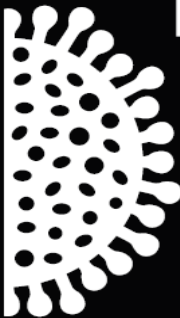





Detection and Response to Novel Influenza Viruses: Users' Guide







Detection and Response to Novel Influenza Viruses

Best Practices Training Development

November 14–17, 2017 • Bangkok, Thailand



With technical support of:



On November 14–17, 2017, international partners from the US CDC, the World Health Organization, the Food and Agriculture Organization, the World Organization for Animal Health, the Association of Public Health Laboratories and the University of North Carolina School of Public Health met in Bangkok, Thailand among 150 attendees from 11 Countries (Bangladesh, Bhutan, Cambodia, China, India, Laos, Mongolia, Myanmar, Nepal Thailand, and Vietnam). The objective of this meeting was to review drafted training materials on the epidemiologic, veterinary, medical, and laboratory components of an effective response to the detection in poultry of an avian influenza A virus of pandemic concern to humans, or a novel influenza A virus detected in humans. The 150 attendees represented human and animal health professionals, including relevant Ministries of Health and Agriculture. Following a day of initial plenary lectures from international experts the week was spent presenting, and receiving

comments, on the training materials you now find on this web site. At the end of each session formal evaluation reports were taken from the attending Member State representatives. In the months following this meeting a first set of the training materials were finalized based on audience input in order to make them adaptable and appropriate to local contexts.



- The training materials include didactic lectures, most with speakers' notes. There are also short 30 minute to 2 hour group exercises and practice scenarios, as well as a full day case study designed to facilitate a coordinated, multi-sectoral, discussion of a response to the detection of an influenza virus of pandemic potential in poultry and human populations.
- Given the current threat of influenza A(H7N9) that is prominent among other circulating influenza viruses, these training materials do focus on preparedness for an influenza virus that may be high or low pathogenic in poultry, yet which may also cause severe disease in humans. Indeed, influenza A(H7N9) is used as a prominent teaching example in many lectures and scenarios.
- The training modules may be used together for a longer (up to one week) training of multi-sectoral rapid response teams; or in a modular manner for specific, epidemiology, veterinary, laboratory or medical audiences, depending on available time and audience needs. Intended lecturers/facilitator and audiences for each module are described below so Member States can select modules based on their most pressing training needs. In cases where an exercise has a pre-requisite lecture, that is indicated as well.
- These lectures and exercises are intended to each have enough information that a national (or in some cases sub-national) level specialist in any of the four aforementioned areas would be able to read them and then train other local responders according to international standards for avian influenza surveillance, response and control.

The training materials as posted on this web site were approved as they appear by the international agency partners mentioned above. They are intended to be downloaded and translated for local use, however these agencies are not responsible for any content that may be altered in that process or changed in translation. These modules will also be updated on an ongoing basis to reflect the ever-changing threats related to influenza globally.

What follows now is a short description of the content each training lecture or exercise; suggested lecturers/facilitators and audiences; and each module's appropriateness for national or sub-national responders.

Introductory Lecture-The ABCs of Influenza

- **Intended lecturer:** A local or national individual respected as a subject-matter-expert in influenza and/or response to respiratory pathogens of pandemic potential.
- **Intended audience:** Multi-sectoral rapid response teams as well as individual audiences of human and animal health responders, medical doctors and laboratorians. These may be responders at the national and sub-national level.

NOTES: Probably any use of these training modules should begin with this lecture. This module provides an introduction to influenza and how preparedness for seasonal, novel, and pandemic influenza are inter-related. It describes the epidemiology of influenza, its viral characteristics, types and sub-types, natural reservoirs, its seasonal burden and mechanism of transmission in humans. While this module briefly touches on clinical management and treatment, those issues are dealt with in more detail in later modules. After providing this background on the ecology of influenza, this module describes how novel influenza A viruses may come to infect humans from contact with poultry, pigs, and/or wild waterfowl, and how this has produced cycles of pandemics followed by the circulation of new influenza A subtypes in human populations through the years. The module concludes with an updated global risk assessment of influenza viruses with pandemic potential, and these slides would need to be updated at regular intervals or as new threats emerge to reflect the current situation.

Lecture C1: Novel Influenza A Clinical Case Presentation and Clinical Course

- **Intended lecturer:** A local or national clinician with experience in managing severe influenza (ideally but not necessarily novel influenza in humans as well), and who is experienced in general pneumonia management.
- **Intended audience:** Clinicians and clinical RRT members who may be asked to manage influenza patients at the national or sub-national level.

NOTES: The learning objectives for this module are to provide the audience a brief understanding of the clinical features and epidemiology of infection with novel influenza A viruses in general. However this talk mostly describes the known clinical spectrum of illness of human A(H7N9) virus infection. This includes the clinical features of patients with A(H7N9) virus infection at hospital admission; estimated incubation periods; the most commonly observed

complications; hospital laboratory and radiographic findings; inflammatory cytokine responses; known complications; and pathogenesis. This lecture also includes observations on clinical differences in patients infected with HPAI as compared LPAI viruses, as well as observed differences between patients with A(H7N9) and A(H5N1) virus infections. A key feature of this module is that novel influenza cannot be distinguished from seasonal influenza on clinical grounds alone, and laboratory diagnosis is needed. However empiric treatment of severe cases should not wait for a laboratory diagnosis.

Lecture C2: Assessment, Diagnosis and Management of Patients with Novel Influenza A Virus Infections

- **Intended lecturer:** A local or national clinician with experience in managing severe influenza (ideally but not necessarily novel influenza in humans as well), and who is experienced in general pneumonia management.
- **Intended audience:** Clinicians and clinical RRT members who may be asked to manage influenza patients at the national or sub-national level.

NOTES: The learning objectives for this module are to provide the audience guidance in the assessment, diagnosis and management of a novel influenza A virus infection in humans. This includes providing key guidance on how to evaluate clinical history, needed data for medical charts, and the proper assessment of exposure history that is critical to determine clinical suspicion for a novel influenza A infection (which cannot be assessed on clinical grounds alone). This module also discusses other viral, bacterial and mycotic pathogens that are in the differential diagnosis for severe respiratory illness, and provides details on proper specimen collection techniques and timing for diagnostic testing. Treatment/usage guidance, mechanism of action, and available evidence is also provided for a growing number of neuraminidase inhibitors, as well as an introduction to appropriate supportive care. Resistance patterns of antiviral medications and their implications for treatment guidance, as well as the resistance of currently circulating viruses to adamantane drugs are also addressed. The module concludes with additional clinical management recommendations, such as those related to the use of antibiotics and corticosteroids. *

* If time allows in resource limited environments this module, and other clinical modules, might ideally be presented in conjunction with existing Integrated Management of Childhood Illness (IMCI) (<http://apps.who.int/iris/bitstream/handle/10665/42939/9241546441.pdf;sequence=1>) and/or Integrated Management of Adolescent and Adult Illness (IMAI) (<http://www.who.int/3by5/publications/documents/imai/en/>) training modules developed by the World Health Organization to provide a training on influenza management within a more holistic concept of pneumonia triage and management.

Lecture C3: Post-exposure Management of Human Infection with Novel Influenza A Viruses: Use of Neuraminidase Inhibitors

- **Intended lecturer:** A local or national clinician with experience in managing severe influenza (ideally but not necessarily novel influenza in humans as well), and who is experienced in general pneumonia management.
- **Intended audience:** Clinicians and clinical RRT members who may be asked to manage influenza patients at the national or sub-national level.

NOTES: The learning objectives for this module are to provide the audience with more in depth guidance on the use of post-exposure management of a human novel influenza A virus infection with neuraminidase inhibitors (particularly oseltamivir). The lecturer needs to know that “antiviral medications” in this module refers to neuraminidase inhibitor use and guidance on other antiviral

use (such as to avoid use of the adamantane drugs) is covered in the broader C2 clinical assessment module. Key concepts taught in this module are that neuraminidase inhibitors should be used to treat symptomatic persons that a clinician thinks may have an avian/novel influenza A virus infection. It reinforces the need to treat as soon as possible, and to test for novel influenza virus infections but *not* to delay treatment by waiting for laboratory confirmation. This module highlights how neuraminidase inhibitors may in some situations be used to prevent influenza virus infection in asymptomatic individuals if treatment doses are started promptly after exposure. It also gives guidance for prioritization of symptomatic individuals in settings with limited antiviral resources. The lecture covers how clinicians may make an epidemiologic assessment of the degree of potential exposure to the virus that may be used to determine which exposed asymptomatic individuals (if resources permit) may benefit from use of antiviral drugs to prevent infection. Given some recent evidence of oseltamivir resistance, it also highlights changes in WHO guidance for the use of antivirals that occurred between guidance for influenza A(H5N1) and the guidance for influenza A(H7N9). *

* If time allows in resource limited environments this module, and other clinical modules, might ideally be presented in conjunction with existing Integrated Management of Childhood Illness (IMCI) (<http://apps.who.int/iris/bitstream/handle/10665/42939/9241546441.pdf;sequence=1>) and/or Integrated Management of Adolescent and Adult Illness (IMAI) (<http://www.who.int/3by5/publications/documents/imai/en/>) training modules developed by the World Health Organization to provide a training on influenza management within a more holistic concept of pneumonia triage and management.

Clinical Short Exercise 1: Clinical Case Scenario in Low Resource Settings

- **Intended facilitator:** A local or national clinician with experience in managing severe influenza (ideally but not necessarily novel influenza in humans as well), and who is experienced in general pneumonia management.
- **Intended audience:** Clinicians and clinical RRT members who may be asked to manage influenza patients at the national or sub-national level.
- **Time allotment:** 2 hours (1 hour, 45 minutes for part 1 and 15 minutes for part 2)

NOTES: In this session, there are two exercises to reinforce the clinical management of patients with novel influenza A virus infection. In Exercise 1, participants will be presented with a scenario and questions for discussion. In Exercise 2, participants will work in pairs and complete a role-playing exercise. After completing this exercise, the participants should be able to describe the clinical manifestations of patients with novel influenza A virus infections and the appropriate assessment and diagnosis of potentially infected individuals; describe appropriate clinical management, including recommended antiviral treatment of patients with novel influenza A virus infections; and describe appropriate medication management and monitoring of potentially exposed persons in healthcare settings. Thus, this exercise is well-placed after participants have received lectures C1-C3 above. Depending on the size of the overall group being trained, it may be appropriate to break into smaller groups to complete this case study. This training has been designed for training breakout groups consisting of <10 persons, with facilitators assigned to each

group. Facilitators should adapt these scenarios, as needed, to their local situation in order to improve the realism of the exercise and more effectively engage students.

Lecture C4: Use of Non-Pharmaceutical Interventions (NPIs)

- **Intended lecturer:** A local or national authority with a history of decision-making for NPI policies in the Country.
- **Intended audience:** National and local policy-makers and RRT members who may be asked to decide about the implementation of NPIs, or the rationale for their use during a novel influenza A outbreak.

NOTES: The learning objectives for this module are to introduce non-pharmaceutical interventions (NPI); to help the participants understand when and how to implement non-pharmaceutical interventions; to provide them an understanding of both legal and ethical considerations for the use of NPI; to describe how NPI fit within a preparedness and response framework for pandemic influenza; and to provide them additional resources that may be useful to them as they consider NPI. As a background the lecture begins with a discussion of the importance of suppressing the impact of a pandemic with NPI, especially while possibly awaiting availability of vaccines and/or antivirals. It also provides guidance on the types of individual protective measures that might be recommended every day, as compared to those reserved for large outbreaks and pandemics. The lecture also describes options for the use of community measures (e.g. school closures, social distancing, environmental cleaning and airport scanning). While decisions for these interventions are often made locally, decision-makers should consider the legal and ethical considerations that are described within this lecture. In sum this lecture provides a menu of options for policy makers to consider based on the local circumstances with a conclusion that community buy-in through risk communications is essential. and concurrent measures are likely more effective than using a single NPI. While the evidence base for some NPI are lacking, I does also provides a link to further web-based NPI training materials.

Lecture C5: Infection Control in Healthcare Settings

- **Intended lecturer:** A local or national clinician with experience/responsibility for maintaining hospital infection control.
- **Intended audience:** Clinicians and clinical RRT members who may operate in clinical settings, either working directly with patients, or to monitor the adequacy of infection control practices.

NOTES: The learning objectives for this module are to train participants to correctly describe the importance of infection prevention and control (IPC) measures, to describe the chain of transmission in healthcare settings, to be able to name the seven components of standard precautions, and to describe current IPC recommendations for emerging respiratory pathogens. The module begins by emphasizing the importance of IPC, and its goals of protecting HCW/responders, patients, and the community. It then describes how general IPC can break the chain of transmission and teaches the participants about standard and transmission-based (contact, droplet, and airborne) precautions. The module then walks the audience through the proper donning and doffing of personal protective equipment (which can be participatory) and then provides an overview of existing WHO guidance for IPC as it relates to influenza A viruses.

Throughout the module there are numerous discussion question and knowledge checks for the lecturer and participant as well.

Lecture C6: Infection Prevention and Control Preparedness

- **Intended lecturer:** A local or national clinician with experience/responsibility for maintaining hospital infection control.
- **Intended audience:** Clinicians and clinical RRT members who may operate in clinical settings, either working directly with patients or to monitor the adequacy of infection control practices.

NOTES: Once the participants have a grasp of the basic concepts and guidance for IPC as mentioned in lecture C5, this lecture takes them through the importance of IPC preparedness, and describes its elements and different strategies that might be implemented to enhance preparedness. The paradigm of "identify, isolate and inform" is used, making use of recent influenza, Ebola, and MERS examples. Key elements of preparedness are then described and they cover the importance of having IPC guidance and standard operating procedures, reporting and communication systems, and appropriate staffing, training, isolation, and supplies. Strategies described for implementing IPC include establishing a tiered referral system, using ring IPC to target resources, ensuring sustainability, and building a strong IPC cultural foundation. The lecture uses multiple examples beyond influenza and includes discussion questions that ask key questions about IPC preparedness to the participants regarding their own facilities.

Lecture E1: Role of Indicator and Event-based Surveillance in Pandemic Early Warning

- **Intended lecturer:** A local or national epidemiologist who would have responsibility for establishing/maintaining early warning surveillance to meet IHR core capacities.
- **Intended audience:** RRT members and epidemiologists, clinicians, veterinarians, and laboratorians who would be in position to detect, report, or respond to outbreaks.

NOTES: The learning objectives for this lecture are to have the participants be able to describe the purpose and rationale for conducting surveillance for respiratory events; to be able to explain the principles of event- and indicator-based surveillance and their complementary roles in pandemic preparedness; to provide them examples of what constitutes a "event" (with an emphasis on respiratory events); to teach them the key steps in an event-based surveillance system; and to then discuss the elements of successful event-based surveillance system. This module discusses the many sources of event-based surveillance (EBS) from the community to those in animal and human health sectors and how a more varied and informal reporting system is essential to complement more structured indicator-based monitoring systems in pandemic early warning. The essential steps of EBS described within include defining events of interest, generating a signal report with basic initial information, assessing if a signal is an event of interest, verification of the event and risk assessment, communications, and response proportional to the risk assessed. The lecture concludes with the elements of a successful EBS and several knowledge check/discussion slides.

Lecture E2: Response to an Outbreak of a Novel Influenza Virus in Poultry: Human Health Perspective

- **Intended lecturer:** A local or national epidemiologist that has undertaken human public health responses to the detection of avian influenza viruses of concern in poultry or non-human population.
- **Intended audience:** RRT members and epidemiologists, clinicians, and veterinarians and possibly laboratorians who would be in position to detect, report or respond to outbreaks.

NOTES: Participants of this lecture will learn to define an outbreak of a novel influenza virus in poultry. They will learn how to identify human populations at risk and how to implement the active surveillance and contact tracing processes. They will also learn how to assess if the response protocol is working, and to communicate results to stakeholders effectively. The goals of all of this is that participants will leave this lecture with an understanding of how to detect novel influenza virus infections early, respond quickly and minimize human exposure to potentially infected poultry and humans. This lecture includes frequent knowledge checks at each step of the active surveillance process and concludes with a discussion of when to end active surveillance.

Epidemiology Short Exercise 1: Event-based Surveillance (EBS) to Support Detection of Novel Influenza Virus Infections in Humans

- **Intended facilitator:** A local or national epidemiologist who would have responsibility for establishing/maintaining early warning surveillance to meet IHR core capacities.
- **Intended audience:** RRT members and epidemiologists, clinicians, and veterinarians and possibly laboratorians who would be in position to detect, report or respond to outbreaks.
- **Time allotment:** 3 hours

NOTES: It is important that these materials be translated to the extent that participants and facilitators can work together in their native language(s). The participants in this exercise will collectively act as a specialized Rapid Response Team (RRT) that has been assigned to work on event-based surveillance for detection of novel influenza A(H7N9) virus in humans. There are 4 scenarios to be discussed and completed within a total time period of about 3 hours. Participants will play the role of a different subnational responders in each scenario. Depending on the size of the overall group being trained, it may be appropriate to break into smaller groups to complete these case scenarios. This training has been designed for training breakout groups consisting of <10 persons, with at least one facilitator assigned to each group. In the scenarios, students will imagine that they have just returned to the district of their country and that they now need to conduct surveillance for novel influenza A(H7N9) virus infection in humans. Facilitators should adapt the scenario, as needed, to their local situation in order to improve the realism of the exercise and more effectively engage students. In these scenarios they 1) set up EBS among live bird market workers; 2) Receive a report of worker absenteeism; 3) Report a positive test for avian influenza A(H7N9) at the love bird market; and 4) Respond to a media report of a suspicious death. Participants should have already received lecture E1 (EBS) above.

Lecture E3: Forming a Rapid Response Team (RRT)

- **Intended lecturer:** A local or national epidemiologist who has led a Rapid Response Team in the field.
- **Intended audience:** National and sub-national staff who may be asked to form RRTs in their jurisdiction.

NOTES: This lecture focuses on four aspects of team organization and standards of conduct for outbreak investigations. These include: 1) Identifying key functions of a rapid response team; 2) Defining roles and responsibilities of each team function in a novel influenza outbreak investigation; 3) Enhancing coordination and communication among team functions; and 4) Recognizing the standards of ethical conduct for case investigations. After defining the roles and responsibilities, as well as core functions of an RRT it moves into the coordination and standard of conduct components. Discussion questions for each of the four core areas of this lecture are included so facilitators can help participants understand the operation and gaps related to RRT in the jurisdictions.

Lecture E4: Epidemiologic Case Investigation of Human Infections with HxNy

- **Intended lecturer:** A local or national epidemiologist who has experience in responding to influenza (ideally novel influenza) outbreaks in humans.
- **Intended audience:** RRT members and epidemiologists, clinicians, and veterinarians and possibly laboratorians who would be in position to detect, report or respond to human outbreaks.

NOTES: This lecture describes the core aspects of an epidemiologic investigation of novel influenza A virus infections in humans. This is intertwined with the basic epidemiologic concepts of outbreak investigations. Upon completion the participants should: 1) know when and how to prepare for investigations of human cases of novel influenza virus; 2) understand the objectives of novel influenza virus outbreak investigations; 3) understand the steps and mechanics of novel influenza virus outbreak investigations; 3) be able to describe how to analyze data and communicate findings from outbreak investigations; and 4) understand the importance of multi-sectoral coordination while undertaking case investigations. The flow of this lecture is that it teaches the objectives and phases of case investigations; the steps of an outbreak investigation; pre-investigation and response planning; the comprehensive gathering of epidemiologic and clinical data, laboratory specimen collection; tracing of contacts; the management and basic analyses and interpretation of data; the implementation of control measures; and reporting and evaluation. It concludes with influenza investigation resources for both influenza A (H5N1) and influenza A (H7N9) virus infection investigations.

Epidemiology Short Exercise 2: Case Investigation of Suspected Novel Influenza

- **Intended facilitator:** A local or national epidemiologist who has experience in responding to influenza (ideally novel) outbreaks in humans.
- **Intended audience:** RRT members and epidemiologists, clinicians, and veterinarians and possibly laboratorians who would be in position to detect, report, or respond to outbreaks.

- **Time allotment:** At least 3 hours based on language familiarity and epidemiologic background of audience.

NOTES: It is important that these materials be translated to the extent that participants and facilitators can work together in their native language(s). The participants in this exercise will again be responders assigned to investigate possible outbreaks of human infection with avian influenza A(H7N9) virus. Depending on the size of the overall group being trained, it may be appropriate to break into smaller groups to complete this case study. This training has been designed for training breakout groups consisting of ≤ 10 persons, with facilitators assigned to each group. In the scenario, students will be deployed to the fictional city of Pao Mai to investigate a severe respiratory disease outbreak. Facilitators should adapt the scenario, as needed, to their local situation in order to improve the realism of the exercise and more effectively engage students. In this scenario they will work through essential information to collect on the initial phone call from a clinician regarding a suspected human case of novel influenza. They will be provided information and then be asked to plan the response in terms of forming a Rapid Response Team, gathering needed materials and making a plan for communications. The scenario then moves to a discussion on developing a three-tiered case definition for the outbreak making use of exposure criteria and the types of laboratory specimens that should be collected from each case identified. The team then goes to the field and must identify locations for case finding, questions for a case investigation, and consider appropriate PPE use. There is a contact tracing activity, followed by development of a line list and an epidemic curve. The scenario concludes by reviewing the epidemic curve to assess possible exposures based on incubation periods and makes an assessment of the likelihood that human to human transmission is occurring. Ideally participants have received, or are familiar with the content of, lectures E1-E4 prior to undertaking this exercise.

Lecture V1: Value Chain Analysis as a Basis for Animal Disease Surveillance and Response

- **Intended lecturer:** A local or national veterinary/animal health specialist who has received training or undertaken value chain analysis and risk-based surveillance.
- **Intended audience:** Veterinary / animal health responders who would be responsible to plan or implement data collection for animal and animal product mapping, determining value chain risk pathways, and to prioritizing surveillance locations based on these data.

NOTES: This lecture is based on FAO guidance and following this lecture the participants should understand value chain analysis and the data needed to inform mapping and the identification of risk pathways for animals and animal products. They will then learn how to use these data to plan surveillance and response activities. The lecture begins with an introduction on the importance of the value chain approach to identify relevant stakeholders and understand their roles; to understand trade networks and identify high risk zones (based on risk factors and commercial links); and to understand risky practices and the drivers that create them. A section on data collection describes the different types of data collection tools that may be used to identify species and products; pathways of movement; volume of movement; the stakeholder reasons for this pattern of movement (drivers); seasonality of movement; and practices related to how movement occurs. The lecture then moves to a data analysis component that introduces the value chain diagram and how it is needed to identify the connections between different stakeholders and how animal disease risk spreads along the value chain. The lecture concludes with concepts on how information are used to inform risk-based

surveillance in animals; to target interventions; to undertake traceback investigations during an outbreak; to send early alerts to areas at risk but not yet affected during an outbreak; and to implement animal movement controls and checkpoints during an outbreak. Discussion questions are interspersed within the lecture and the lecture emphasizes that value chain analysis should be performed before an emergency so critical points are identified and the data can be quickly utilized to disrupt transmission in an outbreak.

Lecture V2: FAO Guidelines for Comprehensive Avian Influenza Active Surveillance in Asia

- **Intended lecturer:** A local or national veterinary/animal health specialist who has undertaken active surveillance for avian influenza
- **Intended audience:** Veterinary / animal health responders, and RRT members and/or other persons who should be familiar with avian influenza active surveillance activities in animals, and how they are undertaken.

NOTES: This lecture is based on FAO guidance and its learning objectives are to help participants understand the guiding principles and recommendations for the development of active, comprehensive, risk-based avian influenza surveillance. Following the lecture, they also should be able to describe the criteria for selecting areas, sites, target species /animals, and sample types for active avian influenza surveillance. They should also be able to develop an understanding of avian influenza surveillance sample sensitivity, frequency of sampling, reporting of results, and risk communication. Following a brief overview of the current global distribution of avian influenza viruses (which may need to be updated from the FAO web site when this lecture is used) the lecture emphasizes the need for a comprehensive approach to active surveillance, especially with the spread of LPAI (H7N9) as a public health pathogen of concern in recent years. However it also builds on lessons learned and expertise from other subtype-specific surveillance projects to inform risk-based, comprehensive and cost-effective decision-making for surveillance. Elements of establishing active surveillance for AI include its design (no one size fits all); area selection and the need for value chain analyses; site selection; selecting species for sampling; sample types; sample size calculations; sampling frequency; results dissemination, and risk communication. The lecture is interspersed with discussion questions for the audience and concludes with the need that any selected strategy needs to be regularly reviewed in an evolving disease situation.

Lecture V3: Avian Influenza Viruses and the OIE, An Overview

- **Intended lecturer:** A local or national veterinary/animal health specialist who has undertaken avian influenza surveillance and/or outbreak investigations and would be responsible for reporting to the World Organization for Animal health (OIE).
- **Intended audience:** Veterinary / animal health responders, and RRT members and/or other persons (including laboratorians) who should be familiar with avian influenza active surveillance activities, international reporting criteria, outbreak response and/or biosecurity measures.

NOTES: This lecture is based on OIE guidance and following this lecture the participants should better understand avian influenza viruses (AIVs), their transmission factors, and their impact globally. They will also learn about the World Organisation for Animal Health (OIE) and its role in AIV monitoring, surveillance, detection, prevention, and response. They should also be able to understand the importance of the OIE-FAO Global Network OFFLU and its functions as well as describe key biosecurity recommendations for use in an avian influenza outbreak. The lecture begins with the OIE mandate and introduces the audience to its global network of reference laboratories and collaborating centers. It then reviews HPAI and LPAI avian influenza viruses, and which are considered reportable to OIE, as well as the international tripartite (OIE, FAO, WHO). The lecture then provides an overview of avian influenza viruses globally (which will likely need to be updated from OIE web site at regular intervals) and review OFFLU, AIV monitoring strategies. From this discussion of surveillance, the lecture moves into epidemiology and traceability of AIV viruses focusing on transmission from wild waterfowl reservoirs to domestic poultry and the need to block this pathway. Prevention and control measures focusing on biosecurity, culling, the pros and cons of vaccination and the self-declaration of freedom following outbreaks are also covered. This lecture is interspersed with discussion questions for the audience and includes links to additional OIE reference materials.

Veterinary Short Exercise 1: Prioritize and Implement Live Bird Market Surveillance Along the Value Chain

- **Intended facilitator:** A local or national veterinary/animal health specialist who has undertaken or has received training on value chain analysis and risk-based surveillance.
- **Intended audience:** Veterinary / animal health responders who would be responsible to plan or implement data collection for animal and animal product mapping, determining value chain risk pathways, and to prioritize surveillance locations based on these data.
- **Time allotment:** 90 minutes.

NOTES: This exercise is based on FAO guidance and the participants should have received Lectures V1 and V2 before taking this exercise. This exercise has three 30 minute parts. Part one is a mapping exercise where participants will learn to map poultry movements and identify risk pathways for disease introduction and spread. In part two the participants will use this information to develop a value chain diagram and use it to identify risk pathways and critical control points along the value chain. In part three they will be provided a limited budget and be asked to design a surveillance system using value chain information. Slides 1-6 provide the scenario for part one, and after group discussion the facilitator can reveal the mapping solution on slides 6 and 7. Slides 9 and 10 introduce part two and the participants receive an incomplete value chain diagram. The participants are then taught how to implement a sequence of interviews with stakeholders to obtain the information needed to complete the value chain diagram, and following discussion the solution on slides 17 and 18 can be provided by the facilitator. Slide 19 presents part three where the group must consider their surveillance options. As there is no “one size fits all” decision that works best for a given location the participants are then asked to present the rationale for their surveillance decision-making to the others.

Lecture V4: Control Strategies for HPAI and LPAI in Poultry Populations

- **Intended lecturer:** A local or national veterinary/animal health specialist who has implemented control strategies for HPAI and/or LPAI in poultry
- **Intended audience:** Veterinary / animal health responders, RRT members and/or other persons who should be familiar with HPAI and LPAI control strategies in poultry, and how they are undertaken.

NOTES: This lecture is based on FAO guidance and its learning objectives are to teach participants about control strategies for HPAI and LPAI and define stamping out and its challenges. Compensation for poultry that are culled is also discussed and participants should come to understand why compensation is used, the compensation schemes that are available, and risks associated with compensation that is either too much or too little. Finally the participants will understand the implications and use of market closures and key considerations involved in making the decision to close a market. Stamping out is intended to reduce exposure of at-risk populations and the lecture describes that the approach taken depends on local resources. At-risk populations may be defined by geography or epidemiologic linkages. The lecture moves forward from this by emphasizing that stamping out should be a part of a package that includes investigation (tracing backward and forward), effective movement control, compensation, and communication. Regarding compensation, the lecture defines stakeholders that should be considered for compensation, mechanisms for determining appropriate compensation, various monetary and non-monetary forms of compensation. Examples of compensation approaches from around the world are provided, the negative consequences of inappropriate compensation discussed, and emphasis is placed on deciding on a compensation plan prior to an outbreak. Market closures are then discussed as well as the challenges that arise from market closures if the value chain isn't properly understood and movement controls cannot be effectively implemented. Finally communications plans to key stakeholders are addressed, and also need to be considered in advance of an outbreak. This lecture is interspersed with discussion questions for the participants.

Lecture V5: Laboratory Algorithms for Comprehensive Influenza A Surveillance in Poultry

- **Intended lecturer:** A local or national animal health laboratory virologist with experience in testing specimens for avian influenza viruses. This person should have command of the regional testing algorithms.
- **Intended audience:** National or subnational animal health personnel responsible for operating an animal health laboratory that may undertake testing for avian influenza viruses, or a person working in such a laboratory. Content in this lecture may be appropriate for laboratory directors and managers; heads of units and laboratory technicians, and those assigned to collect field specimens from chickens, ducks or the environment.

NOTES: The learning objectives for participants in this lecture are that participants will understand the regional diagnostic algorithm for influenza A detection and be able to describe virology/PCR flow charts per species including sample collection from chickens, ducks and the environment. Participants should also be able to describe recommended regional protocols for HA and NA detection for A(H5), A(H7), A(H9), N1, N6, N8, and N9. The lecture also covers virus isolation and

laboratory needs (capacity). This lecture begins with a discussion of diagnostic algorithms (most appropriate for laboratory directors and senior staff). The OFFLU regional diagnostic algorithm is presented as well as the general laboratory testing algorithm for the influenza A (M gene) followed by pathways for HA and NA –specific testing. The value of whole genome sequencing is also emphasized here. From here the lecture described detailed PCR flow charts beginning with slides on appropriate specimens and pooling strategies to be used for chickens, ducks and environmental specimens (for those collecting specimens) as well as detailed virology flow charts for technicians working with different species and pooled or unpooled specimens. Finally recommended laboratory protocols for specific genes are reviewed as well as critical laboratory capacity needs for early diagnosis. Discussion questions for participants are interspersed throughout.

Lecture V6: Avian Influenza Virus Poultry Vaccines and Their Use

- **Intended lecturer:** A local or national veterinary/animal health specialist who has implemented an avian influenza vaccine campaign, or who would be responsible to do so and understands its implications
- **Intended audience:** Veterinary / animal health responders, and RRT members and/or other persons who should be familiar with HPAI and LPAI vaccination strategies in poultry and the implications of poultry vaccine use.

NOTES: The participants in this lecture will learn about avian influenza virus (AIV) vaccines for poultry and understand the three situations in which to consider AIV vaccination. Key considerations for the use of AIV vaccines are presented as are the types of vaccines available. The participants will also learn about the type of protection conferred by AIV vaccination, the DIVA (Differentiating Infected from Vaccinated Animals) approach and factors related to a vaccination exit strategy. The use of AIV vaccines worldwide is discussed initially, as is the importance that they be used in the context of other AIV control measures. AIV vaccine is then discussed for use in routine, preventive and emergency situations. Considerations for the use of AIV vaccines described include financial resources, laboratory capacity for monitoring circulating viruses, restricted movement of vaccinated birds, trade implications, prioritization of resources for highest risk populations, plans for post-vaccination immunity studies, and the potential for viral spread by vaccination teams. Following a review of AIV vaccine types the lecture discusses the mechanism of protection, the fact that they are not 100% effective at preventing viral shedding, and the implications of vaccination for international trade. To conclude the lecture reviews the DIVA approach to demonstrate that exposure to circulating virus has not occurred, and discusses how and when to stop an AIV vaccination program. Discussion questions are interspersed through the lecture and additional resources links included.

Veterinary Short Exercise 2: Controlling Avian Influenza Viruses and Resource Materials

- **Intended facilitator:** A local or national veterinary/animal health specialist who has implemented control strategies for HPAI and/or LPAI in poultry

- **Intended audience:** Veterinary / animal health responders responsible for planning and implementing avian influenza virus control strategies within their jurisdictions.
- **Time allotment:** 30 minutes.

NOTES: This is a short discussion session exercise designed to be taken by participants who are familiar with most, if not all, of the aforementioned veterinary modules. The intent of this exercise is to help start a gap analysis and think about next steps that they may need to take in their jurisdictions to control avian influenza viruses. Several questions are asked with answers provided for the facilitator. These include: 1) If an avian influenza virus is identified in your country, what information would you need to know to develop a national control plan?; 2) In your jurisdiction, what measures are available to control avian influenza viruses in domestic poultry / bird populations?; 3) What resources do you currently have available in your country to respond to avian influenza viruses?; and 4) What additional support and/or infrastructure is needed in your country to better prepare you for avian influenza viruses? The lecture then includes answers and sub-questions that will prompt the participants to think about the specific information/measures/resources/infrastructure that may or may not exist within their jurisdictions. This exercise ends at slide 14. Slides 15 to 52 include extensive surveillance and control recommendations from the World Organization for Animal Health (OIE); U.N. Food and Agriculture Organization (FAO); and the United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS). The facilitator can review these with the participants as much as desired depending on the time allotted to this exercise.

Lecture L1: Human Specimen Collection, Transport & Virus Sharing

- **Intended lecturer:** A respected laboratorian with a comprehensive understanding of proper collection of human specimens for influenza virus diagnosis in the field. Ideally this might be a person from the National Influenza Center/National laboratory or a very experienced surveillance officer with a laboratory orientation.
- **Intended audience:** A local or national RRT member or any person responsible for collecting human specimens for influenza virus diagnosis in the field.

NOTES: After receiving this lecture the participants should be able to describe specimen collection for influenza virus diagnosis; understand proper specimen data collection and tracking; understand specimen handling and storage for better diagnosis; describe proper transport of influenza specimens; and understand the importance of global virus sharing. The lecture begins with the important point that the best laboratory in the world is only as good as the quality of the specimens that it receives, and related to that, its storage and transport conditions. The lecture then discusses the importance of pre-analytic considerations of specimen collection timing and technique, use of appropriate transport media, maintenance of cold-chain, and accurate documentation. Swab type, specimen collection technique, the human specimen collection kit; target cases, and safety/PPE are then covered. From here the lecture moves to critical elements in specimen data collection and tracking (including an example specimen collection form), labelling, packaging and storage. Category A and B infectious substance transport is described as are the reasons virus sharing is of global importance followed by the specific procedures and timing that should be implemented when shipping specimens to a WHO Collaborating Center for Reference and Research on Influenza. Discussion questions are interspersed throughout the lecture.

Lecture L2: General Biorisk Management

- **Intended lecturer:** A laboratorian experienced in maintaining the biosafety and biosecurity of a laboratory (in this context, ideally a National Influenza Center).
- **Intended audience:** Laboratory technicians or managers responsible for biorisk management within their jurisdiction.

NOTES: Following this lecture the participants should be able to define biorisk management, identify the key principles of biosafety, explain the importance of a laboratory biosafety management structure and training program, identify the key principles of biosecurity, and explain the biosafety risk assessment process. The lecture begins by showing that biorisk management exists within a hierarchy of controls including elimination and substitution of hazards, engineering controls, administrative controls and proper use of PPE, with the former items in this list being more effective than the latter. The lecture then discusses biosafety including the mechanisms by which laboratorians may become infected, and the importance of a culture of biosafety. After reviewing key resources the lecture then discusses the importance of strict adherence to standard precautions and discusses the importance of safety equipment and facility design. The importance of biological safety cabinets and their maintenance is covered, as well as biocontainment levels. The lecture then moves to biosecurity where it discusses the importance of threat assessments and inventories, and also provides examples of insider threats, outsider threats and environmental threats. These all must be covered in a comprehensive biosecurity plan. The module concludes with a detailed presentation of the risk assessment process for a laboratory and discussion questions for the participants are interspersed throughout.

Laboratory Short Exercise 1: Specimen Collection, Laboratory Diagnostics, and Biosafety Issues: Laboratory Practice Exercises

- **Intended facilitator:** A respected laboratorian with a comprehensive understanding of proper collection of human specimens for influenza virus diagnosis in the field. Ideally this might be a person from the National Influenza Center/National laboratory or a very experienced surveillance officer with a laboratory orientation.
- **Intended audience:** A local or national RRT member or any person responsible for collecting human specimens for influenza virus diagnosis in the field.
- **Time allotment:** 2 hours

NOTES: Participants in this exercise should have received lecture L1 above. These exercises should be performed in smaller break-out groups, so that questions or problems that participants may have can be addressed. In this exercise the participants work through scenarios related to laboratory diagnosis of novel influenza. Each scenario is preceded by specific instructions. Some scenarios will give participants an opportunity to practice specimen collection methods; others will include discussion questions to answer. The scenarios include: 1) Determining a sampling time schedule for a suspected novel influenza case; 2) Performing antecubital venipuncture and collecting nasopharyngeal, nasal, and throat specimens while wearing personal protective equipment; 3) Completing in a laboratory form; 4)

packaging specimens and labeling the package; 5) Performing a laboratory risk assessment to identify potential hazards as well as control and protection mechanisms; and 6) analyzing laboratory data. Participants will complete the scenarios in the order in which they are listed, just as one would when working with a real suspected novel influenza case. These steps take place within the context of a scenario involving a fictitious outbreak of influenza A(H5) in humans.

Lecture L3: Overview of Molecular and Serological Diagnostics for Influenza A(H7N9)

- **Intended lecturer:** A laboratorian considered to be an expert in influenza diagnostics within their jurisdiction (in this context, ideally from a National Influenza Center). Please note this slide set has limited speaker notes so at this stage it requires a lecturer with a command of the laboratory procedures described below.
- **Intended audience:** Laboratory technicians who may need to undertake influenza diagnostic analyses within their jurisdiction.

NOTES: Following this lecture the audience should be able describe the primary methods for detection and characterization of influenza viruses; summarize antigen detection methods used to detect influenza viruses; describe the challenges and benefits of molecular detection methods for influenza virus; and give examples of antibody detection methods used for influenza viruses. This lecture begins by highlighting the difference between influenza virus detection and characterization and the types of specimens needed (e.g. inactivated virus, live virus, or antibodies) depending on the objectives of the analysis. Advantages and disadvantages of rapid influenza antigen detection tests are covered followed by descriptions of immunofluorescence assays (IFA), ELISA, hemagglutination assays, and conventional and real-time PCR assays. Proper laboratory workflow and laboratory requirements for molecular testing are described, as well as routine testing algorithms and PCR curve interpretations. The CDC/WHO RT-PCR test kit is then presented as are the pros and cons of molecular diagnostics. The lecture then moves to influenza serology and antibody detection, highlighting the importance of quality serum specimens, sera collection guidelines, and the importance of paired sera. Hemagglutinin inhibition (HI) assays are then discussed moving to a focus on recommendations for HI testing for influenza A(H7N9). The lecture concludes with slides on microneutralization assays and considerations for influenza serology. Some discussion questions are included within the presentation.

Lecture L4: Practical strategies for sequencing and molecular characterization of influenza viruses

- **Intended lecturer:** A laboratorian considered to be an expert in influenza diagnostics within their jurisdiction (in this context, ideally from a National Influenza Center). Please note this slide set has limited speaker notes so at this stage it requires a lecturer with a command of the laboratory sequencing procedures described below.
- **Intended audience:** Laboratory technicians who may need to undertake influenza sequencing within their jurisdiction.

NOTES: This module includes key considerations for laboratories that are considering sequencing and characterization of influenza viruses. It begins by discussing resources, the number of specimens to be sequenced, primer design strategies and then moves to the importance of a specimen and data

management system. The importance of sequencing needs (e.g. partial or whole genes and genomes) as well as the reasons for sequencing (e.g. pathogen vs mutation detection, evolution, pathogenicity, or comparison to vaccine strains) as these will determine methods employed. The introduction concludes with high vs. low throughput sequencing and key issues in data management. The lecture then moves to first generation sequencing (Sanger methodologies, deep sequencing, mutation mapping) followed by Next Generation sequencing (NGS) efforts. The pros and cons of various instruments are then highlighted followed by a description of a typical NGS virus pipeline for influenza. At this point the lecture shifts to molecular characterization of A(H7N9) viruses discussing in detail the phylogenetic tree, key receptor binding site mutations, genetic variation and antiviral resistance. As few have these capacities the importance of the WHO Global Influenza Surveillance and Response System network to help countries with these analyses is then highlighted with emphasis on how data analyses are used to develop strain recommendations, the egg-based vaccine production timeline and antigenic drift, and antigenic drift changes currently noted in A(H7N9) viruses leading to a need for new vaccine candidate viruses.

Laboratory Short Exercise 2: Detection, reporting and characterization of novel influenza virus infections

- **Intended facilitator:** A laboratorian considered to be an expert in influenza diagnostics within their jurisdiction (in this context, ideally from a National Influenza Center).
- **Intended audience:** Laboratory technicians who may need to undertake influenza diagnostic analyses within their jurisdiction.
- **Time allotment:** 1 hour

NOTES: Participants in this exercise should have previously received Lecture L3. This exercise includes three scenarios. In the first scenario the participants must interpret an rRT-PCR curve that is positive for a Eurasian lineage H7Nx virus. This involves identifying rises in A and EuH7 fluorescence as well as a rising RNP in the absence of increases in H3, pdm InfA, and pdmH1. The importance of interpreting the RNP and the international significance of reporting the result are emphasized. Because the CDC assay does not discriminate between the Chinese lineage of H7N9 and other Eurasian lineages of H7Nx viruses, it is noted that it is critical that additional testing be performed to determine the specific HA and NA genetic lineages of the virus. In scenario 2 the specimen is positive for the Chinese lineage of A(H7N9) virus and negative for other influenza A viruses. While this is a conclusive diagnosis the importance of confirming understanding the positive controls for H7 and N9 is emphasized. The need for further epidemiologic information and international reporting is again discussed. In scenario 3 the timing of paired sera collection is discussed as well as the optimal timing for a single specimen. HI using horse red blood cells are recommended in the scenario as well as the use of viruses from the same outbreak for serological testing. The third scenario concludes with key epidemiologic and clinical data that should accompany the specimen.

Full Day, Multi-Sectoral Case Study: Response to the spread of Asian lineage avian influenza A(H7N9) virus into a previously unaffected country

- **Intended facilitators:** Persons familiar with the epidemiology, veterinary, clinical and basic laboratory specimen collection training materials defined above.
- **Intended audience:** RRT members, and multisectoral groups of epidemiologists, veterinarians, clinicians and laboratory technicians who can work together to discuss the response to the scenario in a one-health coordinated manner.
- **Time allotment:** 6 to 8 hours

NOTES: This is an all-day case study. It is important that these materials be translated to the extent that participants and facilitators can work together in their native language(s). The case study takes place in a fictitious country of “Tropica” and works through the investigation of suspected and confirmed A(H7N9) in poultry and human populations. This exercise should take place following any of the training implemented above and participants should be able to demonstrate effective strategies to establish human and animal surveillance to detect novel influenza A viruses; demonstrate awareness of the important on-the-ground complexities and management issues during poultry outbreaks of avian influenza and investigations of human infections with novel influenza A viruses; understand influenza virus-specific concepts that include: appropriate surveillance strategies in humans and animals, specimen collection and transport in humans, laboratory testing, epidemiologic risk factors, transmission mechanisms and contact tracing, control and prevention, isolation/quarantine concerns, treatment in humans, control measures in humans and animals, risk communication principles, laboratory diagnostic methods, the pros and cons of poultry vaccination, and ethical considerations. They should also gain an appreciation for important novel influenza A virus coordination efforts involving the interface between animal and human health sectors, key stakeholders such as the WHO, FAO, OIE, Ministries of Health, Ministries of Agriculture and communication processes between field staff, headquarters and relevant subject matter experts. This case study is based on WHO, OIE and FAO guidance documents. Additional country-specific guidance documents can be found, for example, at www.cdc.gov. However, note that CDC guidance is intended for investigations in the United States. The participants should take notes during the story just as they would in a ‘real-life’ epidemic investigation– such as pertinent epidemiological and clinical information, important dates and locations and relevant policies and procedures. Given the complexity of the story line, tell the participants that they will first create a case definition, and then start a line list on their own. Inform them they are already provided these line lists later in the case study but, as it is part of the simulation, they should not look or read ahead in their handouts. This case study helps the participants to assess epidemic curves to suggest modes of transmission, and participants must make recommendations for antiviral use, non-pharmaceutical interventions and control strategies in poultry populations. They must also develop situation reports for communications purposes, press releases, and make assessments if human to human transmission is occurring.