian influenza, but this perspective has evolved to include broader thinking on other influenza subtypes and emerging zoonoses generally. The latest meeting reflected this progression by considering not only influenza but also other emerging viral zoonoses, and by attempting to identify the commonalities among diseases, to provide a scientific basis for collaborative, multisectoral actions.

Overall, it was agreed that important lessons learned through recent experiences with zoonotic influenza emergence can be applied to other emerging zoonoses. However, it was clear that gaps remain in the global understanding of influenza. For example, neither the association between molecular structure and epidemiologic and clinical characteristics, nor the impacts of ecological and other contextual aspects are well understood. Such understanding is crucial for the valid assessment and prioritization of influenza health risks, which provide the basis for developing effective prevention and control measures.

This point - that only looking at the influenza virus itself provides insufficient information to allow effective, valid, risk assessment, prevention, and control because emergence and disease impacts are affected by context, i.e. host factors, ecology and management systems - was echoed during discussion of other emerging diseases. Thus, future data collection for any disease must aim to include a wider range of contextual information and these data must be factored into the subsequent analyses, requiring a multisectoral approach. It was agreed that modelling can be useful for understanding and even predicting some diseases, as long as sufficient appropriate data are available.

Many of the issues raised were not new, but the discussions aimed to develop new approaches to them. The following eight priority areas for action therefore include some well-known topics – data sharing and improved surveillance – along with increasingly recognized but less widely investigated ones, such as ecosystem health and the promotion of behavioural change to reduce disease emergence.

DATA AND DATA SHARING

This discussion focused both on making more data accessible and making these data accessible to a wider group, by breaking down the concept of data ownership and reducing the technical, legal and political/conceptual barriers to data sharing. More tangible and equitable incentives, rewards and benefits for contributing, using and analysing data appro-

priately, and technical solutions for improving data interchange would facilitate wider and more effective sharing.

SURVEILLANCE

Surveillance was identified as a long-standing challenge owing to its complexity. Although all countries conduct disease surveillance among humans and animals, the priority they give to these activities varies based on the national context. Building capacity for surveillance of known diseases is critical in enabling the detection of unusual events, and overall efficiency may be increased by using syndromic, participatory or targeted (both pathogen- and non-pathogen-based) approaches. New and innovative strategies, such as using social networking systems and engaging non-traditional partners, were recognized as opportunities for improving surveillance, especially in under-resourced settings.

ECOSYSTEM DYNAMICS

Routine inclusion of the ecosystem aspects that may underlie or facilitate disease emergence – including changes in land-use practices, agricultural impacts on ecosystems, natural resource extraction, wildlife trade and production systems – was identified as a priority for addressing disease emergence at the human-animal interface.

DIAGNOSTICS

The development of diagnostics for the early, field-based detection of emerging diseases is another long-standing challenge, especially in the identification and characterization of new or evolving pathogens. New technologies are evolving. Finding ways to achieve laboratory sustainability, to identify feasible and appropriate methods for specimen transport and collection and to link data to specimens were identified as crucial to the building of national laboratory diagnostic capacity.

BEHAVIOUR CHANGE AND COMMUNICATION

Behaviours have an impact on health and disease emergence risks. The promotion of activities such as disease reporting must therefore target all stakeholders in all sectors, including the public. Perceptions of risk and cultural motivations must be considered before effective and practicable measures for changing risky behaviours can be identified and communicated. Successful corporate marketing and communication campaigns, such as those against the use of tobacco, might be used as models. To be effective, communications must be transparent, valid and aligned among different partners and stakeholders.

CAPACITY BUILDING, EDUCATION AND RESEARCH

To be sustainable and effective, capacity building should be based on national-level needs and priorities, and should incorporate cross-training among sectors, either by modifying existing training systems or by building new multidisciplinary approaches to capacity building and education. Discussions identified the need for more basic research to fill fundamental gaps in scientific knowledge, more field research, and new research on disease emergence (including for well-studied diseases such as influenza). Such research could be conducted at the local level in affected countries.

MULTIDISCIPLINARY, COLLABORATIVE APPROACHES

The use of collaborative, multisectoral approaches that take into account the goals of all stakeholders was proposed as the solution to many existing and emerging disease issues, although significant barriers remain, including the lack of trust. Funding streams that make collaboration a condition for funding would foster inter-sector cooperation, while creative public-private and non-traditional partnerships would widen the understanding and control of disease emergence risks.

SUSTAINABLE APPROACHES

Maintaining sustainability was a consistent theme across many of the topics discussed, including the need to focus national and international efforts to maximize efficiency and sustainability when resources are scarce, and the broader application of existing principles and strategies. Leveraging assets, working proactively, building cross-cutting systems and engaging new partners were mentioned as contributing to efficiency and sustainability.

These meeting outcomes now need to be used to guide the development or modification of policies and strategies for reducing the risks from unexpected emerging zoonotic diseases, by considering how they relate to specific national interests and contexts. Other critical considerations identified by meeting participants included the need to move forward flexibly, using new strategies and paradigms and building and maintaining trust. Leadership at the international level is crucial in facilitating high-level national collaboration. A commitment to collaborate now provides the foundation on which to build the networks of expertise that are needed to ensure effective prevention of and response to current and future emerging zoonotic disease events. Multisectoral collaboration must expand to meet the needs and fill the gaps at the human-animal-ecosystems interface, and must do so flexibly, to meet expected and unexpected challenges wherever they exist.

Background

The interface between humans and animals is widely recognized as a complex but critical juncture where zoonotic diseases emerge and re-emerge. This interface is continuously affected by increased globalization; the growth and movement of human and livestock populations; rapid urbanization; expansion in the trade of animals and animal products; the increased sophistication of farming technologies and practices; closer and more frequent interactions between livestock and wildlife; increased changes in ecosystems; changes in vector and reservoir ecology; land-use changes, including forest encroachment; and changes in patterns of hunting and consumption of wildlife. Zoonoses can therefore be said to emerge at the human-animal-ecosystems interface.

Lessons learned from the emergence and response to diseases such as severe acute respiratory syndrome (SARS), highly pathogenic avian influenza (HPAI) and pandemic influenza (H1N1) 2009, indicate that new paradigms are needed at the human-animal-ecosystems interface, to improve early detection, prevention and control, and reduce the public and animal health risks from these and other emerging zoonotic diseases.

International multisectoral collaboration on health topics at the human-animal interface has been gaining momentum and support in recent years. The Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO) have been working together to build effective partnerships and leverage resources for addressing zoonoses and diseases with high public health impacts. FAO, OIE and WHO continue to seek opportunities for expanding the knowledge base and fostering the necessary paradigm shifts to achieve increased efficacy when working on health risks at the animal-human-ecosystems interface.

In this aim, the three organizations have called on their respective experts to participate in technical consultations; two meetings in particular have focused on understanding emerging diseases at this interface. The first was organized by FAO, OIE, WHO and the *Istituto Zooprofilattico Sperimentale delle Venezie* in October 2008 in Verona, Italy[1]. This 2008 Verona consultation provided the first opportunity for a group of influenza experts from the animal and public health sectors to gather and discuss the purely scientific aspects of the zoonotic and pandemic threats posed by H5N1 and other zoonotic influenza viruses, focusing specifically on human and animal interactions that might affect these threats.

The second consultation, which is summarized in this report, was convened in Verona in April 2010 with the participation of expert scientists from a broader variety of disciplines (Annex A, List of participants)[2]. As well as following up on the first Verona consultation

[1] http://www.fao.org/avianflu/en/conferences/verona_2008.html; http://onlinelibrary.wiley.com/doi/10.1111/irv.2010.4.issue-s1/issuetoc

[2] http://www.fao.org/avianflu/en/conferences/verona_2010.html

by summarizing and examining the progression of knowledge about the zoonotic and pandemic threats of animal influenza viruses, this second meeting also included a broader examination of other viral zoonoses, to identify the commonalities among them at the human-animal-ecosystems interface. These commonalities were intended to propose a scientific basis for developing policies to reduce the risks from these emerging viral zoonoses.

Setting the scene

Opening presentations by representatives of the Italian Ministry of Health, FAO, OIE and WHO provided background on the issues, context and goals, setting the scene and identifying the tasks for the diverse group of experts attending the meeting (Annex B, Agenda). Common themes emerged, such as the growing desire worldwide to enhance preparedness and response capacity for emerging zoonotic diseases. It was noted that scientists and governments have become increasingly aware of the need for better understanding of the connections among humans, animals, ecological systems and pathogens when considering the emergence of diseases. Maintaining productivity and sustainability were identified as important aspects.

Representatives from FAO, OIE and WHO reiterated the importance of focusing on the human-animal interface, as reflected in the rapidly growing collaboration among these three organizations, and recognized the need for new strategies and methods for solving many emerging issues. The commitment of the Directors-General of the three organizations is outlined in the Tripartite Concept Note in Annex E, "The FAO-OIE-WHO Collaboration: Sharing responsibilities and coordinating global activities to address health risks at the animal-human-ecosystems interfaces". This document was released at the Seventh International Ministerial Conference on Animal and Pandemic Influenza (IMCAPI) on Animal and Pandemic Influenza: The Way Forward, held in Hanoi in April 2010. It describes the existing work at the human-animal-ecosystems interface undertaken by the three organizations, and defines the additional collaboration, based on complementarity, necessary to put into operation the concepts outlined in the document.

This Tripartite Concept Note builds on the ideas developed and expanded in the FAO, OIE, WHO United Nations Children's Fund (UNICEF), World Bank, and UN System Influenza Coordination Strategic Framework for Reducing Risks of Infectious Diseases at the Animal-Human-Ecosystems Interface[3], released at the IMCAPI meeting in Sharm el Sheikh (Egypt) in 2008, and the report of the Expert Consultation on One World One Health: from ideas to action,[4] held in Winnipeg (Canada) in 2009. The evolution of the perspective from the 2008 Verona consultation, through the Joint Strategic Framework and to the Winnipeg consultation reflected a consistent broadening of the scope of technical and strategic thinking, as it expanded from influenza to include other emerging diseases at the human-animal interface. This progression also reflected a continuing search for alternative and innovative ways of working together optimally, to face these growing challenges by using new technical approaches, leveraging existing resources and expertise, and embracing fundamental paradigm shifts.

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[3] www.oie.int/downld/avian%20influenza/owoh/owoh_14oct08.pdf.

[4] www.phac-aspc.gc.ca/publicat/2009/er-rc/pdf/er-rc-eng.pdf.

The structure and objectives of the 2010 Verona consultation were meant to mirror this progression of thinking. Participants were selectively invited for their expertise on the topics under discussion. After presentations of the baseline technical information on influenza and other important viral zoonoses, these experts were charged with making the conceptual transition from principles focused on specific diseases to the identification of commonalities and new perspectives that could be applied to emerging diseases more broadly. These commonalities and perspectives could provide the technical basis for developing or modifying policies and strategies to ensure more effective preparation for and response to emerging events.

The key challenge for the experts was to identify new and innovative approaches that could be applied to long-standing questions, as future threats will undoubtedly have different origins and outcomes from those already encountered. The group was reminded that the questions they were addressing were not new and would not have easy answers; ever since zoonotic diseases were first recognized, the scientific community has been striving to understand the complexity of the human-animal-ecosystems interface and its relationship with disease emergence, and to identify ways of using this understanding to improve the prevention and control of such diseases. The need to focus on these questions has been reinforced in the last decade, as the world faces zoonotic disease challenges of increased frequency and severity.

The consultation was structured to include an initial review of virological and epidemiological factors that are particularly relevant to the human-animal interface and that may have influenced the emergence of known high-public-health-impact zoonoses. Influenza, viral haemorrhagic fevers, infections with human and simian immunodeficiency viruses and other examples were used as the basis for discussions. To encourage broader participation, these concise scientific reviews were presented in plenary, followed by facilitated panel discussions and small group working sessions. The plenary sessions and subsequent panel discussions were moderated by members of the scientific committee, and each was based on a series of framing questions designed to identify concerns and solutions relevant to the session topic.

Examples of emerged or emerging zoonotic viral diseases

Specific viral zoonotic diseases were selected as examples for discussion, to help identify common factors related to disease emergence at the human-animal-ecosystems interface. The diseases selected included zoonotic diseases endemic in humans or animals in some geographic regions; diseases caused by pathogens that cross between animals and humans sporadically; and zoonotic diseases that initially involved animal-to-human transmission, but for which human-to-human transmission has since become the predominant mode of transmission. Special attention was given to zoonotic influenza viruses because many can be classified as emerging or potential zoonoses, and substantial information and experience is available for some, particularly HPAI H5N1. In addition, following the emergence of the influenza virus that led to the pandemic of 2009/2010, the international community has gained not only in-depth knowledge about the pandemic H1N1 (2009) virus but also a much deeper understanding of animal influenza viruses in general and of how influenza viruses emerge, spread and cause pandemics.

To help identify commonalities that might help the scientific community improve its preparation for upcoming emerging zoonotic events, all the presentations and discussions focused on what the selected examples have shown about the emergence (including animal-to-human transmission) and control of the diseases and the pathogens that cause them. For some diseases, the aspects most relevant to their emergence are related to specific characteristics of the viruses, so the pathogen became the main topic of discussion; in other instances, disease epidemiology - for example, knowledge of the animal reservoirs or human behaviour affecting transmission dynamics - are most relevant to current understanding of the human-animal interface. As a result, some findings focus on the pathogen and others on the disease. Summaries of the technical presentations are included in Annex C. Key points from the discussions are presented in the following sections.

ZOONOTIC INFLUENZA WITH THE POTENTIAL FOR HIGH PUBLIC HEALTH IMPACT

Technical reviews included presentations on what has been learned from H5N1 and from the 2009 influenza H1N1 pandemic, other influenza viruses of concern; the influenza gene pool; virological characteristics of public health concern; viral factors involved in reassortment and mutation; and non-virological factors that could affect influenza emergence. Discussions and experts' conclusions are summarized in the following subsections, according to whether they relate to understanding about emergence, transmission, or the prevention and control of emergence.

Factors relating to emergence

- The emergence of pandemic H1N1 (2009) virus in North America, likely from swine origin, is a reminder that the time and location for the emergence of new genetic variants, and their epidemiological characteristics in humans and other animals are unpredictable. This event also emphasized the need to be prepared for a range of influenza emergence scenarios, rather than only one, such as an H5N1 pandemic. Support to countries in improving their surveillance systems, so they can detect and respond rapidly to unusual or unexpected disease events, would be of benefit, even when it is not possible to predict with confidence the emergence of and risks from specific influenza viruses.
- Pandemic influenza viruses may arise at least months before their emergence in humans, providing a window for the identification and implementation of preparedness and response activities before a pandemic occurs. Sufficient understanding of the viral molecular characteristics indicating potential public and animal health risk would improve the effectiveness of such responses.
- H5N1 is an example of an abundant virus with vast human exposure that has not caused a pandemic since the first human infection in 1997, suggesting that in addition to the abundance of a virus in the environment and/or the level of human-animal contact, other factors are also critical to the development of a pandemic.

Factors relating to animal-to-human disease transmission

- Sequence data and associated genetic markers are helpful to understanding the epidemiology and evolution of influenza viruses, and may also indicate potential risks to humans. Expansion of existing knowledge, to include characterization of the viral and host genetic factors that affect the cross-species transmission and pathogenicity of influenza viruses, is critical. Better understanding of these genetic factors will support the earlier identification and improved risk assessment of potentially high-impact emerging influenza viruses, especially when circulation is still limited to animal reservoirs.
- Progress has been made in understanding some molecular determinants (e.g., those determining 2,6 versus 2,3 receptor binding specificity) of influenza viruses. This progress has revealed that the mechanisms underlying the host range and pathogenicity of influenza viruses in the field are more complex and subtle than is reflected in current thinking within existing dogmas (e.g., that 2,6 versus 2,3 receptor binding of the haemagglutinin strictly determines the virus host range). Consideration of the variety of gene constellations, affected species, geographic locations and animal production management contexts related to influenza genes and their markers and mutations will improve this understanding.
- Laboratory-based virological information has advanced our knowledge of influenza, which would be further enhanced using a broader assessment approach. More robust risk assessment could be achieved through assessments of the context in which influenza viruses are found (e.g., species, season, clinical presentation, transmission history, host/herd immunity level, management/environmental systems) and the viral behaviour in these different contexts, accompanied by such factors as cultural aspects, social trends and ecology.

Factors that limit, prevent and/or control emergence

- H5N1 played a valuable role in the creation of pandemic preparedness plans and strategies, leading to improved infrastructure and surveillance capacity. Despite the focus on H5-based scenarios, the world was relatively well prepared to respond to the recent influenza H1N1 pandemic.
- Substantial progress has been made in mitigating the impacts of influenza using knowledge about H5N1 and other animal influenza viruses. However, more work is needed to identify and prioritize key factors for the equitable prevention and control of emerging zoonotic influenza that take into account virological and non-virological factors and human-animal interactions. It will also be important to assess the effectiveness of using this approach for influenza and its potential for use with other diseases.
- Targeting surveillance to areas of increased risk, such as by using data from animal disease surveillance to guide and inform human surveillance, would increase efficiency and provide the potential for more sustainable and efficient influenza surveillance systems. As more is understood about molecular determinants and risk, identification of viruses with certain characteristics in animal populations arising from such targeted surveillance could be a trigger for increased surveillance in humans.
- Influenza vaccine has been used successfully in humans and animals, although important knowledge gaps remain regarding the appropriate settings for vaccination and the optimal vaccines to use. Overcoming these gaps and improving the ability to predict how influenza viruses behave will help to convince policy-makers and taxpayers to invest in the use of veterinary and human influenza vaccines and the development of new vaccine technologies.
- Much of the response to the recent influenza H1N1 pandemic was successful, although the perception of successes was not uniform. More effective and active ways of communicating success and circulating messages about ongoing risks would help build public confidence.
- Collaboration between the animal and public health sectors has greatly improved, especially at the international level, largely as a response to H5N1 influenza. This momentum must be maintained and expanded to the field level.
- The involvement of other branches of science (e.g., ecology and social sciences) and sectors relevant to the human-animal-ecosystems interface would enrich perspectives and increase leverage among existing resources and knowledge. A strong commitment to identifying and achieving mutually beneficial goals is critical for successful collaboration among existing and new disciplines and sectors. The most successful collaborations have occurred when multidisciplinary partners develop goals and objectives of a joint activity to address a scientific question or potential intervention together from the inception of the activity, rather than joining a project designed and initiated by a single partner.

EMERGING OR SPORADIC VIRAL ZOONOTIC DISEASES OF PUBLIC HEALTH CONCERN

Technical reviews at the meeting included presentations on zoonotic diseases of public health importance that were selected to represent a cross-section of issues relevant to the

human-animal interface. These included West Nile fever, Rift Valley fever, Crimean-Congo haemorrhagic fever, and the diseases caused by Nipah, Hendra, Ebola and Marburg viruses and Hantaviruses. Discussion and conclusions from the experts are again summarized in the following subsections according to whether they contributing to our understanding of emergence, transmission, or prevention and control of emergence.

Factors relating to emergence

- The ecology of zoonotic vector-borne diseases is complex, and their epidemiology is driven by multifactor parameters that need to be considered in risk evaluation. For example, the impact of West Nile virus appears to be much lower in Central and South America than in the United States of America and Canada. This may be related to differences in host species and vector diversity, the presence of other flaviviruses, or a range of other biological and environmental factors.
- Predicting or measuring the likelihood of a disease emerging would be more effective when changes in ecology are incorporated, once such data become available.
- A clearer assessment of the roles of livestock and wildlife trade in disease emergence and/or spread would be useful for predicting the possibility of a known disease emerging in new locations via wildlife trade; estimating the risk of introduction to naive species; and assessing other trade-related risks.
- A greater understanding of the population dynamics of reservoir species would inform assessment of the risk of disease emergence and improve predictive capabilities. For example, studies of the population explosion in forest mice in northern Europe suggest that the availability of food (i.e., seeds) plays a role in the mice's abundance, and consequently in the dynamics of disease prevalence in rodent populations and the resulting spill-over to humans.

Factors relating to animal-to-human disease transmission

- Data on diseases in domestic animals are often limited, especially for diseases where clinical signs are mild or absent (e.g., Crimean-Congo haemorrhagic fever). This, combined with an often poor understanding of the role of wildlife, can contribute to an under-estimation of the complexity of disease transmission dynamics.
- It is important to continue monitoring sporadic zoonotic diseases for changes in transmission patterns suggesting that sustained transmission is occurring and disease incidence will rise. For example, there is evidence of sustained transmission of henipaviruses in Bangladesh, and although this is not yet fully understood, it warrants vigilant monitoring.

Factors that limit, prevent and/or control emergence

- Modelling techniques, satellite monitoring of land and ecosystem changes, and other technologies have been useful in predicting potential Rift Valley fever outbreaks in Africa, and may also be useful for other, similar diseases. The effectiveness of modelling tools depends largely on the quality of data and information available and on understanding the disease's epidemiology. In addition, the overall effectiveness and benefit of modelling depend on the existing capacity to implement an appropriate and timely response to predicted events.

- When based on scientifically valid methods, alerts based on predictive modelling approaches are valuable in that they allow the countries implicated to establish a preparedness rather than response mentality and ensure that appropriate response measures are in place. Predictive modelling approaches are still being refined, and the choice of actions taken in response to alerts should be carefully considered.
- The inclusion of a wide array of data types and sources improves the usefulness of modelling technology. Examples of valuable information include sampling results pre- and post-rainfall, livestock population maps, and aerial maps of rivers, creeks and other water bodies.
- Human behaviours contribute to the risk of exposure or infection, and modifying certain behaviours can be an effective control against emerging diseases. There is need and opportunity to define relevant behaviours and develop and implement public awareness campaigns and interventions that promote behaviour change relative to the human-animal interface.

ANIMAL-ORIGIN AGENTS THAT HAVE EMERGED AS HIGH-PUBLIC-HEALTH-IMPACT ZOONOSES

Technical reviews at the meeting included presentations on diseases that have already emerged and have led to at least one pandemic, including infection with human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV), and SARS. The following summaries of discussions and experts' conclusions are again arranged according to their contribution to our understanding of emergence, transmission, or the prevention/control of emergence.

Factors relating to emergence

- HIV type 1 (HIV-1) and HIV-2 can occur simultaneously in different human populations. Historically, HIV-2 was predominant in West Africa, but now HIV-1 is increasing, probably because of its shorter incubation period, higher viral loads and greater transmissibility. However, no single specific virological factor is known to be responsible for this trend.
- Current screening tests for HIV may not detect newly emerging virus types or strains. By sharing information about viruses from non-human primate hosts, existing partnerships and intersectoral collaboration could allow the laboratory detection of new viruses in humans to occur earlier than was previously possible.

Factors relating to animal-to-human disease transmission

- It is unlikely that the real-time detection of cross-species SIV/HIV transmission would have had an effect on disease emergence or animal-human transmission because the incubation period is long and asymptomatic infections occur. It is also unclear whether earlier determination that animal-human transmission of SARS was occurring could have helped reduce the impact of the outbreak.
- Worldwide, the bat population consists of more than 1 200 species. Bat population control and the destruction of bat reservoirs have been shown to be inefficient for the prevention of well-studied bat-borne diseases such as rabies. A deeper understanding of the triggers (e.g., ecological, anthropogenic and cultural) associated with disease

spread from bat populations to domestic animal or human populations would help identify more effective intervention points for the prevention of emerging diseases, while protecting the positive roles of bats, such as in crop pollination and agricultural pest control, through feeding.

- Substantial quantities of both legal and illegal bushmeat are purchased and consumed annually, despite the negligible sanitary regulation of bushmeat and farmed wildlife in most countries. There is a need for better understanding of the economic cycles, supply and demand for bushmeat and farmed wildlife, and for recognition that improved safety of these food sources could be crucial in preventing or minimizing disease emergence.

Factors that limit, prevent and/or control emergence

- Work with SIV/HIV has provided a good model for interdisciplinary work (involving the human and animal health, forest and natural resource sectors) to build local capacity, particularly in laboratories, and to engage and build the awareness of stakeholders at multiple levels.
- Where bushmeat and wildlife food markets (including live animal markets) exist, hygiene, biosecurity and food safety practices that are similar to those applied at domestic animal markets should be implemented.
- During the SARS response, the highest priority activity was halting transmission. However, gaps in preparedness resulted in delays in addressing broader social, developmental and ecological concerns. A key lesson learned from this experience is that preparedness should include plans for addressing the full range of issues, to allow the earlier implementation of diverse interventions.

Commonalities across diseases, and ideas for new approaches

Looking across the various key points brought up in discussions – whether these were related to influenza or to other endemic, sporadic or fully emerged zoonoses – experts identified common priority areas for action. Some of these involved topics that individuals or organizations have been seeking to address for some time; others involved revisiting ideas that have never been fully investigated or that are generally thought to apply only to a specific disease or group of diseases. In addition, some entirely new concepts were identified. For all three categories, however, the experts agreed that "just doing more" of the activities currently implemented was not enough: successful efforts will require a new paradigm that takes into account the fundamental need for collaborative, intersectoral and multidisciplinary approaches. Such collaboration will be sustainable only if the outcomes are mutually beneficial, i.e., not designed to meet the goals of only one stakeholder group. The participants also outlined new and potential strategies for achieving this outcome. Priority areas for action include some well-known topics, such as data sharing and improved surveillance, along with increasingly recognized but less investigated topics such as ecosystem health and the promotion of behavioural change to reduce disease emergence.

DATA AND DATA SHARING

There was strong consensus that effective data and information sharing is critical and needs to be increased. If disease threats are to be addressed effectively, technical data should be available to all the stakeholders who can analyse them appropriately, including groups that may have different approaches to analysis. It was agreed that much information exists that could provide the basis for risk analyses and interventions, but is often available to only one institution or disease-specific research group. It was also recognized that raw data that have not been entered into a database or analysed, particularly in developing countries, or "orphan data" that have been set aside after being used for one project may exist and could be used by others.

The experts discussed some of the factors that are most likely to promote data sharing. They noted that, when successful, data sharing is multi-directional among partners and/or based on participatory systems in which those involved in collecting the data also benefit from sharing them. Data sharing could be improved by finding ways to recognize and reward the sharing of intellectual property by individuals and organizations. The experts also recognized that other valid barriers to data sharing continue to exist – including technical, legal and political challenges – and agreed that the promotion of data sharing should be accompanied by ways of improving the accurate and appropriate use of shared data.

The technical barriers to data sharing include both the information technology component of electronic data interchange – finding the physical means to share data – and the challenge of ensuring that the increasingly complex data being shared are understood

and analysed correctly. Experts highlighted success stories, such as the sharing of virologic sequence data through the National Center for Biotechnology Information (NCBI) GenBank,[5] and posed the question whether other privately held databases could be made accessible through similar, easy-to-use search engines or through access to integrated databases that include data from different disciplines (e.g., ecology and social sciences). As the technical ability to access these data requires the use of established data standards, it was agreed that increased efforts should focus on sharing among existing databases rather than creating new ones. Further efforts are also needed to increase the sharing of rich but complex data that can produce useful results when they are analysed appropriately and with the participation of knowledgeable data gatherers and database architects. Data sharing and dissemination workshops and consultations could further encourage increased sharing of research data in an open, collaborative environment, such as through ad hoc research teams representing prospective users and sources of the data; the feasibility of data sharing using technology such as interactive blogs (applying relevant standards and requirements) as complements to established systems could be explored; and mechanisms that reward scientists for publishing databases as if they were scientific manuscripts could be promoted.

For certain data, increased sharing would require efforts to address the legal and political implications of, and restrictions on, sharing and to understand the incentives for sharing. Data sharing can be impeded by concerns about the preservation of confidentiality, and by the lack of data ownership rights for organizations or entities compiling data at the national or international level. Effective solutions will have to balance two factors: i) the global benefits for risk analysis that result from transparency at many levels; and ii) the need to find solutions or effective incentives that prevent countries, agencies and individuals from being inappropriately penalized (e.g., by trade sanctions, legal action or travel restrictions) for sharing information that contributes to global health. This will require the identification of alternative incentives, so that scientists, institutions and governments are motivated to share raw data, results and tools without the threat of recrimination or financial, professional, proprietary and legal impediments. Another proposal was the investigation of legal agreements that could facilitate the sharing of materials and information for the benefit of global health.

The group expressed interest in providing open access to data and databases, and foresaw potential solutions to the technical, legal and political barriers. Participants overwhelming agreed that the success of any data sharing initiatives requires breaking down the paradigm of data ownership, to benefit national, regional or global animal and human health. This in turn requires trust across disciplines and sectors. All institutions should take the lead in fostering and promoting trust among their partners, to build collaboration for sample and data sharing and the joint discussion of data and results from different analyses.

SURVEILLANCE

Although surveillance is perhaps the most challenging and long-standing issue discussed, experts agreed that broader and more representative global surveillance for a variety of diseases in both animal and human populations is needed. Challenging questions for the

[5] www.ncbi.nlm.nih.gov/guide/.

surveillance of emerging zoonoses include: How can surveillance be conducted when it is not clear what is being looked for? How far in advance can emerging risks be effectively predicted to inform the optimal use of often limited response resources? How can unusual morbidity and mortality events or new causes of common syndromes be detected rapidly in areas where accurate detection of even the most common diseases is lacking? and, perhaps the most challenging of all, How can disease reporting be encouraged and supported? Ultimately, while many longstanding questions and challenges remain for improving surveillance, many opportunities for progress were identified.

When implemented, emerging disease surveillance must occur within the context of national priorities, as countries have constantly to balance their budgets, human resources, infrastructure and political realities. Adequate scientific and political justifications are needed to support the prioritization of surveillance for a pathogen or disease that might emerge (irrespective of its global impact) over surveillance for a disease that is already having health or economic impacts. This raises additional issues, such as how surveillance should be targeted to ensure the most effective use of financial, human and technical resources. Careful examination of the scientific and political justifications at the country level will guide the balance between maintaining and improving existing surveillance for known diseases and the challenge of rapidly detecting emerging threats, because the two objectives are not mutually exclusive. An emerging disease will often not be immediately recognized as such, so ensuring that national capacity exists for detecting known diseases will also enable the recognition of unusual events. Many of the issues discussed are therefore applicable to multiple surveillance goals.

Virtually all diseases need improved early detection and early warning systems, including the ability to identify pathogens rapidly. Approaches that have proved feasible and effective or that show great promise include, among others, syndromic surveillance and participatory epidemiological approaches, which can be applied in all sectors (livestock, wildlife, humans and the environment). The use of indirect indicators of disease emergence can complement these surveillance methods, taking into account ecological, cultural and human behavioural factors. It was agreed that targeted surveillance efforts using a mixture of pathogen- and non-pathogen-based variables are needed, to identify the ultimate drivers of disease emergence. Among the suggestions for expanding and complementing traditional surveillance activities were identification of critical hazard points along the global market chain, sociological analyses to identify high-risk behaviour and activities, coordinated human and animal surveillance around reported "die-off" events in wildlife, and harmonization and alignment of the case definitions and outbreak definitions used by the animal and public health sectors. Successful examples have shown that the interactions among humans, domestic animals and wildlife can be most fully understood when they are investigated through multidisciplinary approaches.

Promising strategies for enabling and focusing the science-based targeting of surveillance were identified, including the expanded use of qualitative and quantitative epidemiological data in risk models, the use of data on how host population dynamics shift in response to environmental changes, and the use of retrospective analysis of past outbreaks. Complementing population-based with targeted surveillance could be a cost effective means of achieving sustainability in developing countries.

The use of technologically advanced tools and strategies (e.g., mathematic, predictive and epidemiological modelling and computer simulations), including new non-traditional surveillance modalities (e.g., Twitter, Facebook, blogs) is opening new horizons. This is particularly true regarding the use of mobile phones, which have been shown beneficial to increase the engagement of people at the grassroots level and to facilitate the real-time reporting of unusual events. Creativity in establishing non-traditional partnerships with other sectors/groups such as hunters, bird watchers and other nature enthusiasts can improve surveillance of diseases in wildlife before they are introduced into domestic animals or humans, and reporting can be supported by innovative methods such as the use of SMS technology.

ECOSYSTEM DYNAMICS

Better understanding of the complex interactions between actual and potential host and reservoir species, including vectors and taking into account ecosystem changes and ecosystem health, would provide details of where, how and why humans, domestic animals and wildlife interact. These details could lead to a clearer understanding of the roles of different agricultural production systems and extractive industries (e.g., mining, oil drilling, the harvesting of lumber) in causing ecosystem change and affecting human-animal interactions. Humans' interactions with animals may introduce changes to ecosystems that could affect ecosystem health. The monetary value of healthy ecosystems as a benefit to human health has never been well quantified, and was proposed as an area for further investigation.

Disease emergence modelling and prediction would be strengthened by the incorporation of indicators of ecosystem health into existing decision-making tools. For example, increased understanding of how agricultural industrial practices and human-animal interactions affect ecosystems could result in these factors becoming indicators of risk for disease emergence. The inclusion of existing ecological data in current systems and models was identified as a feasible strategy for leveraging existing resources rather than seeking new ones. The cataloguing of microbial flows at the human-animal-ecosystems interface – by mapping the diversity of pathogens, connections and interactions in the environment and populations, and the flows and changes at the interface – and routine geo-coding of isolated pathogens, along with their landscape and food chain parameters, are examples of innovative ideas that could advance understanding and risk determination of zoonotic disease emergence.

There is need for better understanding of legal and illegal trade in wildlife, including in wet markets. The rapid growth in wildlife farming is of concern if management systems are not well understood, and few policies and regulations guide wildlife trade or wildlife production systems. As wildlife farming is still in the early stages of development, there is potential for encouraging healthy businesses with good practices, through carrying out risk assessments and identifying emerging zoonoses.

DIAGNOSTICS

The meeting participants highlighted the importance of having rapid, efficient, simple and cost-effective diagnostics for pathogen isolation and identification, both at the local level and in reference laboratories. Of particular importance are diagnostic tests that are appro-

priate to and applicable in the field, to identify new pathogens as early as possible. The crucial question regarding how to develop diagnostics for pathogens that are not yet known was raised, and noted as an area where more research is need. The need for research and capacity building on optimal sample collection and transport methods was also mentioned, as was the importance of ensuring that relevant data are included with the samples as they move from the field through the laboratory system.

Innovative ideas for further investigation include micro-array chips for field polymerase chain reaction (PCR) for earlier characterization of pathogen groups and subgroups. Geolocation of sample collection sites could be complemented by video-location using mobile phones.

Newly built laboratory capacity must be made sustainable, which could be achieved in part through regional cross-training and networking and an emphasis on locally important diseases.

BEHAVIOUR CHANGE AND COMMUNICATION

Changing people's behaviour is a very effective yet challenging way of reducing health risks and humans' contribution to the emergence of diseases. People's acceptance to change their behaviour is key to improving the detection and reporting of disease, the implementation of measures to identify and decrease risk, and vaccine acceptance and usage, among other animal and public health goals. Improved risk communication and outreach should not only target the general public, but also involve all disciplines, media and community leaders, including the ministries responsible for national public and animal health. Better understanding of the sociological, cultural, economic and anthropological elements that affect behaviours and risk perception is needed, so that more effective and practicable measures for changing risky behaviours can be defined and communicated.

Given the scarcity of resources, creative communication and incentive methods are needed to encourage collaboration, innovation, cooperation and compliance among all players. For example, when designing new approaches, the individuals and agencies combating disease emergence might learn from successful corporate health promotions and behaviour change campaigns (e.g., for hygiene or tobacco prevention). The study of human behaviours, attitudes, needs and practices would also be useful for the targeting and communication of behaviour change messages. Collaboration with marketing corporations could assist with the design of appropriate messages, and improved methods for disseminating these to a diverse public. Studies of previous successful human and veterinary vaccination or other campaigns might suggest options for improving outcomes.

Global experiences with H5N1, pandemic H1N1 2009, and a variety of other animal and public health challenges have demonstrated that health agencies and institutions must be proactive in managing public perceptions in the face of adverse events. Ensuring transparent, valid and aligned communication among partners is an effective way of countering or preventing negative perceptions and criticisms.

CAPACITY BUILDING, EDUCATION AND RESEARCH

National capacity building is important in a wide variety of technical areas. Surveillance and sample collection were highlighted as key areas for capacity building, along with improved

understanding of the intrinsic and extrinsic motivations and incentives that ensure economic viability and cultural/practical acceptability for the implementation of national technical programmes (as described in the previous section). Because capacity needs vary widely among countries, and capacity building must focus on specific national needs, countries have the opportunity to take a more active role in identifying and prioritizing their own risks and associated capacity needs to ensure more sustainable policies and technical systems.

In building national capacities, it was agreed that there would be substantial benefits from the cross-training of veterinarians, ecologists and human health practitioners, as both technical and administrative staff are often unaware of the motivations and constraints of their counterparts in other sectors. Existing resources could easily be leveraged, maximized and integrated into existing programmes to promote cross-training. The Field Epidemiology Training Programme[6] (FETP) and FETP-Veterinarians[7] (FETP-V) were mentioned as examples, and new training models including multi-disciplinary professional approaches were among the innovative ideas for further consideration.

Along with training and capacity building, concerns were expressed about fundamental gaps in the scientific knowledge necessary for understanding emergence and transmission in a variety of contexts. For many endemic diseases, there is still a need for basic laboratory research to provide information about the risk of re-emergence or spread. For such diseases, the recent emphasis has often been on field interventions, and ongoing laboratory research has declined, despite the opportunities for increasing understanding that new technologies offer. Existing resources could be leveraged to allow relevant research to be conducted at the local level while building critical national infrastructure.

For example, although the substantial impacts of ecology and changes in population dynamics are commonly described in the scenarios of emergence of new diseases and cross-species transmission, the specific factors involved have not yet been well characterized, even for well-studied diseases such as influenza. Focusing on pathogen discovery and characterization in atypical species, including full genomic sequencing particularly of new viruses, might provide clues to what is common among pathogens that emerge.

A concern was raised about the shortage of new students joining the basic fields of study necessary for understanding zoonotic and vector-borne diseases: if not addressed, this gap could eventually affect the global ability to investigate certain important research questions. It was suggested that subject experts should coordinate efforts to encourage students to pursue degrees in fields of study where future shortages are foreseen, such as entomology.

MULTIDISCIPLINARY COLLABORATIVE APPROACHES

The need to increase multidisciplinary work from individual projects to the institutional level, and to increase the diversity of disciplines in these efforts was identified as a keystone for better understanding of the human-animal interface and disease emergence. This will require strong efforts to engage different disciplines and institutions (including ministries) representing, among other sectors, wildlife, environment, ecology, anthropol-

[6] www.cdc.gov/globalhealth/fetp/.

[7] www.usaid.gov/rdma/articles/press_release_694.html, http://www.fao.org/docrep/013/al842e/al842e00.pdf .

ogy, economics, behavioural and social sciences, and clinical medicine, while strengthening and expanding existing collaboration between Ministries of Agriculture and Ministries of Health. For example, disease detection and reporting would be strengthened by engaging multidisciplinary partners at the field, local, national and international levels.

Although all the participants agreed with this in principle, it was noted that significant barriers to collaboration remain. Incentives and common goals for collaboration are necessary for creating trust among disciplines and individuals, particularly when new types of interdisciplinary collaboration are involved, so understanding these incentives and goals is critical to increasing scientific understanding of the human-animal interface. Such trust is fundamental to the timely and mutually useful exchange of intelligence, information and knowledge, and can also lead to the mutual leveraging of resources for the creation of higher-impact and more efficient results. It was also noted that developed, transition and developing countries may have different barriers to, and probably different incentives for, implementing multidisciplinary collaborative approaches. Funding streams that make collaboration a condition for funding would almost certainly foster collaboration among sectors, so identifying and implementing financial/funding approaches that have multidisciplinary work as a fundamental component should bring benefits. Developing partnerships between the private and public sectors would also capitalize on the strengths offered by these very different systems, creating mutually beneficial synergies.

Some disciplines were recognized as critical partners that are currently underrepresented or otherwise less engaged in the implementation of collaborative approaches to increasing the understanding of the human-animal-ecosystems interface, particularly ecology, wildlife/natural resource management and clinical human medicine. The incentives for encouraging such partners to collaborate would vary; for example, incentives for ecologists and wildlife/natural resource managers could be based on a clear identification of mutually beneficial goals, and those for clinical medical doctors on an understanding of where they themselves could have an important role in the process. For these groups and others, creativity in the establishment of relationships and non-traditional partnerships will bring benefits to all aspects of understanding and controlling the risks of disease emergence at the human-animal-ecosystems interface.

SUSTAINABLE APPROACHES

Another recurring theme during the meeting was where best to focus efforts to maximize efficiency and sustainability. Given the scarcity of resources, governments must make strategic decisions regarding where and how to prioritize and invest, for example in risk assessment, the development of tools and systems for early identification of agents, or systems for rapid response. These questions are also arising at the international level, where prioritization is just as necessary.

The broader application of existing principles and strategies may be a solution. The concept of leveraging assets – by using what is already available to augment, support or inform access to or development of what is lacking (be it technical capacity, financial resources, infrastructure or expertise) – was agreed as a way of ensuring the efficacy and sustainability of programmes, promoting cross-fertilization and optimizing problem solving. Similarly, building infrastructure and systems that are cross-cutting rather than focused on a single

disease might make it possible to address health issues more consistently and proactively than "fire-fighting" as events occur. Engagement of private sector stakeholders may not only contribute additional resources but also build broader partnerships and constituencies to enhance sustainability.

The ideas that emerge for making efforts more sustainable and effective will depend on the questions asked and the goals of the initiative. Targeting efforts such as surveillance, research projects and national control programmes to specific known risks, be they geographic, species-based or management system-based, is known to optimize certain results. However, it was mentioned that – depending on the context – targeting efforts is not always more appropriate than a broader, random or more comprehensive approach. Regional collaboration may also help sustainability. For example, some effective activities and approaches, such as radio telemetry to monitor wild bird movements, are resource-intensive (requiring substantial funds, staff and/or time). For these, implementation may be more feasible if carried out collaboratively at the regional level.

Moving forwards: steps towards translating meeting outcomes into policy

This meeting was held in the context of an unusual circumstance. On 14 April 2010, a long-dormant volcano near Eyjafjallajoekull Glacier in Iceland erupted. This was a totally unexpected event, which shut down European airspace between 15 and 20 April, left approximately 10 million persons stranded throughout the world,[8] and had incalculable direct and indirect global financial impacts. Throughout the meeting, the volcano and its "unpredicted emergence" was a topic of much conversation, and underlined the stark reality of the meeting discussions, by emphasizing that the world needs to expect the unexpected. The volcano also mirrored what was perhaps the main lesson learned from the 2009 influenza pandemic: that no matter how well prepared the world may be for an expected event, the threat that emerges may not follow the expected framework. Current events suggest that this is the more likely scenario.

Expecting the unexpected is important, but preparing for the unexpected is more difficult. The findings of this meeting, both for specific diseases and cross-cutting issues, provide a technical basis for developing or modifying policies that allow more effective preparation for and response to the next event, whether it be expected or unexpected. As a first step to developing new policies or strategies for reducing the risks from emerging zoonotic diseases or modifying those from existing ones, national and regional governments, technical agencies and institutions working at every level can review and consider how the points and key findings presented in this report relate to their own national interests and contexts. They should remember the following:

- Not all the points raised apply to all disease issues; some of the policies and strategies already in place will remain effective and relevant.
- The points can be considered proactively, if existing disease risks are not being mitigated effectively by current strategies.
- Some technical topics, such as understanding the determinants of pathogenicity, and conceptual themes, such as building trust among sectors, were identified as fundamentally and profoundly important. However, the world is just beginning to understand these topics and their relationship to the human-animal-ecosystems interface. Deeper knowledge is necessary before more useful studies and/or more effective interventions can be developed and implemented.
- Effective preparation for certain defined situations has shown to be effective, but preparing for all possible situations can be best achieved by building systems that are flexible and resilient enough to respond to a variety of unforeseen challenges.

[8] Associated Press. 16 August 2011. Eruption at Iceland volcano slows, but not over.

As a first step, all stakeholders at the human-animal-ecosystems interface must re-evaluate existing paradigms and question their effectiveness. As experience shows that the next major global public health event is unlikely to be similar to any of its predecessors, it is necessary to move forward flexibly, using new strategies and paradigms (along with those that have already proved effective) to reduce animal and public health risks at the human-animal-ecosystems interface.

As already mentioned, an overarching theme of the meeting was the need to build trust, to achieve almost all the desired outcomes discussed. Without trust there is no willingness to report known or suspected diseases, share information and materials, or discuss issues of individual or mutual concern that may be seen as weaknesses or could lead to losing resources or other support. This report's proposals for solving health issues at the human-animal interface depend on changing this paradigm, to create one of cooperation, joint consultation and the routine shared leveraging of resources, expertise and capacity to help solve existing and emerging problems and achieve more impactful, mutually beneficial, sustainable and satisfying results. To this end, senior officials and other leaders should consider their policies and ensure that they satisfy and justify the trust put in them by their constituents.

International organizations took a major step forwards in 2010 by aligning their individual goals and mandates and confirming their collaboration within the 2010 FAO-OIE-WHO Tripartite Concept Note described at the beginning of this report. International leadership is crucial to facilitating high-level multisectoral collaboration within and among ministries, other government structures and civil society. The concept note is not an ending point, but rather an expression of the three organizations' ongoing commitment to promoting and supporting similar action from partners at the regional and national levels. A commitment to collaboration provides the foundation for the networks of expertise that are needed for effective prevention of and response to current and future emerging zoonotic events. Multisectoral collaboration must expand to meet the needs and fill the gaps at the human-animal-ecosystems interface, and must do so flexibly, to meet expected and unexpected challenges wherever they exist.

Annexes

Annex A
List of participants

ABELA BERNADETTE
WHO HQ
Department of Food Safety,
Zoonoses and Foodborne Diseases
Tel.: +41 22 791 2072
E-mail: abelab@who.int

ABERNETHY NEIL
Center for Public Health Informatics
1100 NE 45th Street, Suite 405
Seattle, WA 98105, USA
Tel.: +1 206 616 2813
E-mail: neila@u.washington.edu

ALEXANDERSEN SOREN
Foreign Animal Diseases Laboratory
1015 Arlington Street Winnipeg MB R3E 3M4
Canada
Tel.: +1 204 789 2102
E-mail: Soren.alexandersen@inspection.gc.ca

ALFONSO PASTOR
National Center of Animal and Plant Health
PO BOX 10, San Jose Lajas, 32700
La Habana, Cuba
Tel.: +47 863014
E-mail: pastor.alfonso@infomed.sld.cu

BROWN IAN
Central Veterinary Laboratories Agency (VLA)
Weybridge, Woodham Lane
New-Haw, Addlestone, Surrey KT15 3NB, United Kingdom
Tel.: +44 1932 341 111
E-mail: i.h.brown@vla.defra.gsi.gov.uk

CAPUA ILARIA
IZSVe
Tel.: +39 049 8084369
E-mail: icapua@izsvenezie.it

CATTOLI GIOVANNI
IZSVe
Tel.: +39 04 98 08 43 84
E-mail: gcattoli@izsvenezie.it

CHUA KAW BING
National Public Health Laboratory
Ministry of Health Malaysia
Lot 1853, Kg. Melayu
47000 Sungai Buloh
Selangor, Malaysia
Tel.: +603 6126 1200
E-mail: chuakawbing@yahoo.com.sg

CONAN ANNE
Institut Pasteur du Cambodge
5 Monivong Bd
POB 983, Phnom Penh, Cambodia
Tel.: +855 12 893 518
E-mail: aconan@pasteur-kh.org

DASZAK PETER
Wildlife Trust
460 West 34th Street, 17th Floor
New York, NY 10001, USA
Tel.: +1 212 380 4473
E-mail: daszak@wildlifetrust.org;
daszak@conservationmedicine.org

DAUPHIN GWENAELLE
FAO HQ
Tel.: +39 06 570 56027
E-mail: Gwenaelle.Dauphin@fao.org

Food and Agriculture Organization of the United Nations (FAO)
Animal Production and Health Division
Via delle Terme di Caracalla
00153 Rome, Italy
Tel. +39 06 57051
World Organisation for Animal Health (OIE)
12 rue de Prony, 75017 Paris, France
Tel.: +33 1 44151888
World Health Organization (WHO)
20 Avenue Appia
CH-1211 Geneva 27, Switzerland
Tel. +41 22 791 2111
Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe)
Viale dell'Università, 10
35020 Legnaro (PD), Italy
Tel.: +39 049 8084211

DE LA ROCQUE STEPHANE
FAO HQ
Tel.: +39 06 570 54710
E-mail: Stephane.Delarocque@fao.org

DE BALOGH KATINKA
FAO HQ
Tel.: +39 06570 56110
E-mail: Katinka.DeBalogh@fao.org

DONIS RUBEN
Centers for Disease Control and Prevention (CDC)
Influenza Branch
1600 Clifton Road, G16
Atlanta, Georgia 30333, USA
Tel.: +1 404 6394968
E-mail: rvd6@cdc.gov

DUBEY SHIV CHANDR
High Security Animal Disease Laboratory
Indian Veterinary Research Institute
Hathai Kheda Farm, Kokta Road, Anand Nagar, Bhopal 462021, India
Tel.: +91 755 2759204
E-mail: scd_11@yahoo.in

ERGONUL ONDER
Marmara University, School of Medicine
Infectious Diseases Department
Altunizade, Istanbul, Turkey
Tel.: +90 535 8152741
E-mail: onderergonul@yahoo.com

FASSI FIHRI OUAFAA
Unité de microbiologie, Immunologie Maladies Contagieuses
Département de Pathologie et Santé Publique Vétérinaires
Institut Agronomique et Vétérinaire Hassan II
Rabat, Morocco
Tel: +212 660807314
E-mail: o.fassifihri@iav.ac.ma

FIELD HUME
Biosecurity Queensland
Department of Employment
Economic Development and Innovation (DEEDI), Australia
Tel.: +61 7 33629566
E-mail: Hume.field@deedi.qld.gov.au

FORMENTY PIERRE
WHO HQ
Global Alert and Response Department
Tel.: +41 22 791 25 50
E-mail: formentyp@who.int

GLYNN KATE
OIE HQ
Tel.: +33 1 44 15 19 66
E-mail: k.glynn@oie.int

HARDER TIMM
Institute for Diagnostic Virology
Friedrich-Loeffler Institute (FVI)
Suedufer 10, D-17493 Greifswald-Insel Riems
Tel.: +49 38351 7152
E-mail: timm.Harder@fli.bund.de

HENTONNEN HEIKKI
Finnish Forest Research Institute
University of Helsinki
Pl 18, FI-01301 VANTAA, Finland
Tel.: +358 102 112 430
E-mail: heikki.henttonen@metla.fi

HOGERWERF LENNY
Department of Farm Animal Health
Faculty of Veterinary Medicine
Utrecht University
Division of Epidemiology Yalelaan 7,
3584 CL, Utrecht, The Netherlands
Tel.: +31 302531014
E-mail: lennyhw@gmail.com

IPPOLITO GIUSEPPE
National Institute for Infectious Diseases
Lazzaro Spallanzani
Via Portuense, 292
00149 Rome, Italy
Tel.: +39 06 5594223
E-mail: giuseppe.ippolito@inmi.it

JEGGO MARTYN
Australian Animal Health Laboratory (AAHl)
CSIRO Livestock Industries
Private Bag 24. Geelong, Victoria, Australia 3220
Tel.: +61 3 5227 5511
E-mail: Martyn.Jeggo@csiro.au

JOANNIS TONY
National Veterinary Research Institute
Vom, Plateau State, Nigeria
Tel.: +234 8037024280, +234 8052734204, +234 73281453
E-mail: tmjoannis@yahoo.com

JOST CHRISTINE
International Livestock Research Institute (ILRI)
Box 30709 Nairobi 00100, Kenya
Tel.: +254 736 715 417
E-mail: c.jost@cgiar.org

KALPRAVIDH WANTANEE
FAO Regional Office for Asia and the Pacific
39 Maliwan Mansion, Pra Athit Road
Pra Nakorn, Bangkok 10200, Thailand
Tel.: +66 2 6974000
E-mail: Wantanee.Kalpravidh@fao.org

KARESH WILLIAM
Wildlife Conservation Society (WCS)
Field Veterinary Program
2300 Southern Boulevard
Bronx, NY 10460, USA
Tel.: +1 718 220 5892
E-mail: wkaresh@wcs.org

KECK FRÉDÉRIC
Centre National de Recherche
Scientifique (CNRS)
Social Anthropology
59 rue du Faubourg du Temple
75010 Paris, France
Tel.: +33 142393598
E-mail: keck.fred@gmail.com

KLENK HANS-DIETER
Institut für Virologie
Hans-Meerwein-str. 2
35043 Marburg, Germany
Tel.: +49 6421 286 6191
E-mail: klenk@staff.uni-marburg.de

KOOPMANS MARION
Erasmus University, Rotterdam
National institute of public health and the environment
Antonie van leeuwenhoeklaan 9
3720BA Bilthoven
The Netherlands
Tel.: +31.6.5209.8601
E-mail: Marion.Koopmans@rivm.nl

LIU FU QIANG
Epidemic Diseases control Department
Hunan Provincial
Center for Disease Control and Prevention
Changsha, Hunan 410005, China
Tel.: +86 731 4305931
E-mail: liufq2001@163.com;
hncdcliufu@yahoo.com

MACKENZIE JOHN
Australian Biosecurity CRC
Curtin University of Technology
GPO Box U1987
Perth, WA6845, Australia
Tel.: +61 3 9822 6223
E-mail: J.MacKenzie@curtin.edu.au

MAGNUSSON ULF
Faculty of Veterinary Medicine and
Animal Science
P.O. Box 7084
Swedish University of Agricultural Sciences
S-750 07 Uppsala, Sweden
Tel.: +46 18 672324
E-mail: ulf.magnusson@kv.slu.se

MANUGUERRA JEAN CLAUDE
Institut Pasteur
25 rue du Docteur Roux
75724 Paris Cedex 15, France
Tel.: +33 1 40 61 38 08
E-mail: jmanugu@pasteur.fr

MARTIN VINCENT
FAO Representation in China
Jiangoumenwai 4-2-151
Beijing, 100600, China
Tel.: +8610 6532 2835
E-mail: Vincent.Martin@fao.org

MERTENS PETER
Vector Borne Diseases Programme
Institute for Animal Health (IAH)
Ash Road, Pirbright Woking Surrey
GU24 0NF, United Kingdom
Tel.: +44 1483 231 189
E-mail: peter.mertens@bbsrc.ac.uk

MOUTOU FRANÇOIS
Agence Française de Sécurité Sanitaire des
Aliments (AFSSA)
Unité Épidémiologie
23 avenue du général de Gaulle
94706 Maisons-Alfort cedex, France
Tel.: +33 1 49 77 13 33
E-mail: f.moutou@AFSSA.Fr

MUMFORD ELIZABETH
WHO HQ
Global Influenza Programme
Tel.: +41 22 791 2174
E-mail: mumforde@who.int

NEWMAN SCOTT
FAO HQ
Tel.: +39 6 570 53068
E-mail: Scott.Newman@fao.org

OSTERHAUS AB
Erasmus Universiteit
National Influenza Centre
Dr Molewaterplein 50,
P. O. Box 1738, 3000 DR Rotterdam
The Netherlands
Tel.: +31 10 408 80 66
E-mail: a.osterhaus@erasmusmc.nl

PEETERS MARTINE
Laboratoire Retrovirus, UMR145
Institut de Recherche pour le Développement (IRD) and Department of International Health, University of Montpellier I
911 Avenue Agropolis, BP 64501
34394 Montpellier Cedex 5, France
Tel.: +33 4 67 41 61 61
E-mail: martine.peeters@mpl.ird.fr

PEYRE MARISA
Centre de coopération internationale en recherche agronomique pour le développement (CIRAD)
Animal and Integrated Risk Management Unit
Campus International de Baillarguet
34398 Montpellier Cedex 5, France
Tel.: +33 4 67 59 38 68
E-mail: marisa.peyre@cirad.fr

RICHT JUERGEN
Kansas State University
College of Veterinary Medicine
Diagnostic Medicine/Pathobiology
K224B Mosier Hall
Manhattan, KS 66506-5601, USA
Tel.: +1 785-532-4408
E-mail: jricht@vet.k-state.edu

ROLLIN PIERRE
Centers for Disease Control and Prevention (CDC)
1600 Clifton Rd, Atlanta, GA 30333, USA
Tel.: +1 404 6391124
E-mail: pyr3@cdc.gov

SANTINI NICOLA
Italian Ministry of Health
Department of Veterinary Public Health, Nutrition and Food security
General Direction of Animal Health and veterinary drugs
Viale Giorgio Ribotta, 5
00144 Rome, Italy
Tel.: +39 06 59946744
E-mail: n.santini@sanita.it

SANTUCCI VINCENZO UGO
Italian Ministry of Health
Department of Veterinary Public Health, Nutrition and Food security
General Direction of Animal Health and veterinary drugs
Viale Giorgio Ribotta, 5
00144 Rome, Italy
Tel.: +39 06 59946734
E-mail: u.santucci@sanita.it

SECK BOUBACAR
FAO Regional Animal Health Centre
BP 1317, Bamako, Mali
Tel.: +223 6 696 7000
E-mail: boubacar.seck@fao.org; bmseck@ gmail.com

SHIMSHONY ARNON
Tabenkin st 37a
Tel-Aviv 69353, Israël
Tel.: +972 3 648 15 15
E-mail: ashimsh@netvision.net.il

SHINDO NIKKI
WHO HQ
Global Influenza Programme
Tel.: +41 22 791 3446
E-mail: shindon@who.int

SLINGENBERGH JAN
FAO HQ
Tel.: +39 06 570 54102
E-mail: Jan.Slingenbergh@fao.org

SWAYNE DAVID
Southeast Poultry Research Laboratory (SEPRL)
USDA Agricultural Research Service
934 College Station Road
Athens, Georgia 30605, USA
Tel.: +1 706 546 3433
E-mail: David.Swayne@ars.usda.gov

TALLIS GRAHAM
WHO Indonesia Country Office
BinaMulia1, Lt.9,
Jl Rasuna Said, Kav.10, Jakarta, Indonesia
Tel.: +62 21 520 4349 Ext.: 860
E-mail: tallisg@who.or.id

THIERMANN ALEX
OIE HQ
Tel.:+ 33 144 1518 88
E-mail: a.thiermann@oie.int

VAN KERKHOVE MARIA
MRC Centre for Outbreak Analysis and Modelling
Department of Infectious Disease Epidemiology
Imperial College Faculty of Medicine
St Mary's Campus, Norfolk Place
London W2 1PG, United Kingdom
Tel.: +44 75 902 50513
E-mail: m.vankerkhove@imperial.ac.uk

VINCENT AMY
2823 Swine and Prion Diseases Research Unit
USDA Agricultural Research Service
National Animal Disease Center
1920 Dayton Avenue Ames, IA 50010, USA
Tel.: +1 515 337 7557, +1 515 663 7371
E-mail: amy.Vincent@ars.usda.gov

WALLACE ROBERT
Institute for Global Studies
University of Minnesota
214 Social Sciences Building
267 19th Avenue South
Minneapolis, MN 55455, USA
Tel.: +1 61 22 27 60 90
E-mail: rwallace24@gmail.com
walla353@umn.edu

WANG LINFA
CSIRO Livestock Industries
Australian Animal Health Laboratory
PO Bag 24 Geelong, VIC 3220, Australia
Tel.: +61 3 52275121
E-mail: linfa.Wang@csiro.au

WEBBY RICHARD
Department of Infectious Disease
St. Jude Children's Research Hospital
332 North Lauderdale Street
Memphis TN 38105-2794, USA
Tel.: +1 901 595 3014
E-mail: richard.webby@stjude.org

ZELLER HERVÉ
Scientific Advice Unit
Emerging and Vector-borne Diseases
European Center for Disease Prevention and Control
Tomtebodavägen 11A
171 83, Stockholm, Sweden
Tel.: +46 8 58 60 12 27
E-mail: herve.zeller@ecdc.europa.eu

FACILITATOR

NORMANDEAU DANIEL
Consultants Conversart Consulting
Tel.: + 613 837 6061
E-mail: Dnormandeau@conversart.com

SUPPORT STAFF

BEATO MARIA SERENA
IZSVe
Tel.: +39 049 8084 367
E-mail: msbeato@izsvenezie.it

BURGOS SIGFRIDO
FAO HQ
Tel.: +39 06 570 53953
E-mail: Sigfrido.Burgos@fao.org

DE BENEDICTIS PAOLA
IZSVe
Rabies Unit
Tel.: +39 049 8084 385
E-mail: pdebenedictis@izsvenezie.it

DIETZE KLAAS
FAO HQ
Tel.: +39 06 570 53968
E-mail: Klaas.Dietze@fao.org

DOMINGUEZ MORGANE
FAO HQ
Tel.: +39 06 570 54898
E-mail: Morgane.Dominguez@fao.org

MICOLI NADIA
IZSVe
Tel.: +39 049 8084 371
E-mail: nmicoli@izsvenezie.it

MONNE ISABELLA
IZSVe
Molecular Unit
Tel.: +39 049 8084 381
E-mail: imonne@izsvenezie.it

SHEAHAN JENNIFER
OIE HQ
World Animal Health and Welfare Fund
Tel.: +33 1 44 15 18 64
E-mail: j.sheahan@oie.int

WELTER JOELLEN
Independent Consultant
Switzerland
Tel.: +41 71 633 11 14
E-mail: jdethomasis@gmail.com

Annex B
Agenda

Monday **26 April**

15.00-18.00 Meeting of the Planning committee

Tuesday **27 April**

8.00-9.00 Registration

SESSION 1: WELCOMES AND MEETING OBJECTIVES/METHODS OF WORK

Welcomes

9.00-9.10 Welcome from Italian authorities *(Ugo Santucci - from the Italian Ministry of Health)*

Focus on importance of the interface and practical significance of this consultation's work:

9.10-9.20 *Jan Slingenbergh (FAO)*
9.20-9.30 *Alex Thiermann (OIE)*
9.30-9.40 *Liz Mumford (WHO)*

Scope and outcomes of the meeting

9.40-9.55 Transitions from Verona I *(Alex Thiermann)*
9.55-10.10 Theme for Verona II *(Kate Glynn)*
10.10-10.30 Define objectives of the meeting and define methods of work *(Dan Normandeau)*

10.30-11.00 Coffee

SESSION 2: CHARACTERISTICS OF EMERGING "HIGH PUBLIC HEALTH IMPACT" INFLUENZAS

OBJECTIVE: TO REVIEW VIROLOGICAL AND EPIDEMIOLOGICAL FACTORS INFLUENCING EMERGENCE OF "HPHI" INFLUENZAS AT THE HUMAN-ANIMAL INTERFACE, AND COMPARE AND CONTRAST FACTORS ASSOCIATED WITH EMERGENCE OF H5N1 AND PANDEMIC H1N1

MODERATORS: HANS-DIETER KLENK, VINCENT MARTIN

11.00-11.15 Overview of what we learned from H5N1 *(Ilaria Capua)*
11.15-11.30 Overview of what we learned from H1N1 *(Ruben Donis)*
11.30-11.45 Other influenzas of concern *(Juergen Richt)*
11.45-11.55 The flu gene pool *(Liz Mumford)*
11.55-12.30 Clarification and questions *(Dan Normandeau)*

12.30-13.45 Lunch

13.45-14.00 Virological characteristics of Public Health concern *(David Swayne)*
14.00-14.15 Viral factors involved in reassortment and mutation *(Richard Webby)*
14.15-14.30 Non-virological factors that could influence influenza emergence *(Vincent Martin)*
14.30-15.00 Clarification and questions *(Dan Normandeau)*

15.00-15.30 Coffee

15.30-16.45 Panel
16.45-17.00 Wrap up day 1 *(Dan Normandeau)*
18.00-19.30 Break out groups

20.00 Dinner

Wednesday **28 April**

USING SPECIFIC VIRAL DISEASE SCENARIOS TO EXAMINE DISEASE EMERGENCE GENERALLY

OBJECTIVE: TO BUILD UPON INFLUENZA-BASED DISCUSSIONS FROM DAY 1, AND DRAW CONCLUSIONS ABOUT ISSUES/APPROACHES RELATED TO EMERGENCE AND THE HUMAN-ANIMAL INTERFACE FOR OTHER EMERGING OR POTENTIALLY EMERGING VIRAL DISEASES THAT COULD IMPROVE DETECTION, PREVENTION AND CONTROL OF EMERGENCE

8.30-8.50 Summary of day 1 & break out groups *(Dan Normandeau)*
8.50-9.00 Tasks for today *(Dan Normandeau)*

SESSION 3: ENDEMIC ZOONOTIC DISEASES

MODERATORS: STÉPHANE DE LA ROCQUE, PETER DASZAK

9.00-9.15 West Nile Fever (WNV) *(Herve Zeller)*
9.15-9.30 Rift Valley Fever (RVF) *(Pierre Formenty)*
9.30-9.45 Crimean Congo Haemorrhagic Fever (CCHF) *(Onder Ergonul)*
9.45-10.15 Clarification and questions *(Dan Normandeau)*

10.15-10.45 Coffee

10.45-11.30 Discussion *(Dan Normandeau)*

SESSION 4: SPORADIC ZOONOTIC DISEASES

MODERATORS: BERNADETTE ABELA, WILLIAM KARESH

11.30-11.45 Nipah and Hendra Viruses *(John Mackenzie)*
11.45-12.00 Ebola and Marburg Viruses *(Pierre Rollin)*
12.00-12.15 Hantavirus *(Heikki Hentonnen)*

12.15-12.45	Clarification and questions *(Dan Normandeau)*
12.45-13.45	**Lunch**
13.45-14.30	Discussion *(Dan Normandeau)*

SESSION 5: ANIMAL-ORIGIN AGENTS THAT HAVE EMERGED INTO "HIGH PUBLIC HEALTH IMPACT" ZOONOSES
MODERATORS: JOHN MACKENZIE, JAN SLINGENBERGH

14.30-14.45	HIV/SIV *(Martine Peeters)*
14.45-15.00	SARS *(Linfa Wang)*
15.00-15.45	Discussion-Panel *(Dan Normandeau)*
15.45-16.15	**Coffee**
16.15-17.00	Wrap up day 2 *(Dan Normandeau)*
18.00-19.30	Break out groups
20.00	**Dinner**

Thursday **29 April**

SESSION 6: TECHNICAL IDENTIFICATION OF COMMONALITIES
OBJECTIVE: TO IDENTIFY THE MOST SALIENT CROSS CUTTING FINDINGS

8.30-9.00	Summary & reports from break out groups
9.00-9.30	Technical cross cutting issues/ commonalities/risks
9.30-10.30	Panel
10.30-11.00	**Coffee**

SESSION 7: BRINGING IT TOGETHER
OBJECTIVE: TO SUMMARIZE THE TECHNICAL INFORMATION AND IDENTIFY KEY POINTS FROM THE MEETING

11.00-12.50	Bringing it together
12.50-13.00	Closing remarks from Italy *(Giuseppe Ippolito)*
13.00	**Meeting closure**

SESSION 8: DRAFTING OF SUMMARY AND RECOMMENDATIONS
FOR THE SCIENTIFIC COMMITTEE AND FACILITATOR

13.00-14.00	**Lunch**
14.00-15.30	Drafting of conclusions and recommendations

15.30-16.00	**Coffee**
16.00-17.00	Drafting of conclusions and recommendations (continued) Develop press release/immediate outputs for wide circulation

PLANNING COMMITTEE

ILARIA CAPUA, GWENAELLE DAUPHIN, KATE GLYNN, LIZ MUMFORD, ALEX THIERMANN

SCIENTIFIC COMMITTEE

BERNADETTE ABELA, PETER DASZAK, GWENAELLE DAUPHIN, STEPHANE DE LA ROCQUE, PIERRE FORMENTY,
KATE GLYNN, WILLIAM KARESH, HANS-DIETER KLENK, JOHN MACKENZIE, VINCENT MARTIN, LIZ MUMFORD,
PIERRE ROLLIN, ALEX THIERMANN

FACILITATOR

DAN NORMANDEAU

Annex C
Abstracts: examples of emerged or emerging zoonotic viral diseases

ZOONOTIC INFLUENZA WITH THE POTENTIAL FOR HIGH PUBLIC HEALTH IMPACT

Overview of what we learned from H5N1

(Ilaria Capua)

This changing virus, for which poultry vaccinations have been applied extensively, has persisted for over 13 years. It has spread to three continents, has been detected in multiple species including humans, and continues to evolve into lineages and sublineages. In hindsight, expected and unexpected features of the H5N1 virus and prevention and control efforts have been identified. The host range in birds, with a wide array of orders and over 130 species infected by H5N1, facilitates extensive circulation in birds and the perpetuation of H5N1 in poultry. Moreover, infection in animals also occurred via swill-feeding/predation of other species, normally through carcasses of infected birds. In terms of persistence of the virus, factors such as animal reservoirs, illegal trade, cock fighting and human handling of birds through cultural practices were all expected to perpetuate its spread. An important and largely unexpected development was the number of wild birds infected with H5N1; they present different clinical signs (lethality difference among species), which has added implications for surveillance. H5N1 jumps species barriers easily and naturally; the extent of the host range beyond birds to humans, domestic cats, Asian palm civets, dogs, pigs, stone martens and donkeys was also unexpected, as was the limited natural infection in pigs.

At the virological level, three important host-adaptive mutation and pathogenicity features have been identified: i) changes in the receptor specificity (HA); ii changes in the polymerase complex (e.g., PB1 and PB2 genes); and iii) NS1 molecular determinants of pathogenicity. H5N1 underwent extensive genetic reassortment that produced both persistent (such as genotypes Z and V) and transient genotypes. Unexpectedly, intra-H5N1 reassortment is common, but only two inter-subtypic reassortment events have been observed (both in China).

H5N1 has: i) a wide host range; ii) a low probability of reassortment with other subtypes; iii) a high propensity to reassort within H5N1; iv) only a few known genetic markers of pathogenicity; v) demonstrated antigenic variation relevant in countries that vaccinate poultry for animal health and public health prevention/control strategies; and vi) human exposure as a result of contact with birds. It was expected that coordinated interventions were necessary in the animal reservoir to reduce the risk of human infection. However, it

was not expected that H5N1, a "rare" disease of poultry until 2000, was able to draw more resources and attention than any other contemporary animal or zoonotic disease. It prompted debate and brought into the spotlight deficiencies in animal health systems.

Lessons learned from the 2009 H1N1 influenza pandemic

(Ruben Donis)

Over the past ten years, pandemic planning has been based on assumptions gleaned primarily from experiences with avian influenza H5N1. The central, retrospectively incorrect, assessment was that a subtype H5N1 (either wholly avian or a reassortant) posed the greatest pandemic threat, followed by subtype H2 and H9 viruses. It was generally assumed that immunity to seasonal H1N1 and H3N2 in human populations would preclude the emergence of a pandemic H1 or H3 strain. The emergence of the 2009 H1N1 proved this assumption to be incorrect as well. Based on historical precedent, the pandemic virus was predicted to emerge in Asia, and its early spread was expected to be slow owing to inefficient transmission among people. However, early information from Mexico and the United States of America in late April 2009 showed that human-to-human transmission of a swine influenza-like virus was highly efficient, proving that predictions in this regard were erroneous.

An important lesson learned from the emergence of pandemic (H1N1) 2009 virus was that gaps in global swine influenza surveillance allowed the progenitors of the 2009 H1N1 to evolve for over 15 years in some unknown hosts without detection, and the series of events that led to its emergence, including time frame, place and host, remain largely unproven. Consequently, understanding of markers for human transmissibility/pathogenicity – i.e., the properties that make the 2009 H1N1 virus different from other swine H1N1 viruses in its ability to transmit among humans – are still unknown, and these properties of new viruses generally can largely not be predicted.

However, pandemic preparedness activities did facilitate a rapid and effective response to the 2009 pandemic by improving influenza detection, surveillance and diagnostics (including for atypical influenza viruses), guiding the stockpiling and use of antiviral drugs, and allowing rapid production of pandemic vaccine. Improvements in global diagnostic preparedness for avian influenza, and rapid publication of United States CDC sequence data allowed swift development and deployment of molecular tests. Nevertheless, more sensitive and inexpensive tests are needed, as well as diagnostic tests that identify specific subtypes in clinical settings. Although vaccine production started rapidly, it was still insufficient to prevent major disease waves in most countries. Importantly, although early detection of pandemic emergence was not possible, previously established networks and institutional partnerships did allow for a coordinated and effective global public health response.

Other influenzas of concern

(Juergen Richt)

Influenza is an opportunistic and adaptable virus, with many varied host reservoirs, including humans, horses, pigs, cats, dogs, wild and domestic birds, and marine mammals. Although non-human hosts mostly have α 2,3 sialic acid receptors, some (including ferrets, pigs, quail and some other poultry) also have α 2,6 receptors, as do humans.

There is transmission among host species, allowing reassortment and emergence of new strains. Pigs can act as both a mixing and an adaptation host, as demonstrated by the emergence of an H2N3 triple reassortant with genes originating from ducks and humans. It is postulated that ducks living on pig farm ponds were involved in the epidemiology of this emergence. Changes in farming practices may increase the potential of other species to act as mixing vessels. The quail, for example, is a potential intermediate host.

Equine influenza may also be a potential threat. Equine influenza viruses cause disease in horses and circulate in much of the world, facilitated by global transportation of these animals. Although equine viruses are generally not considered a hazard to humans or other species, cross-species transmission of equine H3N8 influenza virus has been widely documented in dogs. There is also some evidence that equine H3N8 viruses might have caused infections in swine and humans. The "Great Epizooty" of 1872 was suspected to have been caused by equine H7N7, and this virus subtype shows pathogenicity in mice.

Thus, subtypes circulating in other animals with potential for zoonotic emergence are H2N3 and H9N2 in pigs, both of which have already been isolated from humans, and equine H3N8 and H7N7.

The flu gene pool

(Elizabeth Mumford)

The "influenza gene pool" concept may be useful as a broader framework or paradigm for thinking about how influenza genes and viruses move and change. Using this concept, all influenza genes can be said to belong to a pool potentially available for reassortment and cross-species transmission.

By contrast, in the current paradigm, influenza viruses are most commonly characterized into one of four related conceptual groupings ("boxes"), namely: animal, human seasonal, pandemic, and zoonotic, based on the host or manner in which they have been circulating. This paradigm influences current thinking, and is the basis for much surveillance, testing and pandemic planning.

Influenza genes or gene constellations are indeed generally well adapted to their hosts (although molecular determinants for host-specificity remain largely unknown), which allows presumptive identification of the host species of most viruses, based on where they are normally found. However, the categorization boxes do not always reflect the true properties of viruses, allowing them to be assigned to different categories depending on the information available. For example, when pandemic influenza (H1N1) 2009 first emerged it might have been considered a seasonal human virus based on its clinical presentation, but once characterized, the previously undetected virus was referred to based on its nearest phylogenetic neighbours (swine influenza viruses). This categorization later proved to be misleading after its pandemic behaviour in humans was realized.

Some categorization is useful. For example, determination of virus subtype and exposure source allows epidemiological understanding of individual influenza events, and phylogenetic analysis provides information on genetic and some antigenic relatedness. However, a virus' further potential public or animal health risks cannot be predicted based on these attributes – i.e., the species of origin cannot be accurately predicted by the position of the HA, NA or other genes in a phylogenetic tree. Near phylogenetic neighbours often behave

very differently. Furthermore, the behaviour of a gene will vary greatly within different constellations of other genes.

Reassortment and cross-species transmission also complicate the categorization paradigm. Genes and viruses are generally named for where they were last found to be circulating, but the conditions under which they stop being called what they were and start being called what they are remain undefined. For example, as swine and human influenza genes are interchanged, how is a "swine" gene distinguished from a "'human" gene? Similarly, there is currently no straightforward way to categorize influenza viruses that emerge in different hosts.

It may be useful, therefore, to consider all influenza genes as part of a global gene pool (made up of eight sub-pools) potentially available for reassortment and cross-species transmission, the effects of which currently can only partially be predicted. Such a paradigm shift could: i) foster a more rational approach to assessment of influenza risk; ii) de-stigmatize risk from influenza in specific animal hosts; and iii) allow a more practical approach to surveillance and testing, which could establish a baseline and identify unusual reassortment events earlier.

Virological characteristics of public health concern

(David Swayne and Ron Fouchier)

The key issues about virological characteristics of public health concern are: i) despite considerable knowledge on HA, NS1 and PB2, influenza remains unpredictable and virus behaviour cannot be predicted solely on the basis of genome sequences; ii) pathogenicity is relatively easy to study (via animal models), however the key challenge is understanding the genetic changes to predict host range and transmissibility of the virus; and iii) genotype-phenotype predictions are difficult to make in most situations (with some exceptions). An analysis of gene constellations, rather than narrowly focusing on one viral factor (e.g., HA), is critical to advancing our understanding of influenza viruses.

By studying genome changes that affect virulence, transmissibility or infectivity among viruses, commonalities can be found and lessons can often be applied to other areas. One important contribution to this growing knowledge base is that the multi-basic amino acids in the proteolytic cleavage site of HA have a substantial impact on virulence in poultry. In addition, the alpha 2,3 and alpha 2,6 receptor binding properties have a serious impact on infectivity, virulence and transmissibility in birds versus humans, respectively. Changes in PB2 have been shown to be predictive of virulence and transmissibility of H5 viruses in mammalian models. Furthermore, research has shown that amino acid stalk deletions in the NA protein are important for infectivity in chickens and other gallinaceous poultry. Information is also available about the predictability of neuraminidase inhibitor resistance, and resistance to adamantanes. However, current knowledge about all the genetic factors or changes that could predict infectivity is insufficient. The genetic diversity within influenza A viruses, specifically within H5N1, has grown tremendously since 1997. Although this diversity is widely recognized, little is known about the phenotypes within the genotypes to help predict properties of future viruses.

Despite considerable accomplishments in research, influenza viruses continue to be unpredictable, and much work is still needed. A balance is needed among laboratory data,

human and animal field situations, and models, to detect viruses with specific features in terms of transmissibility, pathogencity or virulence. Studies need to continue to identify the markers/motifs/characteristics of zoonotic/HPAI influenzas. In receptor binding studies, more attention should be given to the role of binding versus replication versus transmission. With increased availability of high-throughput sequencing, linking genotypes to phenotypes becomes more important.

Viral factors involved in reassortment and mutation

(Richard Webby)

Analyses of viral changes associated with the emergence of pandemic viruses provide a foundation from which to approach future threats. Viruses causing the four known influenza pandemics were likely recent reassortants. Genetic sequencing initially suggested that the 1918 pandemic virus was of avian origin; however, recent examinations of the evolutionary timing of the gene components now suggest it was more likely a reassortant that emerged at least a few months before the pandemic began. The 1957, 1968 and 2009 viruses were all also reassortants. Because pandemic strains are potentially generated through reassortment over a period of years before pandemic recognition, detection (and, ostensibly, prevention of spread or vaccine preparedness) of precursor viruses might be possible with appropriate surveillance strategies. However, it is essential to know what the characteristics and markers of interest are.

Although reassortment is known to be continuously ongoing in specific animal populations, including wild birds, the dynamics of reassortment are not well understood. Different influenza genes have different propensities to reassort and different interactions and compatibilities with other gene types. During individual infections, viruses with different gene constellations replicate at different rates. Those with higher rates outcompete the others and thus seem more viable, which leads to differential emergence and establishment of a small number of reassortants in individuals and populations. Some of these compatibilities are well known (e.g., the triple reassortment TRIG cassette seen in many swine viruses and the pandemic virus) but most are unpredictable.

Sialic acid receptor distributions in different species may impact the likelihood of reassortment. Although the pig has appropriate receptors (i.e. both α 2,3 and α 2,6) for acting as a "mixing vessel", humans and a variety of other animals also have both types of receptors in certain tissue types. Although some information is available on non-virological factors affecting reassortment, such as host or herd immunity, these factors are still not well understood. Simplification of genotype descriptors would be helpful in discussing these questions.

It remains possible that the pandemic H1N1 2009 virus could reassort, and a more pathogenic virus could emerge. It has been shown that its internal gene constellation (the TRIG cassette) may be more capable of picking up HA than most seasonal strains, and that it is compatible with H1, H3 and H2 gene types. In addition, the pandemic virus has been detected in a variety of hosts, including humans co-infected with seasonal strains, and thus has the opportunity to interact with a variety of other influenza genes. However, there is insufficient information to predict which virus (H5N1, a reassorted pandemic H1N1, or perhaps H9) will surface as the next major threat.

Non-virological factors that could influence influenza emergence

(Vincent Martin)

The non-virological factors that influence influenza emergence can, for the most part, be categorized as institutional, cultural, ecological, and farming-related practices. From an institutional perspective, weak public and private veterinary and animal production services play a critical role in jeopardizing the early detection and rapid response capacity of national government, hence potentially fostering disease emergence. Institutional weaknesses often result in the provision of poor quality services, inadequate outbreak investigations and tracking of the sources of infection, weak or non-existent public-private partnerships, and problematic compensation schemes.

Cultural factors that also affect the emergence of influenza include cock fighting, which results in close contact between humans and animals; religious events and festivals, which encourage increased trade of birds and influence temporal patterns of disease; and cultural and traditional practices that involve live bird slaughter and, to a lesser extent, the release of wild birds (e.g., religious practices in China, Hong Kong Special Administrative Region). Key ecological factors are associated with increased opportunities for wild birds to interact with domestic birds, which leads to cross-species transmission of diseases. Examples include commercial poultry farms close to ecological niches visited by wild birds and migratory water birds, and the farming of wild birds.

Farming and production practices are perhaps the most critical non-virological factors influencing emergence of influenza. Central to this issue is the rapid industrialization of animal production systems in Asia. Southeast Asia, particularly some localized hotspots in southern China, have often been referred to as epicentres for disease emergence. Income and population growth are putting pressure on food production systems, which has resulted in sharp increases in poultry production. Increased trade makes cross-border transmission more likely. Likewise, increased semi-commercial and backyard poultry production encourages additional transmission. However, a broader perspective is needed, particularly with regard to countries where trade and productivity are high. The focus should be on all potential opportunities for the generation of pandemic strains or other emerging infectious diseases, not limited to H5N1 and/or developing countries.

The One World, One Health (OWOH) approach, in general, should be strengthened. Veterinary services and early warning systems should be improved; countries and local people who play a crucial role in connecting disease agents with hosts should be engaged in the process; innovative techniques in obtaining a multidisciplinary approach (socio-economic, ecological components applied to traditional epidemiology) should be explored; and research findings should be translated into useable and pragmatic policies by decision makers.

EMERGING OR SPORADIC VIRAL ZOONOTIC DISEASES OF PUBLIC HEALTH CONCERN

West Nile fever

(Hervé Zeller)

Ecological factors must be at the forefront when working with and trying to understand West Nile fever (WNF). This vector-borne *Flavivirus* (Flaviviridae family) has been identified

in many vertebrate species (humans, horses, birds, cattle, sheep, goats, deer, dogs, cats, bats, pigs, squirrels, chipmunks, rabbits and frogs) in which post-infection immunity lasts for several years. The natural cycle of the WNF virus occurs between birds and mosquitoes. Humans are dead-end hosts, and over 70 percent of human infections are asymptomatic. While most symptomatic cases present with mild febrile illness, one in 150 to 300 cases has neuroinvasive illness resulting in fatality (mostly in the elderly). Sporadic outbreaks in humans and horses in Africa, Europe, Asia and Australia have been documented, but an unprecedented number of cases in humans, horses and wild birds were reported during the 1999 outbreak in North America, previously free of WNF and now considered as endemic, with 11 657 neuroinvasive cases reported in the United States of America in humans between 1999 and 2009 and a case fatality rate (CFR) reaching 9.6 percent. Furthermore, over 27 000 WNV cases in horses have been detected since 2001.

Multiple species of mosquitoes have been found infected and able to multiply the virus. However, not all are able to transmit and therefore be regarded as a vector in natural conditions. Indeed, transmission is modulated by complex interfaces between vectors and hosts, which are driven, among other factors, by species composition, host preference and vector competence. Human-to-human transmission is also possible through blood transfusion and organ transplants.

Two main phylogenic lineages prevail over the world. Similarities among isolates confirm the role of migratory birds in the dissemination of the virus. Once established, the epidemiological cycle appears to be sustainable in time and space, and the virus likely survives through winters through possible: i) diapause of infected *Culex* females; ii) vertical transmission in *Culex*; and iii) chronic bird infections. Climatic variations impact mosquito abundance and activity, and therefore the seasonality of disease transmission. Some risk factors will be increased with climate changes. Limited funds have been invested in preventing and controlling WNV, with the exception of the recent outbreaks in North America. Human vaccination is not cost-effective unless disease incidence increases substantially. An important lesson is that learning to live with the virus does not mean being complacent. There is a need to be creative and cost-conscious when finding strategies to mitigate this ongoing risk.

Rift Valley fever

(Pierre Formenty)

Rift Valley fever (RVF) is a viral zoonosis that affects primarily animals but that also has the capacity to infect humans. Infection can cause severe disease in both domestic animals (cattle, sheep, goats and camels are amplifier hosts during major outbreaks) and humans. Vaccines for animals are available, and experimental vaccines have been developed for humans. RVF is endemic throughout sub-Saharan Africa; the disease has occasionally spread to Egypt, Saudi Arabia and Yemen. The major mode of transmission to humans is direct contact with infected animal blood or organs, but the virus can also be transmitted by mosquito bites and laboratory contamination. To date, no human-to-human transmission has been documented.

Several different species of mosquito are able to act as vectors for transmission of the RVF virus. However, when analysing major RVF outbreaks, two ecologically distinct situations should be considered. At primary foci areas, RVF virus persists through transmission

between vectors and hosts, and is maintained through vertical transmission in *Aedes* mosquitoes. During major outbreak in primary foci, the disease can spread to secondary foci through livestock movement or passive mosquito dispersal and amplifies in naive ruminants via local competent mosquitoes such as *Culex* and *Anopheles* that act as mechanical vectors. Irrigation schemes, where populations of mosquitoes are abundant during long periods of the year, are highly favourable places for secondary disease transmission.

Vector and virus activity are modulated by climatic fluctuations; above-average rainfall and flooding, combined with availability of susceptible livestock have been associated with major epidemics in eastern and southern Africa. Real-time RVF monitoring systems have been developed using sea surface temperature data, proxies for rains, and vegetation activity. This tool is used in conjunction with animal and human outbreak notification systems (FAO/OIE/WHO); it can result in the dissemination of warning messages/alerts by FAO/OIE/WHO.

There is still a need to fill the gap between RVF forecasting alerts and implementation of appropriate measures for disease prevention, outbreak response teams and vector control. A more systematic way of sharing forecasting maps with countries needs to be established, and related training to build national capacity should be encouraged. Alert messages should be accompanied with secured capacities for mass animal vaccination campaigns. FAO, OIE and WHO have developed common strategies from forecasting to outbreak response; however, a more integrated approach is needed to improve collaboration with country-level Ministries of Health and Agriculture and Veterinary Services. Some reluctance to report outbreaks is due to animal trade implications, with potentially devastating economic consequences. International organizations should consider taking a role in proposing alternatives to strict animal trade regulations.

Crimean-Congo haemorrhagic fever

(Onder Ergonul)

The Crimean-Congo haemorrhagic fever (CCHF) virus is a Nairovirus from the *Bunyaviridae* group and was initially identified in the Crimea in 1944. Two primary tick species from the genus *Hyalomma* (*H. marginatum* and *H. anatolicum*) serve as vectors in different regions of the world. The number of cases of CCHF has been rising over the last decade, particularly in the Russian Federation, the Islamic Republic of Iran, Bulgaria, Tajikistan and Greece. This disease was largely considered a problem of the past (pre-1960s), as the number of cases declined considerably for several decades leading up to 2000, possibly partly as a result of a series of cold winters in the late 1960s.

This tick-borne disease has become a public health concern in Turkey owing to the recent rise in the number of cases and its ability to cause rapid fatalities. In 2006, predictive maps of at-risk areas in Turkey were developed, including data on vector presence (*H. marginatum)*, number of cases and climate parameters. These at-risk area maps were also used in central Asia, southern and eastern Europe, the Near East and Africa. Further development of such maps should include sero-surveillance data on animals and eco-climatic co-variates identified through environmental studies.

Although the case fatality rate is estimated at 5 percent, it varies by country. Serological studies in Turkey revealed 10 to 20 percent positive IgG and IgM in various regions; in endemic areas, it is estimated that one of every five people living there, and one of

every two with a history of tick bites, will get the disease. Evidence shows that viral load is higher and antibody production is weaker in fatal cases. Ribavirin has shown to be effective against the disease; however, it is more efficient if given in the early phase (first three to five days). The risk from human-to-human transmission is high, which is particularly problematic for health care workers. Prevention and case management efforts should be aimed at raising awareness about the importance of seeking medical care at early stages of disease, and ensuring adequate personal protective equipment (PPE) and anti-viral drugs in health care settings.

Concerns in CCHF diagnostic capacity relate to the lack of standard case definitions, lack of rapid and inexpensive diagnostic tests, and lack of international collaboration. Furthermore, there are no new treatment options or vaccines in development for CCHF, primarily owing to the small market for this relatively rare disease. Repellents are needed as part of improved vector control strategies.

Nipah and Hendra viruses

(John Mackensie)

Several new zoonotic viruses have been associated with fruit bats, including the henipaviruses (Hendra and Nipah viruses), which represent a novel genus in the family Paramyxoviridae. The first detected outbreak of Hendra was in 1994 in Brisbane, Australia. Since 1999, there have been 11 unrelated outbreaks involving horses and occasionally humans along the east coast of Australia. The first outbreak of Nipah virus was in Kampung Sungai Nipah in Malaysia, from 1998 to 1999, in which humans and pigs were affected, and since 2001 there have been 11 outbreaks in India and Bangladesh.

The natural reservoirs of both these viruses are fruit bats (flying foxes) from the family *Pteropididae* and genus *Pteropus*. They are asymptomatic carriers that shed the virus in saliva, urine, birthing fluid and products. Their distribution overlaps with henipavirus outbreak sites. Evidence of virus is common in bats, with serological evidence of infection being found in *Pteropus* bats from various countries, from Australia to Madagascar. Hendra virus is transmitted from bat to horse, rarely from horse to horse, and from horse to human. To date, no bat-to-human or human-to-human transmissions have been documented. Nipah virus is transmitted by ingestion of fruit or fruit products (e.g., raw date-palm juice) contaminated by virus, and from human to human, pig to human, and pig to pig.

Prevention activities include reducing the risk of bat-to-domestic animal transmission or other exposure to bat-contaminated fruits or fruit products, and routine cleaning and disinfections of pig farms and horse stables. In case of an outbreak, potential control measures include quarantine of animal premises, culling or depopulating of infected animals or herds, restriction of animal movements, and establishment of active animal and human health surveillance systems for early warning for veterinary and human public health authorities. Veterinarians and others in contact with sick animals, and clinicians and nursing staff caring for infected patients should use PPE to ensure their safety.

One important lesson from experiences with the emergence of these two viruses is that the ecology appears differ in the various outbreaks, implying that related viruses in different geographic niches may have different epidemiologic patterns. Furthermore, human activities that are causing changes in the environment or the food chain, such as agricultural intensification (particularly the increase in pig production), deforestation or the role of bats

as a food source, potentially play a role in the emergence of these viruses. Lastly, insufficient communication between medical and veterinary authorities inhibited early detection of emergence among animals, again emphasizing the fact that rapid and shared surveillance is essential for detecting novel emergent agents.

Ebola and Marburg viruses

(Pierre Rollin)

Ebola and Marburg haemorrhagic fevers are caused by single strand ribonucleic acid (RNA) Filoviruses. There are five distinct Ebola species (*Sudan ebolavirus, Zaire ebolavirus, Reston ebolavirus, Ivory Coast ebolavirus, Bundibugyo ebolavirus*), and one species of Marburg virus (*Lake Victoria marburgvirus*). Filoviruses are genetically very stable. Ebola and Marburg outbreaks have been identified to date only in Africa, with the exception of the original Marburg outbreak in Germany and former Yugoslavia and the Reston ebolavirus outbreaks.

The ecology of Marburg virus involves an enzootic cycle and an epizootic cycle. The cave-dwelling African fruit bat (*Rousettus aegyptiacus*) is the reservoir host; however, the manner in which the virus is maintained and transmitted within that population is unknown. Marburg virus can also infect wild animals such as monkeys, and the exact mode of transmission to monkeys and/or to humans is still unclear.

Bats are strongly suspected of also being the reservoir of the Ebola virus. The ecology of the virus entails an enzootic life cycle in bats, with secondary infections with a high fatality rate in wild animals such as apes and antelopes. For humans, the suspected initial human infection occurs through contact with an infected animal (live or dead), frequently with subsequent human-to-human transmission. The postulated mechanism of Ebola transmission to wildlife and domestic animals (or humans) is contact with infectious body fluids or tissues. Suspected modes of transmission to humans include direct contact with reservoir species or their products by hunters, miners, ecologist and tourists; contact with secondary hosts (pigs, primates) by hunters and slaughterhouse workers; and contact with human patients by family, during burial practices and by health care workers during nosocomial infections.

In 2008, Reston ebolavirus was identified in pigs in the Philippines. Clinical illness was identified among affected pig herds, in which porcine reproductive and respiratory syndrome virus was co-circulating. There were high nursery house and growing house morbidity and mortality, and serologic evidence of exposure to the virus among humans. It is hypothesized that fruit bats may also play a role in the transmission to pigs, and that humans may be exposed through direct contact or the slaughtering and butchering of pigs. Important questions remain about this outbreak, however, such as the source of virus infecting the pigs, the frequency and breadth of the problem, the existence of pig-to-pig transmission, and the nature of the public health threat.

Hantaviruses

(Heikki Henttonen)

The genus *Hantavirus* comprises over 50 diverse hantaviruses. These rodent-borne (RoBo) RNA viruses have a three-segmented genome (which allows reassortment) and are spread through horizontal transmission. Infectivity and pathogenicity seem to depend on host taxon, leading to diverse epidemiological patterns. The first hantavirus was detected in the

Republic of Korea in 1976/1977, followed by viruses found in Europe (Finland) and North and South America. More new hantaviruses are expected to be found in both Africa and Southeast Asia owing to the presence of high diversity of murine rodents. Recently, an increasing number of hantaviruses of insectivores (*Soricomorpha*) have been found globally, but it is not yet known if these viruses infect humans.

An essential element to understanding Hantaviral human epidemiology is first to understand rodent population dynamics. Owing to the abundance of rodent taxons worldwide, their potential as a reservoir is far-reaching. There are large geographical differences in the dynamics among and within rodent species, as well as in virus transmission and shedding patterns. Chronic infection persists in the rodent host, without visible signs of disease, although excretion of the virus in urine, faeces and saliva occurs for only two months. Nevertheless, breeding, maturation and survival of the rodents may be affected. The hantaviruses are specific to their rodent/soricomorph host species, or to a group of closely related species. While spill-over infection is frequent, secondary rodent species do not spread the virus. The density of fresh infections plays an important role as survival of the virus outside the host depends on temperature and humidity. Evidence suggests that lower temperatures and higher humidity promote virus survival outside the host, thus having serious implications for transmission and possibly explaining some of the geographical patterns.

Biome characteristics and biodiversity (prey and predator guilds) play important roles in rodent population dynamics. Influential factors include the effects of climate change on food web dynamics; crisis and emergency situations (wars); and landscape changes from reforestation in Europe, deforestation in the tropics, and agricultural practices. Climate determines local seasonality, productivity, biodiversity and species dynamics. Comparative longitudinal rodent/virus studies would provide a better understanding of these and other factors affecting the dynamics of these rodent populations, and the subsequent effect on emergence and spread.

Evidence suggests that more hantaviruses will be found in the future. A better understanding of host phylogenies, specifically the genospecies differences in their capacity as a reservoir, is needed. Hotspots need to be identified through the use of predictive models looking at differences in rodent dynamics, landscape structure, diversity, differences in the quality of carrier rodents, and physical environmental conditions. Lastly, progress should be made in vaccine development, improved and quicker diagnostics and rodent control.

ANIMAL ORIGIN AGENTS THAT HAVE EMERGED INTO "HIGH PUBLIC HEALTH IMPACT" ZOONOSES

Human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV)

(Martine Peeters)

HIV/AIDS may be the most important infectious disease to emerge in the past century. Currently, 33.2 million people live with HIV/AIDS and 25 million have already died since the recognition of the disease. There are two virus types: HIV-1, which is found globally; and HIV-2, which is restricted to West Africa. HIV-1 emerged from simian immunodeficiency viruses (SIVs) in chimpanzees and gorillas in central Africa and HIV-2 from SIV in sooty mangabeys in West Africa. At least 12 SIV known cross-species transmissions have so far occurred,

eight for HIV-2 and four for HIV-1, but others have likely occurred, which remained unrecognized if the viruses were not able to adapt to the new host, or the environment was not suitable for epidemic spread. Although the first AIDS cases were observed and identified around 1980 in the United States of America, the virus had already circulated in humans early in the twentieth century in Central Africa. The reservoir of the pandemic HIV-1 strain was identified to be in southeast Cameroon; however, the epidemic started about 1 000 km away in Kinshasa, Democratic Republic of the Congo. Retrospective studies show that the first cases of HIV-1M occurred in two patients in Kinshasa in 1959 and 1960.

Human exposure to SIVs occurs through contact with infected blood/tissues or other secretions, through hunting and butchering. Cross-species transmission and emergence of novel viruses in humans depend on critical factors such as: i) frequency of exposure/contact; ii) ability to infect the new host; iii) adaptation and replication in the new host; and iv) human-to-human spread. Cross-species transmission with SIVs in West and Central Africa is likely directly related to high levels of contact and consumption of bushmeat and a high SIV prevalence in these primates (50 percent of sooty mangabeys and 30 percent of wild chimpanzees in southeast Cameroon harbour SIVs).

SIV prevalence in bushmeat is variable by species and region (e.g., 2.93 percent in Cameroon), however rates as high as 50 percent were detected in some species. SIV prevalence in the frequently hunted red colobus in West Africa is as high as 50 percent, but no evidence exists to date of transmission to humans. Extensive exposure is thus not the only parameter for the emergence of novel HIV variants.

Cross-species transmission and emergence of novel viruses are complex and associated with other factors that promote emergence. Increasing demand and trade of bushmeat, rapid encroachment of human populations into the forest, and commercial logging and road construction in remote forest areas are a few factors that increase the risk of animal-to-human transmission. If a novel HIV variant was emerging, long incubation periods and the inability of diagnostic tests to detect it could slow down its identification and characterization and increase its potential spread.

Additional studies are needed to identify more SIVs in non-human primates and targeted human populations at risk for new SIV infections (e.g., hunters and population near logging areas) and to understand better the dynamics of cross-species transmissions.

Severe acute respiratory syndrome

(Linfa Wang)

A review of the major events of the severe acute respiratory syndrome (SARS) outbreak brings to the forefront its characteristic rapid evolution. The first confirmed case of SARS, caused by a novel coronavirus, was in November 2002. The causative agent was identified in April 2003; ultimately a total of 8 096 cases with 774 deaths occurred in the eight month pandemic. Increased farming and trade of civets (highly susceptible to SARS-CoV) resulted in spill-over into civet populations, either directly from the reservoir species or through one or more intermediate animals. Rapid evolution in civets made the virus(es) more suitable for human infection, after which the virus underwent further evolution in humans during the early phases of outbreaks.

The timing of the outbreak in 2003 coincided with a dramatic increase in the consump-

tion of wildlife meat and the emergence of a major civet farming industry with increased human-civet contact. Evidence suggests that SARS transmission is multi-directional, and possible scenarios include animal-to-animal, animal-to-human, human-to-human, and human-to-animal transmission. There is a postulated role of "super spreaders" (people who shed high levels of the virus), which may have allowed more rapid geographic spread than would be expected.

The overall genome structure of the virus is similar to that of other known coronaviruses, with small but critical differences seen between the viruses affecting humans and civets versus those of bats. The virus has shown to be prone to genetic recombination in reservoir species, which should be taken into account for risk prediction of future outbreaks. Certain subtypes can infect non-reservoir species; however the chance of contact between a spill-over-competent subtype virus and susceptible spill-over host(s) is predicted to be very low.

Surveillance of bats in different parts of the world has identified SARS-like-CoV in horseshoe bats in Asia, Africa and Europe, along with large genetic diversity in bat coronaviruses; combined, these intensify the potential for emergence. International collaboration is needed to widen surveillance in order to identify the true reservoir species for SARS-CoV or its progenitor virus.

A critical opportunity for averting or containing the SARS outbreak in 2003 to 2004 would have been earlier detection of the virus and response in Guangdong Province, prior to introduction into China, Hong Kong Special Administrative Region. This highlights the need for more efficient pathogen discovery/diagnosis through open and transparent collaboration at the beginning of the outbreak. To date, the exact reservoir species and the country origin of the SARS-CoV progenitor virus are still not known.

Annex D
WHO Declarations of Interest

In accordance with WHO policy, the members of the scientific and writing committees, the meeting facilitator, and the writer have completed and submitted a WHO form for declaration of interests prior to the meeting. At the start of the meeting, the following interests were disclosed.

The following participants declared current or recent (past 4 years) financial interests related to commercial organizations as listed below:

R. Donis: Unit: Current Cooperative Research and Development Agreements ("CRADAs") for public health research from Novartis, GSK, Celltrion, and International Federation of Pharmaceutical Manufacturers Associations

J. Mackenzie: Divested of all interests in 2010.

A. Osterhaus: Individual: 20% current employment in private contract research company (Viroclinics BV) that works on vaccines and reagents, and currently-held share interests in private firms Coronovative BV and Isoconova AB (in process of divesting).

Institution: Current research support from EU, DoA Netherlands, and NIH.

R. Webby: Individual: Antiviral short-term consulting with Toyoma (ending in 2009).

No one has declared tobacco interests.

These interests were evaluated by staff from WHO, OIE, and FAO as regards their relevance to the subject of the meeting and with regard to their timing, nature, extent, and potential personal financial impact. After these deliberations it was agreed that Dr. Osterhaus would not take part in session 7. Other interests were determined not to present a conflict of interest with the objectives of the scientific consultation.

The FAO-OIE-WHO Collaboration

Sharing responsibilities and coordinating global activities to address health risks at the animal-human-ecosystems interfaces

A Tripartite Concept Note

April 2010

VISION

A world capable of preventing, detecting, containing, eliminating, and responding to animal and public health risks attributable to zoonoses and animal diseases with an impact on food security through multi-sectoral cooperation and strong partnerships.

BACKGROUND

Pathogens circulating in animal populations can threaten both animal and human health, and thus both the animal and human heath sectors have a stake in, and responsibility for, their control. Pathogens – viruses, bacteria or parasites – have evolved and perfected their life cycles in an environment that is more and more favorable to them and ensures their continuity through time by replicating and moving from diseased host to a susceptible new host.

While the integration of control systems across animal, food and human sectors has been attempted in some countries and regions, most country control systems are generally non-integrated with limited collaborative work.
However, the recent efforts to control highly pathogenic avian influenza (HPAI) and contributions towards pandemic preparedness have re-emphasized the need for enhanced concentration on reducing risks associated with zoonotic pathogens and diseases of animal origin through cross-sectoral collaboration, and have underscored the fact that successful and sustained results are possible when functional collaborations are established as is the case in many countries and internationally.

While FAO, OIE and WHO have long-standing experience in direct collaboration, the tripartite partners realize that managing and responding to risks related to zoonoses and some high impact diseases is complex and requires multi-sectoral and multi-institutional cooperation. This document sets a strategic direction for FAO-OIE-WHO to take together and proposes a long term basis for international collaboration aimed at coordinating global activities to address health risks at the human-animal-ecosystems interfaces.
A complementary agenda and new synergies between FAO, OIE and WHO will include normative work, public communication, pathogen detection, risk assessment and management, technical capacity building and research development.

FAO-OIE-WHO TRIPARTITE STRATEGIC ALIGNMENT

FAO, OIE and WHO recognize that addressing health risks at the human-animal-ecosystems interfaces requires strong partnerships among players who may have different perspectives on some issues and different levels of resources. These partnerships - which could include ones among international organizations, governments, civil society and donors - must be coordinated to minimize the burden on member countries of multiple monitoring, reporting and delivery systems, and to avoid duplicated efforts and fragmented outcomes. A framework for collaboration is necessary at national and international levels, with clear roles and responsibilities.

There is also a need to strengthen animal and human health institutions, as well as partnerships, and to manage existing and novel diseases that will be of public health, agricultural, social and economic importance in the future. When appropriate, protocols and standards for managing emerging zoonotic diseases should be jointly developed. In the cases of high-impact zoonotic diseases, improvements in governance, infrastructure and capacity building will also prove valuable to secure the livelihoods of vulnerable populations.

A joint framework to address gaps and strengthen collaboration in human and animal health laboratory activities should be developed. The framework should cover the upgrading of facilities, training and collaboration between regional and international reference laboratories for diagnosis and quality assurance. The framework should also promote cooperation between human and animal surveillance systems in analysing available evidence and evaluating responses and the timely sharing of comparable epidemiological and pathogen data across the relevant sectors.

The three organizations will work to achieve alignment and coherence of related global standard setting activities (Codex Alimentarius, OIE and IPPC) referred to in the World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary Measures. This approach does not signify integrating these institutions or building new institutions; rather, the three agencies should continue to improve communication and coordination based on their respective existing structures and mechanisms, including consideration for the publication of common standards.

The existing Codex Alimentarius (FAO/WHO) framework for risk analysis can form the foundation for sound, scientifically-based risk assessment, management and communication.
Similarly, the OIE has adopted and published global standards for terrestrial and aquatic animals recognized by the WTO. This alliance could lead to the preparation of tripartite protocols for risk assessment, management and communication, including recommendations and guidance for countries on identifying data gaps.

Effective strategies for improving national, regional and community level pandemic preparedness and response should be further developed or refined. This tripartite relationship envisages complementary work to develop normative standards and field programs to achieve One Health goals.

CURRENT FAO-OIE-WHO COLLABORATION

The three organizations recognize a joint responsibility for addressing zoonotic and other high impact diseases and have been working together for several decades to minimize the health, social and economic impact from diseases arising at the human-animal interface by preventing, detecting, controlling, eliminating or managing disease risks to humans originating directly or indirectly from domestic or wild animals. FAO, OIE and WHO have created governance structures, established early warning systems and developed mechanisms to enhance coordination and support member countries.

The three organizations provide a neutral platform for nations to engage in dialogue and negotiations. WHO and FAO have 194 members and decentralized systems that represent their organizations in regional matters and in many cases have an accredited representative before the government. The OIE, with 175 member countries, has regional and sub-regional representation worldwide. The country delegates to the OIE, usually the national Chief Veterinary Officers, are government representatives nominated by ministers.

The three agencies collaborate to advance their own normative and standard scope-setting. For instance, WHO and FAO participate in OIE's *ad hoc* thematic and working group meetings (e.g. OIE Working Group on Animal Production Food Safety). WHO contributes to FAO's work on reducing biological safety risks, and OIE contributes to the Codex Alimentarius Commission (CAC) and its subsidiary bodies' work (Joint FAO/WHO Food Standards Programme) for food, animal and health aspects prior to processing and marketing guidance to norms that assist in food safety and food-borne pathogens.

The FAO-OIE-WHO Global Early Warning and Response System for Major Animal Diseases, including zoonoses, (GLEWS), combines the alert and response mechanisms of the three organizations in order to avoid duplication and coordinate verification processes. FAO also has numerous databases for which integration into GLEWS is required. To support the notification of cases of the main animal diseases, including zoonoses, and the subsequent analyses of these data, the OIE has developed the World Animal Health Information System and Database (WAHIS and WAHID). The official notifications are in the public domain and contribute to GLEWS.

Similarly, WHO and FAO produce INFOSAN, which alerts national focal points on the occurrence of regional or global concerns for a food safety event. The three organizations also participate in the Working Group on Animal Production Food Safety, established by OIE, to develop guidelines to enhance the responsibilities and effectiveness of Veterinary Services in improving food safety at both the international and national levels. FAO and OIE have developed a joint Network of Expertise on Animal Influenza (OFFLU) to support international efforts to monitor and control infections of avian influenza. Links between OFFLU and WHO's Global Influenza Programme are now strong, facilitating a free exchange of information and the establishment of joint technical projects between the two networks.

The organizations recognize the importance of and assist member countries to improve their national legislation by enabling veterinary and public health authorities to carry out key functions, including animal production, food safety, inspection and certification of animal products, importation or internal quality control of pharmaceuticals, as well as compliance with international obligations. Evaluation and gap analysis tools (such as the OIE Pathway for Veterinary Services) are used at the global level and must be further developed.

FAO, OIE and WHO have together developed numerous coordination mechanisms. Annual tripartite meetings are organized alternatively by the three organizations in order to improve coordination. The tripartite organizations also communicate weekly regarding matters of common interest and have liaison officers that function at the global level, which has facilitated the preparation of joint messages and shared publications. Technical experts from the three organizations regularly participate in technical meetings or consultations hosted by partner organizations and, at times, represent the other organizations at high level conferences.

The two principal agencies dealing with animal health issues, the OIE and FAO, launched in 2004 the Global Framework for the Control of Transboundary Animal Diseases (GF-TADs), which provides a clear vision and framework to address endemic and emerging infectious diseases, including zoonoses. WHO is associated with this mechanism through GLEWS, in the case of zoonoses, where information exchange occurs daily.

The three international organizations have an important role in information generation and dissemination, networking and capacity building at various levels. Expert consultations, technical meetings and the elaboration of various documents ranging from guidelines and practical manuals to strategic and policy papers are readily made available to countries. For example, in 2004, a consortium of agencies, including FAO, OIE and WHO, developed the *International Portal on Food Safety, Animal and Plant Health (IPFSAPH)*, an online source to facilitate international trade in food and agricultural products.

At the regional level, FAO and OIE have established the Regional Animal Health Centres (RAHCs) that provide member countries with technical support and evaluate national and regional projects, supported where necessary by FAO and OIE networks of expertise to further advance international standards, provide guidance and promote capacity building. The Animal Health Regional Centres operate directly within the framework of the GF-TADs Agreement. Finally, FAO, OIE and WHO recognize Farmer Field Schools and livestock owners' training as an important tool in the development agenda, which if successful, can fully address problems surrounding zoonosis prevention and hygiene, best agricultural practices, and care and use of natural resources through concepts such as participatory approaches to learning.

FAO ANIMAL PRODUCTION AND HEALTH PROCEEDINGS

1. Protein sources for the animal feed industry, 2004 (E)
2. Expert Consultation on Community-based Veterinary Public Health Systems, 2004 (E)
3. Towards sustainable CBPP control programmes for Africa, 2004 (E)
4. The dynamics of sanitary and technical requirements – Assisting the poor to cope, 2005 (E)
5. Lait de chamelle pour l'Afrique, 2005 (F[e])
6. A farm-to-table approach for emerging and developed dairy countries, 2005 (E)
7. Capacity building, for surveillance and control of zoonotic diseases, 2005 (E)
8. CBPP control: antibiotics to the rescue?, 2007 (E)
9. Poultry in the 21st century – Avian influenza and beyond, 2008 (E)
10. *Brucella melitensis* in Eurasia and the Middle East, 2010 (E[e])
11. Successes and failures with animal nutrition practices and technologies in developing countries, 2011 (E)
12. Rift Valley fever vaccine development, progress and constraints, 2011 (E)
13. Influenza and other emerging zoonotic diseases at the human-animal interface, 2011 (E)
14. Challenges of national, regional and global information systems and surveillance for major animal diseases and zoonoses, 2011 (E**)

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Ar	-	Arabic	Multil	-	Multilingual
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E	-	English	**		In preparation
F	-	French	e		E-publication
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Given the complexity of zoonotic disease emergence in an increasingly globalized world, effective strategies for reducing future threats must be identified. Lessons learned from past experiences controlling diseases such as severe acute respiratory syndrome (SARS), highly pathogenic avian influenza (HPAI), and pandemic (H1N1) 2009, indicate that new paradigms are needed for early detection, prevention, and control to reduce persistent global threats from influenza and other emerging zoonotic diseases. The Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and the World Health Organization (WHO), in collaboration with the Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe) organised a joint scientific consultation in Verona, Italy (27-29 April 2010) entitled "FAO-OIE-WHO Joint Scientific Consultation on Influenza and Other Emerging Zoonotic Diseases at the Human-Animal Interface". This document is a summary of the consultation. It provides examples of emerged or emerging zoonotic viral diseases. It describes commonalities across diseases and ideas for new approaches and suggests steps towards translating meeting outcomes into policy.

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