



Surveillance and Control of Seasonal and Avian Influenza in Humans

Guidelines for Public Health Services in Ukraine

Second Edition, July 2008

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Ministry of Health of Ukraine

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PATH

US Centers for Disease Control and Prevention

World Health Organization



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For more information about the CDC, visit www.cdc.gov.

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Executive Summary

Outbreaks of highly pathogenic avian influenza are occurring in domestic fowl in many countries, posing a considerable human public health risk. Highly pathogenic avian influenza A (H5N1), the source of many global outbreaks among poultry, has also been known to occasionally infect humans. In such cases, it has been observed to have a 63 percent case-fatality rate. The ability of avian influenza A viruses to rapidly mutate and acquire genes from viruses affecting other species raises the concern that they may spread efficiently among humans and cause a global influenza pandemic.

The early detection of cases of H5N1/novel influenza in humans plays a critical role in combating a potential pandemic. The main benefits of ascertaining clear and fast recognition of transmission to human beings include:

- Prompt implementation of public health and medical interventions aimed at preventing, delaying, or containing human-to-human virus transmission.
- More effective medical care of infected individuals, resulting in reduced mortality.
- Reduced economic and social impact of a potential pandemic.

A strong surveillance network for all types and subtypes of influenza viruses circulating in humans can also enhance a country's ability to respond to H5N1 or another pathogen with pandemic potential. Strengthening a seasonal influenza surveillance system will also provide infrastructure that can be used in an early warning system for a pandemic. For example, establishment of a strong influenza surveillance system will require the enhancement of laboratory capacity for specimen testing, creation of a logistical network for specimen collection and transport, trained epidemiologists to analyze data, a cadre of laboratory technicians who routinely work with influenza viruses and can therefore detect a novel virus, a formal reporting system, and a system for responding to unusual events recognized in the surveillance data. All of these elements are also needed for effective early warning and response to a pandemic.

In addition, a strong seasonal influenza surveillance system may be used to:

- **Develop a national influenza-control policy.** Knowledge of the seasonality, risk groups, and influenza disease burden is needed to assist national public health authorities in formulating control policy, including influenza vaccination.
- **Monitor circulating viruses.** The early detection and characterization of new variants of circulating influenza viruses allow for annual updates of influenza vaccines, the detection of new influenza viruses that may have pandemic potential, and antiviral drug resistance monitoring.
- **Detect and monitor outbreaks.** Early detection and investigation of possible influenza outbreaks are essential to allowing for rapid public health intervention and improved case management.

The guidelines outlined in this report provide comprehensive recommendations to help Ukrainian health care workers establish sentinel site surveillance for severe respiratory disease and seasonal influenza. They should also help Ukrainian health care workers promptly identify, report, confirm, and classify potential cases of avian influenza in humans. In addition, this document includes guidance on the basic parameters for surveillance data analysis, investigation of trigger cases and outbreaks, and improvement of other aspects of an early warning system for humans. The guidelines are most appropriate for the current and the next stages of pandemic preparedness (phases 3 and 4 of the World Health Organization [WHO] Pandemic Alert Period) and are designed primarily for health care personnel working at rayon and regional sanitary-epidemiological stations. In addition to general recommendations for the human avian influenza surveillance system as a whole, the guidelines include specific sections devoted to communication with the public as well as infection control in health facilities.

Based on the latest WHO standards and recommendations, this edition was developed by a multi-agency task force of experts under the leadership of the Ukrainian Ministry of Health. It includes results from the system piloting in Odesa and Donetsk oblasts and Kyiv City in 2007 and 2008. Periodic revisions are expected as more evidence and feedback from users become available.

Contributors

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Acronyms

ARI	Acute respiratory infection
CDC	US Centers for Disease Control and Prevention
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
HA	Hemagglutinin
HHS	US Department of Health and Human Services
HPAI	Highly pathogenic avian influenza
IHR	International Health Regulations
ILI	Influenza-like illness
MoES	Ministry of Emergency Situations
MoH	Ministry of Health
NA	Neuraminidase
NIC	National Influenza Center
PATH	Program for Appropriate Technology in Health
PCR	Polymerase chain reaction
PPE	Personal protective equipment
RIC	Regional influenza center
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SARI	Severe acute respiratory infection
SES	Sanitary-epidemiological station
SST	Serum separator tube
VTM	Viral transport medium
WHO	World Health Organization

Surveillance for Seasonal Influenza Virus Infection in Humans

1. Introduction: Seasonal, Avian, and Pandemic Influenza

Influenza illness is caused by the influenza virus. Although they are inter-related, human influenza, avian influenza, and pandemic influenza must be understood as distinct entities. Preparedness and understanding of each is essential to enhancing preparedness and understanding of all forms of influenza virus infection in humans. A strong seasonal or human influenza surveillance and response system will serve the purposes of pandemic preparedness, and vice versa.

While there are three types of influenza viruses—A, B, and C—only two cause significant disease worldwide: A and B. Influenza type C infections cause a mild respiratory illness in humans and are not thought to cause epidemics. Type B influenza viruses are usually found only in humans and in general are associated with less severe epidemics (chiefly among children) than influenza A viruses. Although influenza type B viruses can cause human epidemics, they do not cause pandemics. In contrast, Type A viruses can cause severe disease in humans, including severe epidemics as well as pandemics. Influenza A infects multiple species including humans, birds, pigs, cats, dogs, horses, and other animals. Wild waterfowl are the natural reservoir for influenza viruses.

Influenza A viruses are further subtyped by two proteins on the viral surface: hemagglutinin (HA) and neuraminidase (NA). HA allows the virus to attach to host cells, while NA allows the virus to escape infected cells and then go on to infect more cells. There are 16 known HA and 9 known NA subtypes for influenza A. Each HA subtype is named using an “H” plus a number, such as type H1, H2, and so on. In the same way, each NA subtype is named with an “N” plus a number, such as type N1, N2, and so on. Many combinations of HA and NA proteins are possible.

Seasonal or human influenza is endemic and seen every year at regular intervals. The same HA type circulates around the globe year after year, mutating slightly as it goes. The result of these mutations is that, over time, susceptibility is renewed because of changes in the virus’ surface proteins that allow it to evade the immunity built up by previous influenza infections. The season in which the influenza occurs may be different in temperate climates, where influenza occurs in the winter, and tropical climates, where transmission probably occurs throughout the year but is largely unstudied. Currently circulating types and subtypes of human influenza include influenza A (H1N1), influenza A (H3N2), and influenza B.

Avian influenza (“bird flu”) is a disease of birds that can occasionally infect humans when there is significant exposure. Avian influenza viruses are thought to be the reservoir for new types of influenza viruses that cause pandemics when they acquire the ability to circulate in humans. The factors that must be present to enable the virus to have this ability are unknown. Influenza A virus infection in birds may be minimally or highly pathogenic. To date, all outbreaks of the highly pathogenic form of influenza infection in birds have been caused by subtypes A/H5 and A/H7.

Pandemics occur when there is a shift in the type of HA that circulates in human populations. The introduction of a new subtype into human circulation can be caused by a process called reassortment, in which animal and human influenza viruses combine their genes, or through direct entry into the human population with a virus that has mutated from an avian species and acquired the ability to spread easily from human to human.

2. Background and Rationale for Seasonal Influenza Surveillance

Surveillance for seasonal influenza provides the tools needed to monitor, evaluate, and offer prevention modalities for annual respiratory outbreaks. In addition, a solid surveillance system provides the framework to detect novel influenza viruses with pandemic potential.

Virological surveillance for influenza is currently being implemented in Ukraine. However, cases are detected in a non-standardized manner, and epidemiological data on cases are lacking. While critically important, virological surveillance systems alone cannot provide the information needed to support influenza-control efforts, including vaccination. Improvements in national surveillance systems that facilitate the collection and analysis of both virological and epidemiological data are critical to providing a more complete understanding of the burden of influenza.

3. Routine Surveillance of ARI and Seasonal Influenza in Ukraine

Health service organizations and government bodies perform surveillance of acute respiratory infection (ARI) and seasonal influenza to prevent the spread of these infections. Routine surveillance is carried out at the national level by the Ministry of Health (MoH) and the National Influenza Center (NIC) and at the regional level by oblast sanitary-epidemiological stations (SES). At the local level, surveillance is carried out by rayon and municipal SES with assistance from the nationwide network of health facilities. These facilities provide clinical materials for laboratory tests and monthly information about registered cases.

In cooperation with the World Health Organization (WHO), the NIC and the SES virological laboratories provide laboratory diagnosis and systematically research the etiology and dynamics of influenza virus strains during epidemic and inter-epidemic periods. In cooperation with WHO, the NIC researches antiviral resistance and antigenic and genetic characteristics. With the support of the MoH and the NIC, the country's SES' carry out basic epidemiological analyses and monitor the circulation of influenza virus strains in Ukraine.

Based on the current epidemiological analysis and laboratory test results, prevention and infection-control measures aimed at reducing incidence rates and preventing outbreaks—particularly in organized settings—should be planned and implemented. These activities may include restrictive measures, such as temporary school closings. Recommendations on immunization and planning of supplies for pharmacological prophylaxis and treatment should be provided. Use of appropriate seasonal human influenza vaccine during the pre-epidemic period has been an effective measure in the prevention of the infection among risk groups and at industrial enterprises. It is a tool that may be used more aggressively in Ukraine.

4. Rationale for Sentinel Sites

To meet the needs of seasonal and avian/novel influenza surveillance, two synergistic types of activities are needed. The first is establishing sentinel surveillance for severe ARI. The second is establishing an early warning system for outbreaks of influenza A (H5N1) in humans or the emergence of a new pandemic virus.

A sentinel site is a polyclinic or hospital where patients that meet the severe acute respiratory infection (SARI) or influenza-like illness (ILI) case definition are identified and respiratory specimens and patient information are collected. Several sentinel sites in a particular oblast may collect epidemiological and laboratory data from SARI and ILI cases. Sentinel-site surveillance for SARI cases should occur within all adult and pediatric infectious disease, therapeutic, and pulmonary wards of a hospital. ILI surveillance takes place at selected polyclinics in that area.

A surveillance coordinator responsible for surveillance activities within each sentinel site should be identified and trained. These sentinel-site coordinators will be responsible for ensuring that the SARI case definition is applied consistently and accurately in all relevant adult and pediatric infectious-disease, therapeutic, and pulmonary wards of the sentinel site. These coordinators will also ensure that epidemiological data collection is complete and accurate; that laboratory specimens are appropriately collected, packaged, and transported; that surveillance data reports are submitted in a timely manner to the oblast SES; and that ILI outpatient data collection is appropriately undertaken. Sentinel-site coordinators at the oblast and national levels will also provide quality control and data feedback to the sentinel sites. The oblast SES and the MoH will provide training on surveillance operations to the sentinel-site coordinators. These coordinators will be responsible for the ongoing training of clinicians who work within their sentinel sites.

In an effort to include persons who have SARI but do not access inpatient health care services, home care visits will also be included in the sentinel-site surveillance system. Physicians who routinely undertake home care visits will also be trained in the sentinel surveillance procedures. If they detect a case meeting the SARI case definition during a home care visit, they will arrange for respiratory specimens and epidemiological data to be collected from the patient within the next 24 hours. The acceptability and feasibility of this home-care surveillance will be regularly monitored, and procedures will be adapted or modified to local contexts.

Sentinel sites collect epidemiological and virological information from patients enrolled in the surveillance system. Thus, a more complete understanding of the influenza burden can be accomplished through the acquisition of a greater amount of very useful information about influenza from just a few representative, well-run sentinel sites.

The objectives of sentinel surveillance are to:

- Provide data on the burden and epidemiology of seasonal influenza.
- Obtain specimens for analysis and confirmation of influenza.
- Provide influenza isolates to WHO's international influenza surveillance system.

The establishment of a sentinel system will also provide the infrastructure necessary not only to respond to seasonal influenza but also to outbreaks of other respiratory viruses or virus strains with pandemic potential. Establishment of a sentinel influenza surveillance system will strengthen the:

- Laboratory capacity for specimen testing.
- Logistical network for specimen collection and transport.
- Network of trained epidemiologists to analyze data.

- System for responding to unusual events recognized in the surveillance data.
- Situational awareness¹ when a novel influenza virus is detected.

5. Key Components of Sentinel Site Surveillance

A. Case Definitions

Patients meeting the SARI and ILI case definitions will be enrolled in the sentinel surveillance system. These case definitions will only be used at participating sentinel-site surveillance locations.

SARI in Hospitalized and Home-Care Patients

SARI case definition for *persons >5 years old*

Moderate to severe acute lower respiratory tract illness **requiring hospital admission or requiring a physician visit to the home** consisting of:

- Temperature $\geq 38^{\circ}\text{C}$ **and**
- Cough or sore throat **and**
- Shortness of breath or difficulty breathing.

SARI case definition for *persons ≤ 5 years old*

Hospitalized child presenting with:

- Fever $\geq 38^{\circ}\text{C}$ **and**
- Tachypnea (>60 breaths per minute for infant aged 0 to 1 month, >50 breaths per minute for infant aged 2 to 11 months, or >40 breaths per minute for child aged 12 to 59 months).

and at least one of the following symptoms:

- Inability to drink or breastfeed.
- Lethargy or unconsciousness.
- Repeated vomiting.
- Convulsions.
- Chest in-drawing.

Note: Temperature does not have to be documented; subjective history of fever over the previous 3 days is sufficient.

ILI in Outpatient Clinics

Acute illness with fever $\geq 38^{\circ}\text{C}$ **and** cough or sore throat **and** an absence of other diagnoses.

¹An unusual case, such as an outbreak of avian influenza at a poultry farm, may serve as an example. Health managers can look at the outpatient ILI data or inpatient SARI data from the case or outbreak area to determine whether there is an increase that could be an indication of the virus spreading in the community. Over time, epidemic thresholds can be established.

B. Laboratory Aspects

Specimens should be collected and routinely submitted to the oblast SES laboratory for testing to determine etiology of respiratory infections from:

1. All cases admitted to the sentinel hospitals or requiring a physician visit to the home that meet the above SARI case definition with onset of symptoms within 1 week.

Epidemiologic information and laboratory specimens may be collected by a visiting nurse upon the request of an investigating physician who has determined that the home-care case meets the SARI case definition.

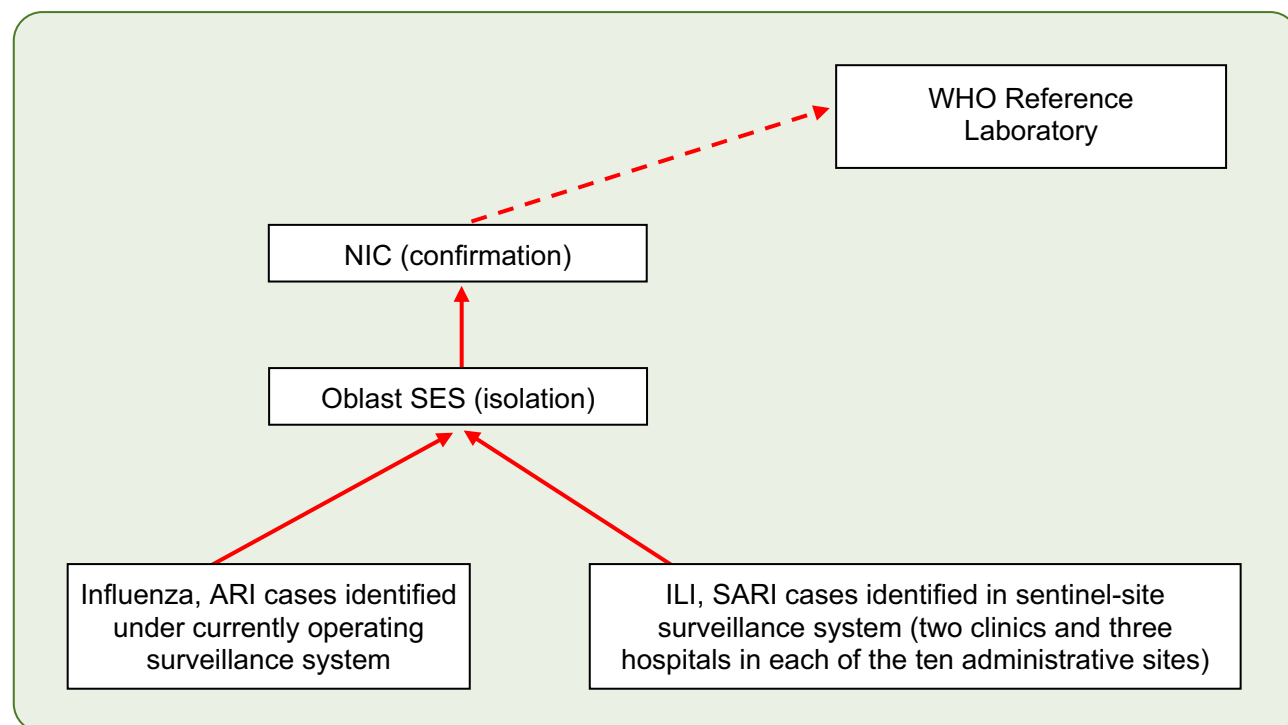
2. A sample of ILI cases representing the served population if onset of symptoms falls within 72 hours.

- The first three to five cases with ILI symptoms on a regular day per week (e.g., every Tuesday) will be selected for testing.
- At least three cases from each respiratory disease outbreak reported in an organized setting served by the clinic should be included.

Note: If the patient is part of a cluster of respiratory illnesses or has coincided with another trigger for investigation specified in Chapter 7, Section B, then specimens must be collected irrespective of when symptom onset occurred or any sampling strategy.

In cases involving ILI, a nasopharyngeal swab should be taken from adults and children. For SARI cases, a nasopharyngeal swab or aspirate is recommended. If an ILI or SARI case also meets one of the H5N1 trigger criteria specified in Chapter 7, Section B, then throat swabs or lower-respiratory specimens should be collected as well. Procedures for specimen collection, storage, and transport are described in more detail in Annex 1.

FIGURE 1. Flow of Laboratory Specimens for Routine Surveillance



The following form should be completed in duplicate by sentinel stations and laboratories undertaking influenza testing.

National Influenza Surveillance System

Specimen Collection and Laboratory Test Results Form

Part 1 (to be completed by health workers who collect specimens)

Sentinel station name _____

Source of specimen: ☐ Sporadic case ☐ Outbreak
 Patient type: ☐ ILI ☐ SARI

Patient name: _____ Age: _____ Sex: ☐ Male ☐ Female
 Testing location: ☐ Polyclinic ☐ Inpatient ☐ In-home

Patient's address: Street: _____ District: _____
 City: _____ Oblast: _____

Date of disease onset: ____/____/20____
 Date of sample collection: ____/____/20____

Type of specimen:
☐ Nasopharyngeal swab ☐ Nasal swab ☐ Throat swab
☐ Nasopharyngeal aspirate ☐ Tracheal aspirate
☐ Other: _____

2. Laboratory test results (to be completed by laboratory staff)

Registration number (in the laboratory record book): _____

TECHNIQUE	TYPE OF SPECIMEN	TEST DATE	RESULT
RT-PCR		____/____/20____	
IFA		____/____/20____	
Rapid test		____/____/20____	
Cell culture		____/____/20____	
Other: _____		____/____/20____	

Final result: ☐ A/H1 ☐ A/H3 ☐ A/H5 ☐ A not subtyped ☐ Influenza B
☐ Negative ☐ Other (specify): _____

C. Epidemiological Data Collection and Reporting

All specimens from influenza sentinel sites should be sent to the regional SES laboratory and accompanied by the standard specimen collection/laboratory test form. The laboratory will assign an identification number according to the laboratory register.

Sentinel ambulatory clinics and hospitals also should record the following data for all individuals tested for respiratory viruses:

- Patient's name.
- Patient's date of birth.
- Patient's sex.
- Patient's address.
- Surveillance ID number (from the SES laboratory register).
- Date of disease onset.
- Date of sampling.
- Contact with disease and/or outbreak.
- Antiviral treatment provided (if yes, indicate antiviral name).
- Symptoms (e.g., fever, cough, sore throat, shortness of breath).
- Laboratory test results.

These data should be compiled in a register (electronic register) and submitted to the oblast SES on a weekly basis.

The oblast laboratory should, at a minimum, record the following data for each respiratory specimen received:

- Medical record/surveillance number.
- Date specimen was received.
- Patient's date of birth.
- Patient's address.
- Date of disease onset.
- Date of sampling.
- Test method.
- Date lab investigation started.
- Date lab investigation ended.

The oblast SES should forward the case-based SARI and ILI data from the sentinel sites to the NIC on a weekly basis.

Aggregate data with case counts of hospitalized SARI and outpatient ILI cases by age group should be submitted by sentinel facilities to SES on a weekly basis according to the format below:

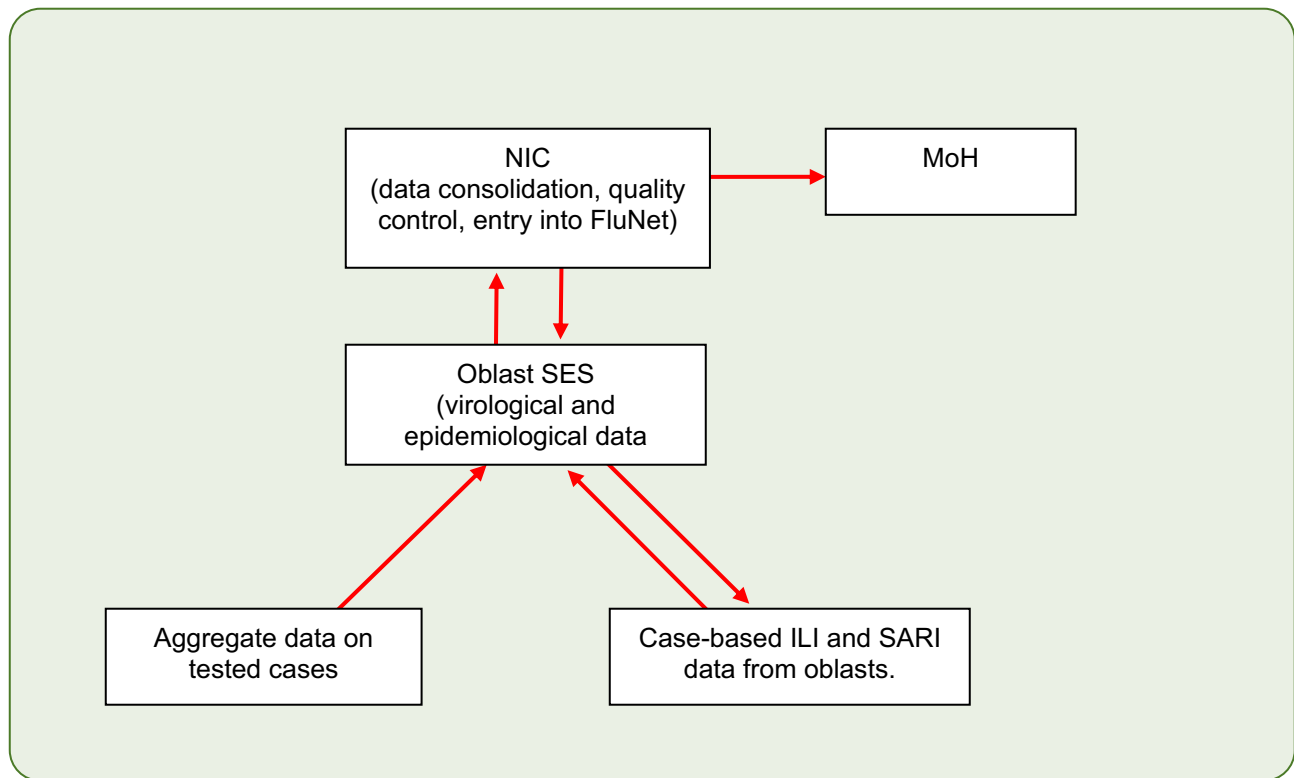
INFLUENZA SENTINEL STATION SARI / ILI MORBIDITY REPORT							
Influenza sentinel facility:	Month:			Week:			Year:
Disease/age group	<2	3–6	7–14	15–18	19–59	≥60	Total cases
Total no. of ambulatory visits							
No. of ambulatory patients meeting the influenza-like illness (ILI) definition							
No. of ambulatory patients meeting the ILI definition from whom laboratory specimens have been collected							
No. of home-care visits conducted							
No. of home-care cases meeting the severe acute respiratory infection (SARI) case definition							
No. of home-care cases meeting the SARI case definition from whom laboratory specimens have been collected							
Total no. of hospitalizations							
No. of hospitalized cases meeting the SARI case definition							
No. of hospitalized cases meeting the SARI case definition from whom laboratory specimens have been collected							
No. of SARI deaths in the current week							

No space can be left blank on the form. If no ILI or SARI cases have occurred in a particular age group, a zero must be reported.

The responsible officer at each of the sentinel facilities should oversee collection and reporting of data and specimens and monitor trends in ILI and SARI over time. Increases in ILI or SARI cases above a baseline or clusters of SARI with abnormal epidemiological characteristics (such as age) may indicate an outbreak requiring further investigation. Oblast and rayon epidemiologists should review sentinel-site records on a semiannual basis to ensure quality control and completeness of reporting. These epidemiologists are also responsible for providing reporting clinicians with timely feedback of influenza laboratory testing results.

If infection with a novel influenza virus is confirmed, or if a case is classified as a suspected or probable H5N1 infection, a case investigation and response measures should be initiated promptly as specified in Chapters 7 through 10.

FIGURE 2. Weekly Reporting of Sentinel Site Data for Seasonal Influenza



The SES should provide weekly reports to the chief physician at the sentinel site on the circulation of influenza viruses and the epidemiological characteristics in their region. The chief physician should share this information with specialists of the sentinel-site surveillance system. The SES will receive weekly information on influenza virus circulation and epidemiological characteristics of influenza cases from the NIC. The NIC will also send weekly reports to the MoH.

D. Data Analysis and Interpretation

Suggested Scope of Influenza Sentinel Surveillance Data Analysis

The following parameters should be used by sentinel stations for a weekly analysis of surveillance data by age category and in aggregate:

- Number of new cases of ILI and SARI.
- Total number of hospitalizations at the sentinel site.
- Total number of home visits conducted.
- Number of outpatient visits at the sentinel site.
- Number of new SARI fatalities detected.
- Number of laboratory specimens submitted for influenza testing.
- Proportion of ILI cases per total ambulatory consultations.
- Proportion of SARI hospitalizations per total hospitalizations.
- Proportion of SARI home-care visits per total home-care visits.
- Number of feedback meetings (during which reporting clinicians are informed of influenza testing results) that have been completed with reporting clinicians.

“Zero reporting” procedures must be observed at all times.

The following parameters should be used by the oblast SES for a weekly analysis of surveillance data by age category and in aggregate:

- Number of new cases of ILI and SARI.
- Total number of hospitalizations at sentinel sites.
- Total number of outpatient visits at sentinel sites.
- Total number of home-care visits conducted.
- Number of new SARI fatalities.
- Number of new laboratory-confirmed influenza cases and fatalities.
- Number of laboratory isolates submitted to the NIC for influenza confirmation.
- Proportion of ILI cases testing positive for influenza.
- Proportion of SARI cases testing positive for influenza.
- Proportion of laboratory-confirmed influenza cases per total number of SARI cases.
- Proportion of laboratory-confirmed influenza deaths per total number of SARI deaths.
- Proportion of ILI cases per total ambulatory consultations.
- Proportion of SARI hospitalizations per total hospitalizations.
- Proportion of SARI home-care visits per total home-care visits.
- Number of feedback meetings (during which reporting clinicians are informed of influenza testing results) that have been completed with reporting clinicians.

“Zero reporting” procedures must be observed at all times.

In addition to the items mentioned above, the oblast SES should use the following parameters for a quarterly analysis of surveillance data:

- Proportion of laboratory-confirmed influenza among SARI and ILI cases.
- Weekly trends in the counts and proportion of outpatient/inpatient visits due to ILI, SARI, and laboratory-confirmed influenza.
- Demographic characteristics of SARI and laboratory-confirmed influenza cases.

Based on information aggregated over 5 or more years, monthly baselines can be calculated for the above analyses.

E. Control Efforts

Surveillance provides information on which control efforts are based: circulating strains, epidemiological risk factors, disease burden. The primary goal of ILI and SARI surveillance is to decrease the health impact of seasonal influenza. The following actions might be considered to control disease spread:

- **Health education/personal protection:** Promotion of personal protective practices (e.g., handwashing, using tissues when coughing or sneezing, encouraging persons with febrile respiratory illness to stay at home) to reduce the transmission of respiratory viruses within the community.
- **Vaccination of risk groups:** Promotion of influenza immunization on an annual basis with an appropriate vaccine for high-risk groups as determined by the MoH. Surveillance data can be used to refine vaccination strategies.
- **Optimization of health facilities work:** Collection and dissemination of information on the local circulation of influenza virus, symptoms of the infection, use of antiviral medications, algorithms/criteria for hospital admissions, and use of infection control measures.
- **Suspension of school education:** Although the evidence supporting effectiveness of suspending school activities is unclear, school education may be suspended to reduce transmission of the virus during influenza epidemics.

F. Monitoring and Evaluation

Sentinel Surveillance Performance Indicators

To evaluate the efficiency and success of the system, the MoH has established a number of indicators. At least once a year, local surveillance reviews by regional SES should be carried out to ensure data quality, protocol adherence, and standardization across the country. Such reviews may incorporate the following:

- Audits of hospital and clinic records to determine whether cases of ILI and SARI are being accurately recorded.
- Assessment of local staff knowledge of protocols and case definitions.
- Laboratory equipment and staff assessment, including biosafety assessments.
- Laboratory data audits to determine reporting accuracy.
- Continuing education concerning notifiable disease surveillance and sentinel surveillance protocols.
- The opportunity for local staff to give feedback about inefficiencies in the surveillance system.
- Other quality-assurance data.

The outcome indicators presented in Table 1 allow for system evaluation in accordance with the specific objectives of the sentinel surveillance system. The goal of the system is to establish and/or improve surveillance to detect seasonal and avian influenza in humans and to improve national capacity to detect any new strains of influenza in Ukraine.

TABLE 1. Sentinel Surveillance Performance Indicators

OBJECTIVE	INDICATOR	TARGETS
Describe the epidemiology of seasonal influenza and burden of disease.	SARI and ILI case data (including number of specimens submitted for influenza testing) from the sentinel sites are analyzed weekly at the oblast and national levels.	>95% of reported SARI cases are captured in the surveillance system.
	Number and proportion of sampled ILI and SARI cases confirmed by laboratory as influenza are reported by oblast weekly.	At least 20 ILI cases per sentinel station and all qualifying SARI cases have samples submitted and tested on a monthly basis during influenza season. Laboratory-confirmed influenza cases appear in oblast SES weekly reports within 7 days. Sentinel sites report the number of new cases of ILI, SARI, and laboratory specimens submitted for influenza testing, with zero reporting, during 100% of weeks. Oblasts with sentinel sites report the number of new cases of ILI, SARI, and laboratory confirmations of influenza, with zero reporting, during 100% of weeks.
	Incidence of laboratory-confirmed influenza in sentinel-site catchment areas is estimated quarterly.	Quarterly incidence reports are based on yearly estimates of the populations served by sentinel-site hospitals.
	Seasonal trends in influenza and demographic characteristics of cases are analyzed regularly.	Analyses of seasonal trends and epidemiological descriptions of laboratory-confirmed influenza, ILI, and SARI are performed quarterly.
Provide isolates for identification of influenza viruses.	The NIC receives all influenza isolates from oblasts participating in the surveillance system.	Each oblast submits 100% of its influenza isolates to the NIC. Laboratory staff from all oblasts with sentinel sites have been trained and follow standard protocols provided by the NIC.

Other Possible Sentinel-Site Performance Indicators Analyzed by the NIC

- Number of sites submitting aggregate data weekly.
- Epidemic criteria established with a plan to notify physicians' networks when the threshold is exceeded.
- Number of isolates sent to WHO.
- Publications of surveillance data in peer-reviewed journals.
- Adherence to the timeframe for specimen delivery to the laboratory from the time of specimen collection or freezing (-70°C or below).
- Percent of oblast negative samples testing positive at the NIC.

Surveillance for Avian/Novel Influenza Virus Infection in Humans

6. Background

A. What Is Avian Influenza?

Avian influenza (“bird flu”) is an infectious disease of birds caused by various subtypes of type A influenza virus that can occasionally infect humans when there is significant exposure. Sixteen hemagglutinin (HA) subtypes and nine neuraminidase (NA) subtypes of type A influenza virus are known. To date, all outbreaks of the highly pathogenic form of influenza infection in birds have been caused by subtypes A/H5 and A/H7.²

Avian influenza viruses are thought to be the reservoir for new types of influenza viruses that cause pandemics when they acquire the ability to circulate in humans.

B. Description of the Disease in Birds

Influenza infections occur naturally among birds worldwide. Infection causes a spectrum of symptoms in birds, ranging from mild illness to a highly contagious and rapidly fatal disease that can cause severe epidemics. The latter is known as “highly pathogenic avian influenza,” or HPAI. HPAI is characterized by sudden onset, severe illness, and rapid death, with a mortality rate that can approach 100 percent. Some birds, such as ducks, can become infected and spread the disease without showing signs of illness.

The current outbreaks of HPAI began in mid-2003. The causative agent, the H5N1 virus,³ began to circulate widely in poultry in parts of Southeast Asia, spreading within months to affect eight countries in an outbreak that was unprecedented in its geographical extent. Never before had so many countries been simultaneously affected by HPAI; the outbreak has already resulted in the loss of more than 200 million birds. The disease remained confined to Southeast Asia until mid-2005, when the virus spread through parts of Central Asia to Europe, Africa, and the Middle East—affecting more than 60 countries in all.

Migratory waterfowl—most notably wild ducks and geese—are the natural reservoir of avian influenza viruses. Direct or indirect contact of wild migratory waterfowl with domestic flocks (e.g., through droppings from infected wild birds) has been implicated as a frequent cause of bird epidemics, as have the legal and illegal trade of poultry and poultry products.

Transmission routes and patterns of avian influenza viruses from bird to bird remain unclear and are a focus of study. Some species are more resistant to infection than others. Domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza.

²The subtypes differ based on proteins on the surface of the virus: the HA protein governs entry of virus into cells; immunity to the HA subtype prevents infection. The NA protein governs release of new virus into the body; immunity to the NA subtype reduces severity of the disease.

³The H5N1 virus is also of particular concern for human health, as explained in Section C.

C. The Risk and Significance of Transmission to Humans

The current outbreaks of HPAI are closely monitored by experts around the globe because one of the subtypes, H5N1,⁴ has crossed the species barrier on a number of occasions and caused severe illness with high case fatality in humans (Table 2). This poses a theoretical risk of a new influenza pandemic—that is, a global epidemic affecting a large proportion of the population.

TABLE 2. Cumulative Number of Laboratory-Confirmed Human Cases of Avian Influenza A (H5N1) Reported to the World Health Organization as of May 28, 2008

COUNTRY	TOTAL CASES	TOTAL DEATHS
Azerbaijan	8	5
Bangladesh	1	0
Cambodia	7	7
China	30	20
Djibouti	1	0
Egypt	50	22
Indonesia	133	108
Iraq	3	2
Lao PDR	2	2
Nigeria	1	1
Pakistan	3	1
Thailand	25	17
Turkey	12	4
Vietnam	106	52
Total	383	241

Likely influenza pandemics have been documented since the 16th century and have occurred at intervals ranging from 10 to 50 years. There were three pandemics in the 20th century; each was caused by the emergence of a new influenza A virus subtype into human circulation.

All previous pandemics in the 20th century have been caused by H1, H2, or H3 viruses. After an antigenic shift event that led to their circulation in human populations, these viruses adapted to their human host and became the cause of annual epidemics of seasonal influenza over time. Influenza A (H5N1) has never consistently circulated in human populations, so it meets the requirement of a novel influenza A virus.

Pandemic influenza viruses in the 20th century

1918–19	H1N1, “Spanish flu”	40 million deaths
1957–58	H2N2, “Asian flu”	2 million deaths
1968–69	H3N2, “Hong Kong flu”	1 million deaths

⁴In addition to H5N1, two avian influenza strains—H9N2 and H7N7—have caused illness in humans, but the outbreaks were not as severe as those caused by the H5N1 strain.

Three prerequisites are normally required for a pandemic to occur. H5N1 meets the first two criteria.

1. (+) A novel virus A subtype must emerge.
2. (+) The virus must be able to replicate in humans and cause serious disease.
3. (–) The virus must be efficiently transmitted from one human to another.

It is thought that there are two mechanisms by which an avian influenza A virus can evolve into a pandemic strain. In the 1918 pandemic, it is believed that an avian influenza A (H1N1) virus mutated sufficiently over time to acquire the ability to be transmitted easily from person to person. In contrast, the 1957 and 1968 pandemics were caused by reassortments, or mixing of genes, between human and avian viruses.

The spread of infection in birds increases the likelihood of human contact with infected birds. If more humans become infected over time, the likelihood increases that humans, if concurrently infected with human and avian influenza strains, could serve as the “mixing vessel” for a novel strain with sufficient human genes to be easily transmitted from person to person. Such an event could mark the start of an influenza pandemic because the human population has little or no immune protection against novel virus subtypes. Moreover, existing vaccines, which are developed each year to match currently circulating strains and protect humans during seasonal epidemics, would likely be ineffective against a novel influenza A virus.

The longer the current H5N1 strain circulates, the greater the possibility that people will become infected with H5N1—and the greater the risk of a pandemic.

To date, human H5N1 infections have not resulted in sustained human-to-human transmission. Although a certain percentage of confirmed H5N1 cases are from disease clusters involving two or more individuals from a single family, possible human-to-human transmission of the H5N1 virus cannot be conclusively demonstrated in most instances because of family members’ potential concurrent exposure to infected birds. However, these reports do highlight the concern that changes in the circulating avian H5N1 virus might transform it into a virus that can be transmitted efficiently from human to human.

H5N1 is currently considered the most likely virus to ignite the next pandemic. Theoretically, however, any influenza strain has pandemic potential.

D. How Human Infections Might Occur

Avian influenza viruses do not usually infect humans. Nevertheless, as mentioned above, several instances of human infections and outbreaks have been reported since 1997.

To date, most cases of H5N1 infection in humans are the result of direct contact with poultry or with objects or surfaces contaminated with feces from infected poultry (with a few cases of suspected human-to-human transmission among persons with intimate contact). These observations suggest a respiratory route of transmission from birds to humans. Exposure risk is considered highest when slaughtering, defeathering, butchering, and preparing poultry for cooking. Infections have not occurred when individuals have used personal protective equipment (PPE) in the culling process.

Food safety: There is no evidence that properly cooked poultry or poultry products, such as eggs, can be a source of infection. Normal cooking at temperatures greater than 70°C inactivates the virus.

E. WHO Phases for Pandemic Influenza

The World Health Organization (WHO) has designed a six-phase system for informing the world of the seriousness of the threat of pandemic influenza and to facilitate pandemic planning (Table 3).

TABLE 3. Summary of WHO Phases of Pandemic Influenza

PERIOD	PHASE	DESCRIPTION	PUBLIC HEALTH GOAL
Inter-pandemic	1	No new influenza virus subtypes in humans.	Strengthen influenza pandemic preparedness at all levels.
	2	No new influenza virus subtypes in humans. A circulating animal influenza virus subtype poses a substantial risk of human disease.	Minimize the risk of transmission to humans; detect and report such transmission rapidly if it occurs.
Pandemic Alert	3	Human infection with a new subtype but no human-to-human spread, or at most, rare instances of spread to a close contact.	Ensure rapid characterization of the new virus subtype and early detection, notification, and response to additional cases.
	4	Small cluster(s) with limited human-to-human transmission, but spread is highly localized, suggesting that the virus is not well-adapted to humans.	Contain the virus within limited foci or delay spread to gain time to implement preparedness measures, including vaccine development.
	5	Large cluster(s), but human-to-human spread is still localized, suggesting the virus is better adapted to humans but may not yet be fully transmissible.	Maximize efforts to contain or delay spread, to possibly avert a pandemic and to gain time to implement pandemic response measures.
Pandemic	6	Efficient and sustained transmission in the general population.	Minimize the impact of pandemic.

Source: WHO, 2006.

As of June 2008, the world was in phase 3: a new influenza virus subtype causing disease in humans but not yet spreading in an efficient and sustained way between humans.

F. Epidemiology of WHO-Confirmed Human Cases of Avian Influenza A (H5N1) Infection

Results from the first analysis of epidemiological data on 340 laboratory-confirmed H5N1 cases officially reported to WHO (analyzed by onset date from December 2003 through December 2007) have allowed the following preliminary conclusions on the epidemiology of this infection:

- Cases have occurred year round. Increases in human cases of influenza A (H5N1) have been observed during cooler months in association with increases in outbreaks among poultry.
- Half of the cases occurred in people less than 20 years of age; 90 percent of cases occurred in people less than 40 years of age.
- The overall case-fatality rate was 61 percent. Case fatality was high in all age groups but highest in persons aged 10 to 19 years and lowest among persons 50 years of age or older.
- The case-fatality profile by age group differs from that seen in seasonal influenza, where mortality is highest in the elderly.
- Direct avian-to-human H5N1 virus transmission is the predominant means of human infection, although the exact mode and sites of influenza A (H5N1) virus acquisition in the respiratory tract are incompletely understood. Handling of sick or dead poultry during the week before the onset of illness is the most commonly recognized risk factor.
- Clusters of human influenza A (H5N1) illness with at least two epidemiologically linked cases have been identified in 10 countries and have accounted for approximately one quarter of cases. Most clusters have involved two or three persons; the largest affected eight. More than 90 percent of case clusters have occurred among biological family members. Most persons in case clusters probably acquired infection from common-source exposures to poultry, but limited, nonsustained human-to-human transmission has probably occurred during very close, unprotected contact with a severely ill patient.
- After exposure to infected poultry, the incubation period generally appears to be 7 days or less, and in many cases this period is 2 to 5 days. In clusters in which limited, human-to-human transmission has probably occurred, the incubation period appears to be approximately 3 to 5 days, although in one cluster it was estimated to be 8 to 9 days.
- The time from the onset of illness to presentation (median: 4 days) or to death (median: 9 to 10 days) has remained unchanged from 2003 through 2006.
- Assessment of mortality rates and the time intervals between symptom onset and hospitalization and between symptom onset and death suggests that the illness pattern did not change substantially during the four years.

G. Clinical Description of Human Cases of H5N1 Avian Influenza

The incubation period for influenza A (H5N1) infection in humans usually ranges from 2 to 7 days.

The reported symptoms of avian influenza in humans have ranged from typical influenza-like symptoms (e.g., fever, cough, sore throat, and muscle aches) to viral pneumonia and acute respiratory distress. Gastroenterological symptoms are sometimes reported as well (Table 4). Lower respiratory symptoms develop early in illness, and overall severity of the disease is high. Clinically apparent pneumonia with chest x-ray changes is seen in most patients, although the x-ray changes have been nonspecific.

Common laboratory findings have included lymphopenia ($<1 \times 10^9/\text{liter}$), thrombocytopenia, and slightly or moderately raised alanine aminotransferase and aspartate transaminase. In fatal cases, the illness has rapidly

progressed to respiratory distress and subsequent respiratory failure within one week of the onset of symptoms, despite ventilator support.

TABLE 4. Prevalence of Selected Clinical Symptoms and Findings Among 59 Patients with Confirmed Avian Influenza A (H5N1) in Hong Kong, Thailand, Vietnam, and Cambodia (1997–2005)

CLINICAL PRESENTATION	PREVALENCE (%) [*]
Fever $\geq 38^{\circ}\text{C}^{\dagger}$	98
Cough [†]	88
Shortness of breath [†]	62
Rhinorrhea	55
Sore throat [†]	52
Diarrhea	39
Headache	28
Myalgia	29
Abdominal pain	23
Vomiting	31
Pulmonary infiltrates	88
Lymphopenia	64
Increased aminotransferase levels	67
Thrombocytopenia	54

^{*}On average, based on several studies. For more details, see Beigel JH, Farrar J, Han AM, et al. Avian Influenza A (H5N1) Infection in Humans. *New England Journal of Medicine*. 2005;353:1374–1385.

[†]These most-prevalent symptoms have formed a basis for influenza A (H5N1) clinical (probable) case definition to increase its specificity. Chapter 7, Section A, provides additional details on this case definition.

7. Key Components of Avian/Novel Influenza Surveillance

The signs and symptoms of pneumonia caused by avian influenza A (H5N1) infection in humans are non-specific and can occur with many other respiratory pathogen infections, including human infection with seasonal influenza viruses.

The early detection of H5N1 influenza cases in humans plays a critical role in combating a potential pandemic. The main benefits of having ascertained clear and fast recognition of transmission to human beings will ultimately include:

- Prompt implementation of public health and medical interventions aimed at preventing, delaying, or containing human-to-human virus transmission.
- Prompt international reporting and leveraging of available resources.
- Effective medical care of infected persons, resulting in reduced mortality.
- Reduced economic and social impact of a potential pandemic.

A. WHO Case Definitions⁵ for Avian Influenza A (H5N1) Infection in Humans

Suspected H5N1 Case

Clinical Presentation

Unexplained acute lower respiratory illness with fever ($\geq 38^{\circ}\text{C}$) and cough, shortness of breath, or difficulty breathing

AND

Epidemiological Criteria

One of the following exposures within 7 days prior to symptom onset:

- Close contact (within 1 meter) with a person who is a suspected, probable, or confirmed H5N1 case (e.g., caring for, speaking with, or touching this person).
- Exposure to poultry or wild birds or their remains (e.g., handling, slaughtering, defeathering, butchering, or preparing for consumption) or to environments contaminated by their feces in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month.
- Consumption of raw or undercooked poultry products in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month.
- Close contact with a confirmed H5N1-infected animal other than poultry or wild birds (e.g., cat or pig).
- Handling samples (animal or human) suspected of containing the H5N1 virus in a laboratory or other setting.

⁵**Note 1:** The case definitions apply to the current phase of pandemic alert (WHO's pre-pandemic phase 3) and may change as new information about the disease or its epidemiology becomes available.

Note 2: The case definitions are *not intended to provide complete descriptions of disease in humans, nor are they to be used as screening criteria to determine who should have specimens collected for H5N1 screening*. Rather, they are intended to standardize reporting of cases to WHO and ensure comparability of data.

Note 3: In clinical situations requiring decisions concerning treatment, care, or triage of persons who may have H5N1 infection, decisions should be based on clinical judgment and epidemiological reasoning, and not on adherence to the case definitions. While most patients with H5N1 infection present with fever and lower respiratory complaints, the clinical spectrum is broad.

Probable H5N1 Case (Notify WHO)

DEFINITION 1: A person meeting the criteria for a suspected case

AND

one of the following additional criteria:

- Infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (e.g., hypoxemia, severe tachypnea) **or**
- Positive laboratory confirmation of an influenza A infection, but insufficient laboratory evidence for H5N1 infection.

OR

DEFINITION 2: A person dying of unexplained acute respiratory illness who is considered to be epidemiologically linked by time, place, and exposure to a probable or confirmed H5N1 case.

Confirmed H5N1 Case (Notify WHO)

A person meeting the criteria for a suspected or probable case

AND

one of the following positive results in a national, regional, or international laboratory whose H5N1 test results are accepted by WHO as confirmatory:

- Isolation of an H5N1 virus.
- Positive H5 PCR results from tests using two different PCR targets (e.g., primers specific for influenza A and H5 hemagglutinin).
- A fourfold or greater rise in neutralization antibody titer for H5N1 based on testing of an acute serum specimen (collected 7 days or fewer after symptom onset) and a convalescent serum specimen. The convalescent neutralizing antibody titer must also be 1:80 or greater.
- A microneutralization antibody titer for H5N1 of 1:80 or greater in a single serum specimen collected at day 14 or later after symptom onset and a positive result using a different serological assay (for example, a horse red blood cell hemagglutination inhibition titer of 1:160 or greater or an H5-specific western blot positive result).

B. Triggers Requiring Case Notification, Public Health Investigation, H5N1 Laboratory Specimen Collection, and Response

An early warning system for human cases aims at detecting unusual cases or events (triggers) that elevate the index of suspicion of a possible human case of avian influenza or signal the emergence of a new pandemic virus. Any such case should lead to appropriate public health and laboratory investigations and response. **All cases that meet trigger criteria must have specimens collected and tested for influenza A (H5N1) and seasonal strains.** Trigger cases that also meet the International Health Regulations (IHR) 2005 Public Health Event of International Importance criteria as defined in IHR Annex 2 should be immediately reported to the IHR National Focal Point in Ukraine.

The following cases or events identified by providers require immediate notification of the rayon sanitary-epidemiological station (SES) without any delay, by any existing means of communication (telephone, fax, email, or in person).

1. Any report about a *suspected* or *probable* influenza A (H5N1) case in humans by a health care provider or a laboratory (WHO case definitions are provided above).
2. An unexplained death from severe acute respiratory illness (pneumonia or a respiratory illness with acute onset).
3. Two or more cases of severe acute respiratory illness with onset occurring within a 14-day period among people who share a living space.
4. Severe acute respiratory illness cases in health care workers who have cared for another case with severe acute respiratory illness.

In turn, the rayon SES must notify the following institutions within 1 hour:

- The oblast SES (which must notify the Ministry of Health [MoH] and the National Influenza Center [NIC] within 1 hour).
- The rayon veterinary service and the rayon administration (to coordinate epidemic and epizootic response measures).
- The regional/rayon hospital (to prepare for transportation and admission of the patient[s]).

They must also initiate public health investigation and laboratory specimen collection for influenza A (H5N1) testing.

C. Monitoring High-Risk Occupational Groups for Early Signs of Influenza-Like Infection

During a suspected or confirmed outbreak in animals or humans, the head of each rayon SES must update a rayon-specific list of persons in occupational groups that are at high risk of contracting influenza A (H5N1) infection. The head must also ensure control over monitoring the health status of these individuals using the register suggested in Figure 4.

At a minimum, these groups should include:

- People involved in the culling of infected or potentially infected birds.
- Farmers exposed to potentially infected animals.
- Health care workers caring for patients with probable or confirmed influenza A (H5N1) infection.

- Laboratory workers handling clinical specimens from patients with probable or confirmed influenza A (H5N1) infection.
- Mortuary room workers dealing with bodies of probable or confirmed influenza A (H5N1) cases.

Each of the people in the register should be informed about clinical symptoms of ILI and provided with the contact information for a designated health care official or health facility (contactable 24 hours a day, 7 days a week). They should be instructed to:

- Check their temperature and the presence of respiratory symptoms twice daily for 7 days following their last contact with the potentially infected animals or humans.
- Not self-medicate if a fever develops. Instead, they should limit interactions with others and immediately seek assistance from the designated health care official/health facility.

While self-reporting is encouraged, SES personnel are advised to actively contact identified individuals and/or cooperate with their employers to verify the absence of ILI during the entire monitoring period.

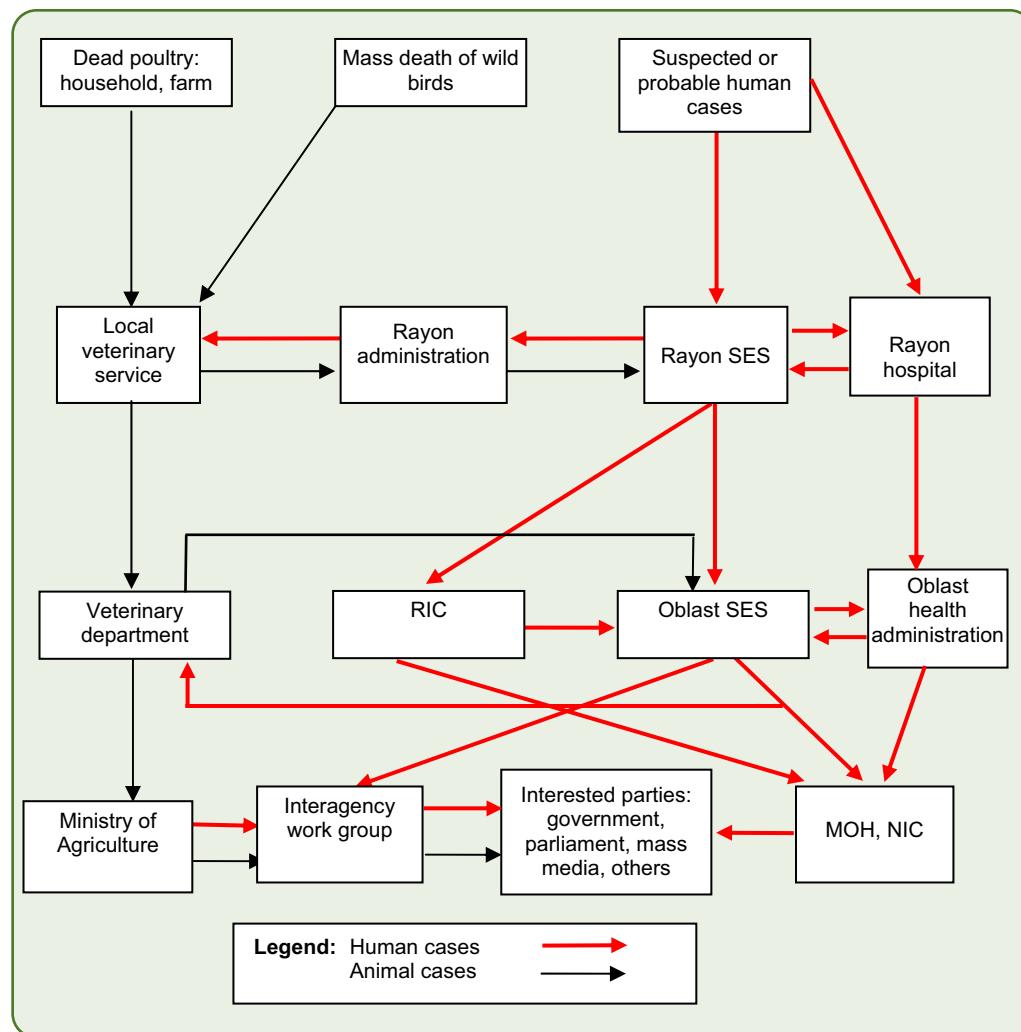
If a probable influenza A (H5N1) infection is suspected, a prompt investigation and response should be initiated as specified in these guidelines.

D. Active Search for Human Respiratory Infections in Cases of Unexplained or Unusual Mortality or Confirmed Cases of Influenza A (H5N1) in Birds or Animals

Unexplained or unusual mortality in poultry, wild birds, or animals may indicate an outbreak of HPAI A (H5N1).

As shown in Figure 3, the rayon veterinary office will normally be the first office to be notified about such an event. They should promptly notify the rayon SES and veterinary department and convene the rayon avian influenza response commission.

FIGURE 3. Reporting Channels for Suspected Cases of Avian Influenza



This notification may be followed by testing of deceased birds/animals and, in the case of a positive result, measures to control the animal infection, such as culling.

SES should initiate active surveillance following HPAI signals from the veterinary service or upon identification of suspected and probable human cases.

Health services must carry out active surveillance to detect and investigate probable human cases as early as possible and implement containment measures to prevent further spread.

These activities are performed by surveillance teams composed of SES personnel and health facility workers. The teams should be equipped with transportation, PPE, mobile telephones, flashlights, thermometers, and sufficient supplies of case investigation and contact monitoring forms.

The first step is to determine target population groups. Depending on the scope of the problem, these groups may include:

- People living in villages with suspected H5N1 outbreaks in poultry or wild bird die-offs.
- Persons and health care workers involved in H5N1 poultry investigations and response.
- Workers, buyers, and vendors in live animal markets (especially bird markets).
- Poultry cullers.
- Poultry or swine farm workers.
- Veterinarians.
- Hunters.
- Dealers or traders in wild/exotic birds.
- Zoo workers.

Through hospital-based records and ward reviews, interviews with possibly exposed persons and their families, and other active surveillance procedures (e.g., house-to-house visits), the surveillance team should interview the target population to verify the presence of *both* clinical symptoms and epidemiological exposure with a potential source of infection, or close contact with a suspected, probable, or confirmed human case. For example:

Exposure to sick or dead domestic poultry, wild birds, or their droppings or close contact with another suspected, probable, or confirmed human case

AND

Evidence of fever $\geq 38^{\circ}\text{C}$

For each case, the team's actions should be as follows:

IF THERE ARE:		THEN:
NO fever and NO exposure to suspected source of infection	→	Deliver appropriate health education messages on infection prevention and health care-seeking behavior (see Annex 2).
ONLY fever and no known source of exposure	→	Refer patient to health facility. Deliver appropriate health education messages on infection prevention (see Annex 2).
ONLY contact with sick or dead poultry, wild birds, animals, or a human source of infection	→	Include patient on the list of exposed persons for close observation (Figure 4) and begin monitoring for signs of infection for 7 days. Consider voluntary home quarantine. Advise patient not to self-medicate if fever develops, limit interactions with others, and <i>immediately seek assistance from the designated health care official/health facility</i> that can be contacted 24 hours per day, 7 days per week.
BOTH fever and contact with a potential source of infection within 7 days of symptom onset	→	Collect throat and nasal swabs and other laboratory specimens. Investigate any suspected or probable case of avian influenza on the spot using the case investigation form (Figure 5). Initiate control measures as recommended in Chapters 9–10.

FIGURE 4. Form for Monitoring Contacts Potentially Exposed to Influenza A (H5N1) Infection (Monitor Until 7 Days After Last Exposure)

Rayon: _____ Patient's name or suspected animal source/place of exposure: _____

Facility name and telephone (for monitoring of contacts among occupational groups): _____

N	First and Last Name	Address and Telephone	Sex	Age	Occupation	Potential Sources of Exposure*	Last Date of Exposure	Fever (≥38°C) After Last Exposure? (Y/N)							Acute Respiratory Symptoms?	If the Contact Falls Ill During the Observation Period
								Day								
								1	2	3	4	5	6	7		
1							/ /							/ /	Place: / /	
2							/ /							/ /	Place: / /	
3							/ /							/ /	Place: / /	
4							/ /							/ /	Place: / /	
5							/ /							/ /	Place: / /	
6							/ /							/ /	Place: / /	
7							/ /							/ /	Place: / /	
8							/ /							/ /	Place: / /	
9							/ /							/ /	Place: / /	
10							/ /							/ /	Place: / /	
11							/ /							/ /	Place: / /	

*Household member (H), friend (F), work colleague (W), other (O) (specify).

E. Investigation of Human Cases/Outbreaks of Avian Influenza A (H5N1)

Every reported suspected or probable human case of avian influenza A (H5N1) must be investigated by oblast SES specialists in cooperation with a local SES epidemiologist, Regional Influenza Center (RIC) experts, and facility health care workers within 24 hours of notification. Additional team members should include Ministry of Emergency Situations (MoES) experts, veterinarians, and others. The size and composition of the team should depend on the size and complexity of the anticipated investigation.

Appropriate PPE should be worn when in contact with symptomatic persons or when entering agricultural premises known to be infected.

Investigation of human cases of influenza A (H5N1) is essential to achieving the following objectives:

- Confirmation of the diagnosis of recent infection with influenza A (H5N1).
- Reduction of morbidity and mortality through rapid identification and isolation of cases.
- Follow-up with contacts and institutions regarding appropriate precautions, treatment, and clinical management.
- Reduction of further spread by identification of potential human, animal, and/or environmental sources of exposure, risk factors for infection, and implementation of appropriate prevention and control measures, including stamping out vulnerable flocks, performing environmental decontamination, and conducting communication and social mobilization activities.
- Determination of whether the risk for pandemic influenza has increased as evidenced by increased efficiency of human-to-human transmission.
- Determination of key epidemiological, clinical, and virological characteristics for cases.
- Timely exchange of information among clinicians, investigators of public and animal health, and government officials to facilitate critical and informed decision-making at all levels.

The following steps are required in an investigation:

1. Collect data according to the *Suspected or Probable Human Case of Avian Influenza A (H5N1)*

Investigation Card (Figure 5) by reviewing medical records and interviewing health care personnel and the patient as needed.

The collected data should be verified against the information found in the health facility's infectious disease register #60 and SES register #60. All newly identified cases resulting from the investigation should be recorded in these registers as well. Facilities should continue filling out the investigation cards for all clinical (probable) cases identified.

2. Verify that all cases meet the suspected or probable influenza A (H5N1) case definition.

If a case does not meet the definition, the investigation team should discuss the case with the physician(s). Any case meeting the H5N1 trigger criteria must have a laboratory specimen collected and submitted for influenza A (H5N1) testing. A case that is incompatible with the clinical and epidemiological description and is not confirmed by specific laboratory tests will be eliminated from epidemiological surveillance reporting.

FIGURE 5. Suspected or Probable Human Case of Avian Influenza A (H5N1) Investigation Card

Facility number and date: _____ Epidemiological registration number: _____
 Autonomous republic/region: _____ Rayon: _____

Case identification	Full name of patient:		
	Date of birth:	Day/ / Month/ / Year/ /	
	Address/telephone:		
	Occupation/place of study:		
Case detection and notification history	Date and facility at which the patient presented for the first time:	Day/ / Month/ / Year/ /	Health facility name:
	Date case was reported to SES:	Day/ / Month/ / Year/ /	
	Date case investigation started:	Day/ / Month/ / Year/ /	
	Date and place:	Day/ / Month/ / Year/ /	Hospital 1 name: Hospital 2 name:
Hospitalization	Date of disease onset:	Day/ / Month/ / Year/ /	
	Symptoms (indicate date of onset for each symptom, if known):	Fever $\geq 38^{\circ}\text{C}$?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
		Shortness of breath?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
		Cough?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
		Sore throat?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
		Rhinitis?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
		General weakness?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
		Conjunctivitis?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
		Muscle/joint aches?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
		Diarrhea?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
Pulmonary infiltrates on a radiogram?		<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	
Outcome:	<input type="radio"/> Alive <input type="radio"/> Dead <input type="radio"/> Unknown	If dead, date of death: Day/ / Month/ / Year/ /	
Prophylaxis against influenza	Was patient vaccinated against seasonal influenza in the last 6 months?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	
	Was the patient taking any antiviral influenza medications during the 7 days prior to symptom onset?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	If yes, name of antiviral: _____ Received at facility: _____ Start date: Day/ / Month/ / Year/ /

Exposure history During the 7 days prior to the onset of symptoms, has the patient:	Been in close contact with a person who is a suspected, probable, or confirmed case of avian influenza A/H5N1?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	If yes, give dates and other details:
	Been in close contact with a person who died from ARI who is considered to be epidemiologically linked to a probable or confirmed case of avian influenza A/H5N1?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	If yes, give dates and other details:
	Handled samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	If yes, give details (location, type, frequency, duration of exposure):
	Been exposed to poultry or wild birds or their remains (e.g., handling, slaughtering, defeathering, butchering, or preparing for consumption) or to environments contaminated by their feces in an area where H5N1 infection in animals or humans has occurred in the last month?	Domestic poultry? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown Specify type: _____ Wild birds? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown Specify type: _____	If yes, location: _____ Date: _____ Duration (hours, days): _____ Sick or dead: _____
	Consumed raw or undercooked poultry products in an area where H5N1 infection in animals or humans has been suspected or confirmed in the last month?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	
	Been in close contact with a confirmed H5N1-infected animal other than poultry or wild birds (e.g., cat or pig)?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	
	If exposed, was he/she wearing PPE?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown Specify: <input type="radio"/> Respirator <input type="radio"/> Mask <input type="radio"/> Gloves <input type="radio"/> Gown <input type="radio"/> Eyewear	
Laboratory testing	Date of sample collection: Shipped to: _____ Specimen number: _____	Day/ / Month/ / Year/ / <input type="radio"/> Nasopharyngeal swab <input type="radio"/> Oropharyngeal swab <input type="radio"/> Serum <input type="radio"/> Nasopharyngeal wash/aspirate <input type="radio"/> Other: _____	
Classification	Final case classification:	<input type="radio"/> Suspected H5N1 case <input type="radio"/> Probable H5N1 case <input type="radio"/> Confirmed H5N1 case <input type="radio"/> Discarded	

This form should be promptly sent to the regional SES and the NIC.

Responsible person: _____ Telephone: _____ Signature: _____

3. Identify the potential source of infection by analyzing exposure history of the case 7 days prior to the onset of symptoms.

Inquire about possible exposure to sick/dead birds, animals, people, or a contaminated environment. Examine the house and its surroundings for evidence of domestic poultry. Use the case investigation form (Figure 5).

4. Collect specimens for laboratory investigation.

Laboratory testing is currently mandated for confirmation of every case meeting influenza A (H5N1) trigger criteria, including suspected or probable cases of influenza A (H5N1) and symptomatic contacts of suspected or probable cases.

Samples should be collected by specially trained professionals—members of a case investigation/rapid response team. All activities should be carried out following standard biosafety guidelines—in particular, using full PPE, including a respirator mask, gown, gloves, and eye protection. (Annex 1 provides instructions for specimen collection, storage, and transport.)

The use of available rapid diagnostic tests for the detection of human influenza A (H5N1) infections is not recommended for surveillance purposes, although these tests may be useful in making rapid treatment decisions or confirming an outbreak if many persons are tested. The diagnostic accuracy of available rapid tests for human influenza A (H5N1) infections is unknown; if the test result is positive, differentiation between influenza A subtypes is not possible, and confirmatory tests must be done.

5. Assess potential for transmission and identify contacts.

The potential for transmission is usually determined by the number of susceptible contacts. At the present time, the risk to humans is believed to generally be low because avian influenza viruses usually do not cross the species barrier. If sporadic cases and clusters of human-to-human transmission are detected, this may indicate that the virus is adapting to humans and signal the need to intensify pandemic-preparedness measures, including improving the capacity to contain cases.

The investigation team should identify all close contacts of suspected, probable, or confirmed human influenza A (H5N1) cases during their infectious period (1 day before through 14 days after the onset of symptoms) and follow up with them promptly.

6. Search for additional cases.

An active search should be conducted to determine if additional cases exist. The search can be performed by identifying areas and populations of likely risk (i.e., people exposed to or closely associated in time and place with the same animal or human source of infection) and visiting those places to determine if anyone else near the potential source of infection has developed signs or symptoms of febrile respiratory infection. The search team should focus on health facilities and community settings. See Chapter 7, Section D, for more information.

7. Analyze outbreak data in the case of a cluster of probable or confirmed human cases.

Following detection of a cluster of probable or confirmed cases, epidemiological data should be analyzed to characterize patients by person, place, and time. More specifically, the analysis should include a description of the illness in terms of clinical presentation, demographic information, and occupational data; the proportion of cases requiring hospitalization and resulting in death; clinical outcomes and case-fatality ratio; estimated incubation period; and a description of disease transmission patterns and mechanisms.

Close contact with a human case is defined as:

- Having intimate contact (within 1 meter).
- Living in the same household.
- Providing care.
- Having direct contact with respiratory secretions, body fluids, or excretions.

Within 7 days of symptom onset.

One of the investigation's most critical objectives is to determine whether there is evidence of an increase in the virus' ability to cause human disease and spread with improved efficiency. Examples of situations that might indicate a change in the transmission pattern of influenza A (H5N1) include:

- Sharp increase in the number of confirmed/possible influenza A (H5N1) cases despite adequate control measures in the animal population.
- Absence of exposure to birds or animals among confirmed/probable influenza A (H5N1) cases.
- Clustering of cases with evidence of two or more generations or chains of transmission.
- Increase in cluster frequency, size, duration, or spread within a specific area.
- Changes in epidemiological characteristics (e.g., age distribution, severity of disease).

Detection of two or more cases of confirmed, probable, or suspected influenza A (H5N1) infection that have onset of illness within the same two-week period, are in the same geographical area, and/or are epidemiologically linked requires careful and detailed investigation to assess whether transmission was likely due to a common source of exposure or to human-to-human transmission.

8. Implement control and prevention measures in partnership with the rayon avian influenza response commission and rayon veterinary authorities. (See Chapters 9 and 10.)

9. Document the findings in a report for the MoH (NIC). The report should include:

- The *Suspected or Probable Human Case of Avian Influenza A (H5N1) Investigation Card* (Figure 5) completed for each case.
- An analysis of epidemiological and clinical data and a description of the control and prevention measures taken and their effectiveness.

8. Preparedness and Organization of Response at the Rayon Level

The epidemic response commission undertakes planning and coordination of response activities at the rayon level. The recommended composition of the commission is as follows:

- Head of local administration.
- SES (chief doctor and epidemiologists).
- Health administration.
- Rayon veterinary service and agricultural department.
- Rayon hospital and polyclinic ambulatory unit.
- Nongovernmental organizations and private-sector entities.
- Representatives of the MoES and the militia.
- Representatives of other agencies (e.g., managers of industrial and agricultural enterprises, heads of communal services).

Representatives of the commission should meet as needed to do the following:

- Review the latest human and animal avian influenza surveillance data and the latest pandemic-preparedness directives and materials.
- Review the functioning of the early warning system for humans and identify deficiencies and measures to correct them. This involves ensuring ease and openness of trigger reporting and broad-based clinician sensitization of trigger criteria and reporting mechanisms.
- Review and update the inventory of supplies needed for disease response (including antiviral drugs for treatment and chemoprophylaxis, antibiotics, antipyretics and other medicines, PPE, specimen-collection equipment, cold-chain storage, and transport material) based on the burden assessment. Ensure they are ready for use.
- Review other resources (e.g., personnel, transportation, communications) and identify materials and training needs.
- Determine concrete roles and responsibilities of different services/agencies for response actions.
- Assign clear responsibilities to individuals and units for specific response activities.

In the event of a probable or confirmed case(s) of influenza A (H5N1) in humans or animals, the commission representatives should start planning and implementing response measures. Based on the scope of the problem, central- and/or regional-level involvement should be considered. Financial resources at a certain minimum level should be secured at all times to support investigation and control activities as well as to ensure that there is a safe minimum stock of medicines and supplies.

9. Initial Human Case of Avian Influenza A (H5N1) Control/Response Measures

Control measures are aimed at reducing opportunities for further transmission. They should be initiated immediately upon the case investigation and should not await laboratory confirmation of the causative agent.

1. If an animal source is confirmed, quickly and safely control the infection in birds.

The key to reducing human exposure is control of the virus in birds. Veterinary services must ensure immediate destruction of all infected or exposed poultry, including quarantining and rigorously disinfecting farms to limit avian influenza spread and to reduce opportunities for human exposure.

2. Hospitalize the patient(s) to ensure adequate treatment, laboratory specimen collection, and enforcement of infection-control measures. If a lack of resources precludes hospitalization, ensure that treatment and follow-up will occur at home and that adequate precautions can be taken to prevent the potential spread of infection.

The routine care of patients meeting these criteria should include infection-control precautions described in the next chapter.

3. Ensure that personnel transporting and providing care to suspected, probable, or confirmed cases wear—and are instructed and trained in how to wear—the following PPE:

A **medical mask** that fits well. Masks should fit snugly over the nose and mouth, fully cover the nose and mouth, and prevent fluid penetration. For this reason, masks that have a flexible nose piece and can be secured to the head with string ties or elastic are preferred. In addition, personnel should:

- Wear masks once and then discard them.
- Change masks when they become moist.
- Do not leave masks dangling around the neck.
- Wash hands after touching or discarding a used mask.

If aerosol-generating procedures are performed, PPE should include a particulate respirator instead of a medical mask.

Clean gloves. Most patient-care activities require the use of a single pair of non sterile gloves made of latex, nitrile, or vinyl. Gloves should fit the user's hands comfortably; they should not be too loose or too tight. They also should not tear or damage easily.

A **long-sleeved (preferably fluid-resistant) gown**, if direct contact with the patient or infected poultry is anticipated. If a water-resistant gown is not available, a waterproof apron should be worn over the gown, particularly if splashing of potentially infectious material is anticipated. There are three factors that influence the selection of a gown or apron as PPE:

- First is the purpose of use. Isolation gowns are generally the preferred PPE for clothing, but aprons occasionally are used where limited contamination is anticipated. If contamination of the arms is anticipated, a gown should be selected. Gowns should fully cover the torso, fit comfortably over the body, and have long sleeves that fit snugly at the wrist.
- Second are the material properties of the gown. Isolation gowns are made either of cotton or a spun synthetic material that dictates whether they can be laundered and reused or must be disposed. Cotton and spun-synthetic isolation gowns vary in their degree of fluid resistance, which also must be considered in the selection of this garment. If fluid penetration is likely, a fluid-resistant gown should be used.
- The last factor is whether a clean, rather than sterile, gown can be used. Clean gowns are generally used for isolation. Sterile gowns are only necessary for performing invasive procedures, such as inserting a central line. In such cases, a sterile gown would serve purposes of both patient and health care worker protection.

Protective eyewear (face shield or goggles), if close contact (less than 1 meter) with the patient is anticipated. Personnel should clean and disinfect reusable equipment after each use.

Goggles provide barrier protection for the eyes; personal prescription eyeglasses do not provide optimal eye protection and should not be used as a substitute for goggles. Goggles should fit snugly over and around the eyes or eyeglasses. Goggles with anti-fog features will help maintain clarity of vision. When skin protection is needed or desired in addition to mouth, nose, and eye protection—for example, when irrigating a wound or suctioning copious secretions—a face shield can be used as a substitute to a mask or goggles. The face shield should cover the forehead, extend below the chin, and wrap around the sides of the face.

PPE donning procedures

1. Collect all equipment needed.
2. Wash hands with an alcohol-based hand rub (preferably) or soap and water.
3. Put on PPE in the following order:
 - Fluid-resistant gown.
 - Mask or respirator. Perform user seal-check of particulate respirator.
 - Hair cover (if used, for example, during an aerosol-generating procedure).
 - Face shield or goggles.
 - Gloves. (Make sure gloves cover cuff of gown sleeves.)

PPE removal procedures

1. Remove PPE, preferably in a separate room, making sure that neither the environment nor other persons can become contaminated.
 - Remove gloves.
 - Remove face shield.
 - Remove gown and discard in rubbish bin.
 - Wash hands with an alcohol-based hand rub (preferably) or soap and water.
 - Remove mask or particulate respirator by grasping elastic bands; do not touch front of particulate respirator (front of particulate respirator may be contaminated). Discard in rubbish bin.
2. Single-use items must be discarded in rubbish bin. Reusable items must be placed in a container for decontamination.
3. Wash hands with an alcohol-based hand rub (preferably) or soap and water.

4. Minimize the number of people exposed. Separate people from known or potential sources of avian influenza virus in animals or humans.

First, advise health care professionals dealing with influenza A (H5N1)-infected patients on **infection-control measures to minimize the risk of nosocomial transmission** (Chapter 10).

Next, conduct public-awareness campaigns and deliver appropriate **health education messages to the public** (Annex 2).

Carry out **disinfection** using household disinfection products to reduce transmission from infectious respiratory secretions on surfaces and via objects such as clothing, towels, bed linens, and utensils that could harbor the virus and are capable of transmitting it. **Disinfect areas where infected poultry are kept** (Chapter 10 and Annex 2).

If influenza A (H5N1) infection is confirmed in humans or animals, it may be prudent to restrict local movement of people in and out of the affected area, both to reduce the number of people exposed and to lower the risk of extending infection among animals.

5. Conduct targeted prophylaxis* of close contacts with antiviral medications according to the risk stratification described in Table 5.

TABLE 5. Risk Stratification for Targeted Prophylaxis

EXPOSURE GROUP		TAMIFLU (OSELTAMIVIR) OR RELENZA (ZANAMIVIR)
High risk	Household or close family contacts of a probable or confirmed H5N1 case.	This recommendation places a high value on preventing an illness with high case fatality and a low value on adverse effects, development of resistance, and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure. The dose should be that used in seasonal influenza. This recommendation also applies to pregnant women in the high-risk exposure group.
Moderate risk	<p>Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal) if PPE may not have been used properly.</p> <p>Individuals with unprotected and very close direct exposure to sick or dead animals infected with the H5N1 virus or to particular birds that have been directly implicated in human cases.</p> <p>Health care personnel in close contact with probable or confirmed H5N1 patients (for example, while performing intubation or tracheal suctioning, delivering nebulized drugs, or handling inadequately screened/sealed body fluids without sufficient PPE). This group also includes laboratory personnel who might have had unprotected exposure to virus-containing samples.</p>	<p>Should be administered as chemoprophylaxis continuing for 7–10 days after the last known exposure.</p> <p>Might be administered as chemoprophylaxis, continuing for 7–10 days after the last known exposure.</p> <p>The bioavailability of zanamivir outside the respiratory tract is lower than that of oseltamivir. Zanamivir may be active against some strains of oseltamivir-resistant H5N1 virus. Consequently, it may be a reasonable choice for health care workers with a high-risk exposure to an oseltamivir-treated H5N1 patient.</p>
Low risk	<p>Health care workers not in close contact (distance greater than 1 meter) with a probable or confirmed H5N1 patient and having no direct contact with infectious material from that patient.</p> <p>Health care workers who used appropriate PPE during exposure to H5N1 patients.</p> <p>Personnel involved in culling non-infected or likely non-infected animal populations as a control measure.</p> <p>Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal) who used proper PPE.</p>	<p>Should NOT be administered for chemoprophylaxis.</p> <p>This recommendation places a high value on avoiding adverse effects, potential development of resistance, and cost. It places a lower value on preventing the low risk of H5N1 disease.</p>

*Possible funding sources: local budgets, funds of companies and individuals, other sources permitted by law.

6. Initiate enhanced surveillance: actively search for and establish monitoring of symptom onset in people potentially exposed to influenza A (H5N1) infection for 7 days after the last contact (Figure 4).

These people include:

- Persons who have had close contact with a suspected, probable, or confirmed case.
- Persons who could potentially have been exposed to the same source of infection as the patient (e.g., infected poultry, poultry products, or potentially infected environments).

If the number of contacts/potentially exposed people is large, brigades consisting of two or three health care workers should be mobilized as needed. Follow-up should be prioritized based on:

- Increased probability of infection, such as contact with a laboratory-confirmed case.
- Duration and closeness of contact.
- A high-risk (e.g., unprotected) exposure.

Enhanced surveillance should consider the health care-seeking behavior of the population and may include such measures as:

- Active surveillance in hospitals, particularly targeting inpatient and emergency departments.
- Active surveillance of groups that may be at higher occupational risk of exposure (e.g., health care workers or persons in contact with live or dead birds/animals).
- Active surveillance among family members and close contacts of suspected cases.
- Active surveillance in the general community in affected areas (e.g., door-to-door or use of public service announcements).
- Initiation of targeted ILI and SARI surveillance in the community where the outbreak exists.

If possible, other resources—such as private practitioners, private laboratories, or medical students—should be engaged. Sensitization of practitioners is a cornerstone of a population-based early warning system. A toll-free reporting hotline should be strongly considered.

The duration of enhanced surveillance activities will need to be assessed for each investigation. Typically, however, it would be expected to be undertaken for a minimum of 2 weeks (i.e., two incubation periods) after the last human case is identified. It will be necessary to maintain enhanced surveillance in areas where human cases have occurred until influenza A (H5N1) outbreaks are controlled in poultry.

Febrile close contacts should be referred for collection of specimens for laboratory testing and appropriate medical care, including antiviral therapy. Depending on the severity of illness and the availability of hospital beds, contacts who are ill may be isolated at a health facility or at home while awaiting test results.

Asymptomatic contacts/potentially exposed people should be informed of the signs and symptoms of the illness and the need to immediately report the onset of fever to the health facility. The chief of the health facility should ensure medical supervision of potentially exposed people daily (for 7 days after the last exposure) to ascertain their clinical status and appropriately refer contacts who show symptoms. Voluntary quarantine of exposed persons may be necessary if exposure to influenza A (H5N1) is strongly suspected. In such a situation, the quarantine would last for 7 days after the last exposure. Persons in home quarantine may need to be provided with food, access to communications, psychological support, and supplies of their usual medications, especially for any acute or chronic conditions.

Antiviral chemoprophylaxis should be initiated as specified above.

7. Targeted vaccination with normal seasonal influenza vaccine of selected population groups.

Targeted vaccination with the current seasonal influenza vaccine is now recommended as one of several measures for reducing opportunities for the simultaneous infection of humans with avian and human influenza viruses.

Minimizing the opportunities for dual infections reduces the chance for viral reassortment and for the emergence of a novel influenza virus with pandemic potential.⁶

In addition to the main target groups, the following populations should be considered for current seasonal influenza vaccination:⁷

1. All persons who could have been in contact with poultry or work on poultry farms potentially affected by HPAI and personnel of the poultry handling/processing industry.
2. Hunters, zoo workers, or vendors in live-animal markets.
3. Health care workers involved in the daily care of human cases of influenza A (H5N1).
4. Health care workers in emergency care facilities in areas where there is confirmed occurrence of HPAI in birds.
5. Personnel of the MoES and veterinary medicine.

These vaccinations should be undertaken as part of any existing seasonal influenza vaccination campaign. See Annex 3 for detailed recommendations on seasonal influenza immunization.

Additional Exceptional Response Measures if Sustained Human-to-Human Transmission Is Highly Probable or Confirmed

8. Implement “social distancing” measures as needed.

- Close schools and workplaces.
- Cancel mass gatherings and public transportation.
- If the MoH decides to establish a “containment zone” around the index cluster, clearly mark the perimeter of the zone with signs and discourage all non-essential movement of persons in and out of the containment zone to the extent possible. Establish clear entry and exit points, and communicate them to the local population. Put screening procedures in place at these points to reduce the spread of pandemic influenza outside the containment zone.

These measures are socially disruptive and may cause considerable discomfort in the affected population.

9. Mass antiviral prophylaxis.

If a containment zone is established, the global WHO antiviral stockpile as well as regional and national stockpiles of antiviral drugs will be accessed, and all persons in the zone who are not ill with influenza will be given 20 days of antiviral prophylaxis.

If a vaccine that protects against the newly identified pandemic virus is available (which is possible if the pandemic virus is identified as H5N1 and if that stockpile is available to the country through WHO for this purpose), then such vaccine may be used to supplement antiviral prophylaxis within the zone.

⁶This vaccine does not protect against infection with bird flu. This fact must be understood by those exposed so that they are still aware of the need for general protective measures.

⁷Vaccination should be performed in advance of any outbreak. Vaccines will not produce immunogenicity in recipients quickly enough to be effective during an outbreak.

10. Intensify active surveillance in the containment zone and laboratory testing of all possible cases.

This is critical for:

- Allowing such cases to be laboratory-confirmed or excluded as cases of pandemic influenza.
- Monitoring the evolution of the outbreak.
- Evaluating the effectiveness of the containment operation.
- Helping guide decisions to modify, continue, or end the containment operation.

Household and other close contacts should be traced and placed in voluntary home quarantine while laboratory testing is pending for the possible case.

10. Influenza A (H5N1) Infection-Control Recommendations for Health Facilities

The recommended infection-control precautions should be implemented when the patient is infectious—that is, **for 14 days after the onset of symptoms**.

Standard Precautions

- Wash hands with soap and water (using a single-use towel for drying hands) or an alcohol-based hand rub before and after patient contact, after removing PPE, and after using the restroom.
- Use PPE based on risk assessment. Avoid contact with blood, body fluids, excretions, and secretions.
- Prevent needlestick/sharps injuries.

Respiratory Etiquette

Persons with respiratory illness should be educated to:

- Cover the mouth and nose with a tissue when coughing and dispose of used tissues in waste containers.
- Use a mask when coughing (when a mask can be tolerated).
- Wash hands with soap and water after contact with respiratory secretions.
- Stand or sit at least 1 meter from other persons, if possible.

Isolation Precautions

Barrier precautions

All individuals providing care for patients with probable or confirmed avian influenza infection should use PPE as specified in Chapter 9.

Patient placement

- Patients should be placed in single rooms or, if rooms are unavailable, placed in rooms with other patients with the same infection. If single rooms or cohorting is not possible, then patients should be separated by at least 1 m with a privacy curtain placed in between patients to minimize the risk of close contact.
- Doors should be kept closed when not being used for entry/exit. Isolation rooms should have their own hand-washing sink, toilet, and bath facilities when possible.
- Laboratory-confirmed cases should not be mixed with suspected or probable cases.

Room preparation

- Ensure appropriate signage on the door.
- Place a recording sheet at the entrance. All health care workers and visitors should provide their names so that follow-up/contact tracing is possible if necessary.
- Use only essential furniture that is easy to clean.
- Stock linens as needed outside the isolation room.
- Place appropriate waste bags in a foot-operated bin.
- Place a puncture-proof container for sharps inside the isolation room.
- Dedicate non-critical patient equipment (e.g., stethoscope, thermometer, sphygmomanometer) to the patient. Any patient-care equipment that is required for use by other patients should be thoroughly cleaned and disinfected prior to use.
- Set up a trolley outside the door to hold PPE.
- Place an appropriate container with a lid outside the door for equipment that requires disinfection and sterilization.
- Keep adequate equipment required for cleaning and disinfection inside the patient's room and ensure scrupulous daily cleaning of the isolation room.
- Recommend setting up a telephone (e.g., mobile telephone) in the patient's room to enable the patient or family member/visitor to communicate with health care workers to minimize the necessity for health care workers to enter the room.

Family Member/Visitor Recommendations

Visitors should be strictly limited to those needed for the patient's well-being and care. They should be advised about the possible risk of viral transmission. Visitors should be provided PPE and instructed in their use and hand-washing practices prior to entering the patient's room.

Patient Transport Within the Health Facility

- Limit the patient's movement from the isolation room for essential purposes only and notify the receiving area as soon as possible prior to the patient's arrival, informing them of the diagnosis and precautions.
- Ensure that the patient wears a surgical mask (if tolerated) during transport.
- If there is patient contact with surfaces, clean and disinfect these surfaces afterward.

Pre-Hospital Care and Transport Outside Health Facilities

- Place a surgical mask on the patient (if tolerated). If a mask is not available, have the patient cover his or her mouth and nose with a tissue when coughing.
- Ensure that health care workers use full barrier precautions as indicated above.
- When possible, use vehicles that have separate driver and patient compartments. Optimize the vehicle's ventilation to increase the volume of air exchange during transport.
- Notify the receiving facility as soon as possible prior to arrival, informing them of the suspected diagnosis and precautions.
- Follow recommended procedures for disposing of waste and disinfecting the vehicle and reusable patient care equipment.

Waste Disposal

Use standard precautions when working with potentially infectious solid waste outside of the isolation room.

Clinical (infectious) waste includes waste directly associated with blood, body fluids, secretions, and excretions; laboratory waste that is directly associated with specimen processing, human tissue, blood, animal tissue, or carcasses; and discarded sharps.

- All generated waste should be removed from the isolation room in bags or containers that do not allow for spillage or leakage. Later, the waste should be treated as infectious waste.
- When transporting waste, use gloves followed by hand washing.
- Liquid waste—such as urine or feces—can be flushed into the sewage system if there is an adequate sewage system in place. Close the toilet cover when flushing feces.

Dishes and Eating Utensils

- Recommend the use of disposable dishes and utensils.
- Reusable items should be washed and disinfected after use with a detergent and hot water using rubber gloves. A dishwasher with detergent at the recommended water temperature can be used as well.
- If family members are caring for the patient, they should designate dishes and eating utensils for the patient's use only.
- After disinfection, disposable items should be discarded with other general waste.

Linens and Laundry

- Place soiled linens directly in a plastic laundry bag in the isolation room. Heavily soiled linens should be folded to contain the heaviest soil in the center of the bundle.
- Mattresses must have protective covers.
- Linens contaminated with biological fluids should be collected in a separate plastic bag for subsequent disinfection and washing.
- Large amounts of solid material (e.g., feces) should be removed from the linens with a gloved hand and toilet tissue and then placed in the toilet for disposal before the linens are placed in the laundry bag.
- When transporting soiled linens, use gloves followed by hand washing.
- Disinfect, wash, and dry linens according to routine facility standards and procedures.

Environmental Cleaning and Disinfection

- Cleaning must precede disinfection.
- Patient rooms should be cleaned at least daily and terminally cleaned upon discharge. Disinfection should be performed using preparations registered in Ukraine following the manufacturer's recommendations.

Patient Care Equipment

- If possible, place contaminated patient-care equipment in suitable bags before removing it from the isolation room.
- When transporting contaminated equipment, use gloves followed by hand washing. Equipment should be disinfected in specially designated premises.

Patient Discharge

- Perform terminal cleaning of the patient's room.

Care of the Deceased

- Use recommended PPE and standard precautions for routine care of the body and hygienic preparation of the deceased.
- The body should be fully sealed in an impregnable body bag prior to removal from the isolation room. No leaking should occur, and the outside of the bag should be kept clean.
- Transfer of the body to pathology or the mortuary should occur as soon as possible after death. If an autopsy is considered, the body should be held under refrigeration in the mortuary.
- The body can be safely removed from the body bag for storage in the mortuary or placed in a coffin for burial.
- If the patient's family wishes to touch the body, they may be allowed to do so. If the patient died during the infectious period, the family should wear gloves and gowns and follow contact with hand washing.
- If family members want to kiss the dead body (e.g., the hands or face), these body parts should be disinfected using a common antiseptic (e.g., 70 percent alcohol). If the family wants only to view the body, there is no need to wear any PPE.
- Traditional ceremonies should be avoided, if possible, during a confirmed outbreak or for a suspected human H5N1 case. Cremation is the safest method.
- Traditional and religious issues must be addressed and discussed with religious authorities as appropriate.

Annex 1

Guidelines for Collecting, Storing, and Transporting Specimens for Influenza Diagnostics⁸

Procedures for Specimen Collection for Sentinel-Site Surveillance

Materials Required

- Sputum/mucus trap
- Polyester fiber-tipped swab
- Plastic vials
- Tongue depressor
- 15-mL conical centrifuge tubes
- Specimen collection cup or Petri dishes
- Transfer pipettes
- Viral transport medium (VTM)

Viral Transportation Medium for Use in Collecting Throat and Nasal Swabs

1. Add 10 g of veal infusion broth and 2 g of bovine albumin fraction V to sterile distilled water (to make a total volume of 400 mL).
2. Add 0.8 mL of gentamicin sulfate solution (50 mg/mL) and 3.2 mL of amphotericin B (250 µg/mL).
3. Sterilize by filtration using a disposable membrane filter with pore diameter of 0.2 µm.

Collection Methods

Clinical specimens should be collected as described below and added to transport medium. Nasal, nasopharyngeal, and throat swabs can be combined in the same vial of VTM. The following information should be recorded on the field-data collection form: general patient information, type of specimen(s), date of collection, and contact information of person completing the form. Standard precautions should always be followed, and personal protective equipment (PPE) should be applied during sampling. For sentinel site surveillance, nasopharyngeal swabs, nasopharyngeal aspirates, nasal washes, or nasal swabs are the best specimens to collect.

⁸A significant portion of this section is based on WHO's *Collecting, Preserving, and Shipping Specimens for the Diagnosis of Avian Influenza A (H5N1) Virus Infection: Guide for Field Operations* (2006).

Nasal swab

A dry polyester swab is inserted into the nostril, parallel to the palate, and left in place for a few seconds. It is then slowly withdrawn with a rotating motion. Specimens from both nostrils are obtained with the same swab. The tip of the swab is put into a plastic vial containing 2 to 3 mL of VTM, and the applicator stick is broken off.

Nasopharyngeal swab

A flexible, fine-shafted polyester swab is inserted via the nostril into the nasopharynx and left in place for a few seconds. It is then slowly withdrawn with a rotating motion. A second swab should be used for the second nostril. The tip of the swab is put into a vial containing 2 to 3 mL of VTM, and the shaft is cut.

Nasopharyngeal aspirate

Nasopharyngeal secretions are aspirated through a catheter connected to a mucus trap and fitted to a vacuum source. The catheter is inserted into the nostril parallel to the palate. The vacuum is applied, and the catheter is slowly withdrawn with a rotating motion. Mucus from the other nostril is collected with the same catheter in a similar manner. After mucus has been collected from both nostrils, the catheter is flushed with 3 mL of transport medium.

Nasal wash

The patient sits in a comfortable position with the head slightly tilted backward and is advised to keep the pharynx closed by saying "K" while the washing fluid (usually 0.9 percent sterile saline) is applied to the nostril. With a transfer pipette, 1 to 1.5 mL of washing fluid is placed into one nostril at a time. The patient then tilts the head forward and lets the washing fluid flow into a specimen cup or a Petri dish. The process is repeated with alternate nostrils until a total of 10 to 15 mL of washing fluid has been used. Approximately 3 mL of washing fluid should be diluted 1:2 in transport medium.

Throat swab

The tongue is depressed with a tongue depressor. Under visual observation, the tonsillar and posterior-pharyngeal area is vigorously swabbed. The swab is placed in transport medium as described for nasal swabs.

Procedures for Specimen Collection for Sentinel Site H5N1 Testing

For each type of specimen, two specimens should be taken in separate specimen tubes on each occasion. One can be used for immediate analysis and the other retained for reference purposes, such as retesting.

Each patient sample should be accompanied by an appropriate laboratory notification form containing a unique identifier (such as the patient's first and last names and age). Specimen tubes should also be marked with information about the type of specimen in the tube and the date on which the specimen was taken.

Specimens That Should Be Collected From Suspected Cases

Preferred samples

- **Upper respiratory tract.** Take both types of specimens to allow for detection of influenza A (H5N1) and other influenza viruses:
 - Posterior-pharyngeal (throat) swabs are currently the highest-yield upper respiratory tract specimen for detecting influenza A (H5N1). (This is not the case with human influenza.) Nasopharyngeal swabs may be collected as well (see below).
 - Nasal swabs with nasal secretions (from the anterior turbinate area) or nasopharyngeal aspirates or swabs are appropriate specimens for detecting human influenza A and B.
- **Lower respiratory tract.** If the patient is intubated, take a tracheal aspirate or collect a sample during bronchoalveolar lavage.
- **Blood.** For serum, obtain acute and convalescent specimens, if possible.
- **Secondary specimens.** These are not essential but can be useful if materials are available.
 - Plasma in ethylenediaminetetraacetic acid (EDTA) for detection of viral ribonucleic acid (RNA).
 - Rectal swab—especially if the patient has diarrhea.
 - Spinal fluid, if meningitis is suspected and a spinal tap is to be performed for diagnostic/therapeutic purposes.

When to Collect the Specimens From Suspected Cases

- **A throat swab should be taken (if possible) within 3 days of symptom onset.** Note that the virus is generally detectable in throat swabs from most patients from the onset of symptoms (or even just before) until the end of the second week and, infrequently, the beginning of the third week. Cases whose initial specimens are negative for influenza A (H5N1) but continue to show symptoms suggestive of this type of infection (or who have a history of exposure that supports the diagnosis) should be sampled again, at least once, as soon as possible.
- Virus may be detectable **in tracheal aspirates** from the onset of lower respiratory complaints (e.g., dyspnea, difficulty breathing, marked cough) or pneumonia **until the second or third week of illness.**
- **An acute-phase serum sample** should be taken **7 or fewer days after symptom onset.** This will usually be done when the patient presents and begins treatment. A convalescent sample should be taken after 3 to 4 weeks. Note that the limited available data on antibody kinetics indicate a development of positivity (initially enzyme-linked immunosorbent assay [ELISA] and not necessarily neutralizing antibody) from day 10 onward.
- **Single serum samples** should be collected at **day 14 or later** after symptom onset, since the likelihood of detecting neutralizing antibodies increases over time, especially during the first 3 to 4 weeks after onset of symptoms.
- **Blood serum or plasma** for the detection of viral RNA should be taken **during the first 7 to 9 days** after the development of symptoms because the patient is most likely to have detectable RNA in the bloodstream at that time.
- Ideally, initial specimens (respiratory and blood) should be collected from suspected patients before antiviral therapy is begun—but treatment must not be delayed in order to take specimens. (Note that standard treatment may render throat swabs negative for virus after 3 or more days of treatment but probably has no effect on the development of neutralizing antibody.)
- Specimens should be collected from deceased patients as soon as possible after death.

Sampling Human Contacts

Taking single respiratory tract or blood specimens from contacts of human cases who remain healthy in the days immediately after potential contact with influenza A (H5N1) is unlikely to yield useful results. Individuals who have had contact with human cases or exposure to sick animals should be observed (including their daily temperature) for 7 days after the last contact. If they become ill with an ILI, they should be sampled as outlined above. Blood specimens for serological studies can be taken from contacts for several reasons:

- As a tool for searching for asymptomatic/subclinical cases.
- For studies of the prevalence of influenza A (H5N1) infection.
- To assess possible susceptibility to influenza A (H5N1) infection.

Obtaining Specimens From the Respiratory Tract

Sampling from the respiratory tract is hazardous, as the operator is very close to the patient, and the procedure can generate aerosols and droplets. Full PPE is therefore essential.

Chose a sitting position for adults and a supine position for infants and young children. Children may need to be restrained during the sampling process (see photo). It is generally best to avoid having the parent(s) in the room during the sampling procedure, since the sampling procedure can generate aerosols that could present a risk to others in the immediate vicinity.



When taking throat (or nasal) swabs, the swabs must be held correctly. They should be held between the thumb and the first and second fingers, with the shaft protruding beyond the web of the thumb (like a pencil), which ensures greater control (see photo). The swab should not be held between the thumb and forefinger with the base in the palm of the hand.

- Use only sterile dacron swabs with plastic shafts. Calcium alginate or cotton swabs or swabs with wooden sticks may contain substances that inactivate some viruses and inhibit polymerase chain reaction (PCR) testing. They should only be used if dacron swabs are not available.
- Prepare two vials containing at least 2 to 3 mL of a suitable transport/preservative medium (e.g., VTM) for each specimen. These should be marked with:
 - The unique identifier.
 - The specimen date.
 - The type of specimen in the tube (e.g., blood serum, throat swab).



Note: Always mark the tube itself—not the cap, which can get switched during handling—with identifying details. Use an indelible and alcohol-resistant marker. Be aware that stick-on labels can easily come off, especially when the specimen is chilled to very low temperatures. Relevant field data sheets should also be filled in.

- Take two specimens and put one into each vial.
- If VTM is not available, or if specimens cannot be stored at appropriate temperatures (e.g., no freezers are available), swabs can be stored and shipped in absolute (100 percent) ethanol. If pure ethanol cannot be used, 99 percent industrial methylated spirit—without additives other than methanol—may be substituted. Put 1 to 2 mL ethanol into a vial, and place the swab tip in the tube. Note that such specimens are suitable only for PCR.

- After a specimen is taken, the tip of the swab should be placed in the vial, and its shaft should be broken or cut off sufficiently short for the lid to be closed. Plastic swab handles usually have a weak point in them to allow them to be broken off in this manner. Others have a handle made of a brittle plastic that will snap easily.

If the shaft cannot easily be broken off short enough to be put into a small tube such as a Cryovial®, it will have to be cut. To do this:

- Cut the shaft with scissors, taking care not to touch the tip.
- Allow the tip to slide into the VTM and then cap the tube. Do not let cut portions of the bag or wrap fall into the tube.

Sterilize the cutting edge of the scissors by using a flame (e.g., by using a spirit burner, a Bunsen burner, or another suitable heat source). Allow the scissors to cool before reuse. If this procedure cannot be followed, agitate the swab tip in the medium for 30 seconds and squeeze it against the side of the tube before removing it from the medium and disposing of it in a safe manner (not suitable for ethanol storage).

Posterior-Pharyngeal and Nasopharyngeal Swabs

Posterior pharyngeal swabs are the best upper-respiratory tract specimens to take; evidence to date suggests that they are more likely to be positive than anterior nasal swabs in sporadic influenza A (H5N1) infection. However, if it is difficult to obtain the former (e.g., from babies and young children), nasopharyngeal swabs should be obtained instead.

Posterior-pharyngeal swab (throat swab)

- Hold the tongue out of the way with a tongue depressor.
- Use a sweeping motion to swab the posterior-pharyngeal wall and tonsillar pillars. Have the subject say “aahh” to elevate the uvula. Avoid swabbing the soft palate, and do not touch the tongue with the swab tip. (Note: This procedure can induce the gag reflex.)
- Put the swab into VTM.

Nasopharyngeal swab

- Insert a flexible, fine-shafted polyester swab into the nostril and back to the nasopharynx. The swab should be slid straight into the nostril, with the patient’s head held slightly back. The insertion technique should follow the base of the nostril toward the auditory pit. In adults, the swab will need to be inserted at least 5 or 6 cm to ensure that it reaches the posterior pharynx. (Do not use rigid shafted swabs for this sampling method—a flexible shafted swab is essential.)
- Leave the swab in place for a few seconds.
- Withdraw slowly with a rotating motion.
- Put the swab into VTM.
- A second swab should be used for the other nostril and put into a second tube. This can serve as the second sample from the patient.

Note: Nasopharyngeal sampling is an invasive process that can cause considerable distress to the patient.

Nasopharyngeal aspirate

The nasopharyngeal aspirate is easier and safer than swabbing in infants and young children.

- Use an aspiration trap.
- Insert a silicon catheter into the nostril toward the auditory pit and aspirate secretion gently by suction.

Blood Specimens

- Standard precautions should always be observed when taking and handling blood specimens because the patient may be infected with a blood-borne pathogen (for example, HIV or hepatitis B).
- Use PPE—at least gloves, plus face shields, masks, and gowns if splashing is anticipated.
- Remove and discard PPE items *immediately* after completion of task.
- Wash hands every time gloves are removed.

Serum is the best “all around” specimen to collect. Acute and convalescent sera are useful for detecting changes in antibody titer, and serum can be used for detecting viral RNA. An acute-phase serum specimen should be taken soon after onset of clinical symptoms and no later than 7 days after onset.

EDTA-anticoagulated plasma is also valuable for detecting viral RNA in blood and may be better than serum for this particular purpose, since EDTA inactivates RNA present in the specimen. Heparin is not suitable as an anticoagulant for this type of specimen because of its potential to inhibit PCR reactions.

Note that specimens for the detection of viral RNA in the blood should be collected during the first week after the development of symptoms. At least 1 mL of whole blood is needed to obtain a sufficient amount of serum or plasma for tests. This is the maximum that should be taken from infants. However, larger specimens of 3 to 5 mL should be taken from older children and adults, as this will allow a greater range of tests or repeat tests if necessary.

A convalescent-phase serum specimen should be collected 3 to 4 weeks after the onset of symptoms. When a patient is critically ill, a second antemortem specimen should be collected. Blood should be collected by use of either a vacuum venipuncture system or syringes and needles. The specimens should be collected in a serum separator tube (SST) or a clotting tube (for serum) or an EDTA tube (for plasma).

1. Label the tubes, including the unique patient identification number, using an indelible marker. Always check to ensure that the correct tubes are used for each patient.
2. Place a tourniquet above the venipuncture site. Palpate and locate the vein.
3. Disinfect the venipuncture site meticulously with 70 percent isopropyl alcohol (an alcohol swab) or 10 percent polyvidone iodine. Swab the skin concentrically from the center of the venipuncture site outward. Let the disinfectant evaporate. Do not repalpate the vein.
4. Perform venipuncture.
5. If withdrawing blood with conventional disposable syringes, withdraw 3 to 5 mL of whole blood from adults and older children and 1 mL from infants. Under asepsis, transfer the specimen to appropriate transport tubes. Secure caps tightly.
6. If withdrawing blood with a vacuum system (e.g., Vacutainer®), withdraw the desired amount of blood directly into each transport tube.
7. Remove the tourniquet. Use a cotton swab to apply pressure to the venipuncture site until bleeding stops, and apply a bandage.
8. Never recap used sharps. Discard directly into a suitable container (a proper sharps-disposal container if available, or a container such as a coffee or other metal can that was appropriately labeled before use).
9. Recheck that the tubes used for sampling have been correctly labeled.
10. After taking all the samples, complete the appropriate field-data sheets or case investigation forms and the required laboratory request forms using the same identification numbers used on the tubes.

Separation of serum and plasma

Blood samples need to be centrifuged for at least 5 minutes at 1,500 g (3,000 rpm). This requires an electric centrifuge (ideally one with a swing-out head rather than an angle-head rotor). Hand centrifuges are not adequate for the separation of serum or plasma from red cells.

Serum separator tubes

The instructions for using these tubes must be followed carefully for the tubes to work properly.

The tubes contain a gel with an intermediate density between blood cells and blood plasma and, usually, a coagulation (clot) activator.

- Put the blood sample into the tube and then follow the instructions for mixing the contents.
- Allow the clot to form. (Follow the instructions with the tube; do not cut the clotting process short.)
- Centrifuge the tube according to the relevant instructions.

When a filled SST has been properly centrifuged, the sample will separate into a top layer of serum separated by a gel barrier from the cell/clot layer and the clot activator.

Clotting tubes

If a basic sampling tube without any additives is used, the clot can be allowed to form overnight, and the serum can be pipetted off the next day. Serum should not be left in contact with the clot for more than 12 hours, as lysis of the red cells can occur.

Whichever type of tube is used, once the serum has been separated, it should be pipetted off without disturbing the gel barrier or the clot. Put the serum into a vial such as a Cryovial® (without VTM). Ideally, vials for transport of serum should have external caps and internal o-ring seals. If there is no internal o-ring seal, ensure that the cap is closed tightly and then sealed with an inert sealing film, such as Parafilm®.

EDTA tubes

Centrifuge the tubes at high speed (approximately 10,000 g) to compact the cellular fraction. Then pipette off the plasma, taking care not to draw blood cells off at the same time.

Filter paper

Blood or serum specimens can also be shipped in air-dried form on filter paper discs or special filter paper strips (e.g., Nobuto strips). Volumes of 0.1 mL of whole blood or serum are put onto the strip, which is then air dried. Strips of this sort can be stored for months at room temperature.

Transport

Blood specimen bottles and tubes should be transported upright and secured in a screw-cap container or in a rack in a transport box. They should have enough absorbent paper around them to soak up all the liquid in case of spillage (see more details below).

Specimens From Patients Who Have Died

If the corpse has an endotracheal tube in place, collect a deep endotracheal aspirate. If circumstances allow, perform tissue sampling by incision or by needle from the affected lung(s). The operator may use chest radiograph results to guide the sampling, aiming for areas at the margins of interstitial infiltrates, which are most likely the sites of active virus replication for the best diagnostic yield. The lung tissue sample will provide excellent material for various laboratory tests, including reverse transcriptase polymerase chain

reaction (RT-PCR), virus isolation, histopathology, bacterial cultures, direct antigen detection or immunohistochemistry, and cytokine/chemokine analyses. The needle aspiration or the core needle sampling may give sufficient sample for microbiologic studies.

To perform this aspirate, clean a small area on the lateral chest wall between two ribs and make a small incision between the ribs, overlying the lungs with a sterile scalpel. Cut wedge sample(s) from the lung (1 to 2 cm³ minimum) or insert a large-bore needle (e.g., 18G) into the lung tissue, and aspirate or cut available material into the needle/syringe. Put the specimen into VTM. The needle sampling should be performed as soon as possible after death.

Throat swabs, nasopharyngeal aspirates, or stool samples may be collected if time, sampling materials, and safety considerations permit, but this should not supersede or delay the collection of the deep endotracheal or lung material.

Storing Specimens

Table 6 below indicates the different storage and shipment conditions that can be used and which methods are recommended (based on the likelihood of obtaining a positive influenza A [H5N1] result on laboratory analysis).

TABLE 6. Suitability of Various Storage/Shipment Conditions for Different Specimen Types

STORAGE/ SHIPMENT CONDITIONS	SWABS OR OTHER SPECIMENS IN VTM FOR ISOLATION OF VIRUS	SWABS OR OTHER SPECIMENS IN VTM FOR PCR	SWABS IN ETHANOL FOR PCR*	BLOOD SERUM FOR VIRUS ISOLATION	BLOOD SERUM FOR PCR	BLOOD SERUM FOR ANTIBODIES
-70°C or dry ice or liquid nitrogen	Strongly recommended		n/a	Strongly recommended		
-20°C	Not recommended	Adequate	n/a	Not recommended	Adequate	Strongly recommended
+4°C	Adequate for up to 4 days storage	Adequate		Adequate for up to 4 days storage	Adequate	
Room temperature	Not recommended	Adequate		Not recommended	Adequate for up to 4 days storage	
Dried blood spot on filter paper	n/a				Adequate	

*Where refrigeration is not available.

- Aliquots of specimens should be taken before the specimens are frozen.
- Repeated freezing and thawing of specimens must be avoided.
- If specimens in VTM (or blood sera/plasma) for viral isolation can be taken to the laboratory within 4 days, they may be kept at 4°C and frozen at -70°C on arrival if they are to be stored. Otherwise, they should be frozen at or below -70°C until they can be transported to the laboratory. Freezing at -20°C is not recommended, because the virus does not survive well at this temperature, particularly in frost-free freezers.
- In the absence of freezers (or VTM), ethanol-preserved swabs are a possible alternative. Storage of such specimens at 4°C (in a standard refrigerator) is better than at room temperature.
- Blood serum samples should be frozen at -70°C for PCR and at -20°C or lower for antibody determination, but they can be stored at 4°C for approximately 4 days.

Specimen Transport

Specimens should be collected and transported in a suitable transport medium on ice or in liquid nitrogen. Specimens for influenza should not be stored or shipped in dry ice (solid carbon dioxide) unless they are sealed in glass or sealed, taped, and double plastic-bagged. Carbon dioxide can rapidly inactivate influenza viruses if it gains access to the specimens through shrinkage of tubes during freezing. The receiving laboratory should be notified before the specimens are shipped.

All specimens to be transported must be packaged in packaging consisting of three layers. Packaging should be strong enough to withstand the shocks and loads normally encountered during transport. Packaging should be constructed and closed so as to prevent any loss of contents that might be caused under normal conditions of transport (e.g., by vibration or by changes in temperature, humidity, or pressure).

Primary receptacles should be packed in secondary packaging in such a way that, under normal conditions of transport, they cannot break, be punctured, or leak their contents into the secondary packaging. Secondary packaging should be placed in a final outer package with suitable cushioning material. Any leakage of the contents should not substantially impair the protective properties of the cushioning material or of the outer packaging.

The primary receptacle(s) should be leak-proof. Absorbent material should be placed between the primary receptacle and the secondary packaging; if several fragile primary receptacles are placed in a single secondary packaging, they should be either individually wrapped or separated so as to prevent contact between them. There should be enough absorbent material to absorb the entire contents of the primary receptacle(s), and there should be a secondary packaging that is leak-proof.

Safety

The use of PPE is mandatory if direct or close contact with a patient is anticipated. It is also required when entering a room where aerosol-producing procedures are being performed on infected patients. The level of PPE needed will be determined by the exposure risk.

In general, PPE should include:

- A suitable form of respiratory protection.
- Non-sterile latex gloves (or equivalent if allergic).
- Goggles or a face shield.
- Gown.
- Head covering.

It may also be necessary to include:

- An impermeable apron.
- Suitable rubber boots.

High-risk activities—such as post-mortem examination of a confirmed or strongly suspected human case—should only be conducted in a full-body coverall with easily cleaned waterproof boots, heavy rubber gloves, and eye protection.

PPE is essential for preventing infection during sampling, but it does not alleviate all safety concerns. Individuals taking specimens should comply with all recommended infection-control precautions, including specific personal hygiene measures and the correct use of disinfectants.

Hand-Washing Techniques

When hands are visibly dirty or contaminated with biological materials, disinfect hands and wash them with soap and water. If hands are not visibly dirty, use an alcohol-based cleanser.

Soap and water. Liquid or bar forms of plain soap are acceptable when washing hands with a non-antimicrobial soap and water. Wet hands with water and apply the amount of product necessary to cover all surfaces. Vigorously perform rotational hand-rubbing on both palms, and interlace fingers to cover all surfaces. Rinse hands with water and dry thoroughly with a single-use towel. Use the towel to turn off the tap/faucet. Make sure the hands are dry. Ensure that towels are not used multiple times or by multiple people. Use running, clean water for hand hygiene whenever possible. Avoid using hot water, as repeated exposure to hot water may increase the risk of dermatitis. When bar soap is used, small bars of soap in racks that facilitate drainage should be used.

Hand cleansers. When using an alcohol-based formulation (or another disinfectant-based hand cleanser), apply a palmful of the product and cover all surfaces of the hands. Rub hands until they are dry.

Respiratory Protection

The level of respiratory protection required when sampling will depend on a number of factors, including the type of sample to be taken (e.g., sampling for blood is less risky than taking a throat swab, which may cause the patient to cough) and the type of respiratory risk (e.g., droplets and aerosols require different types of protection).

Many types of respirators and masks are available, and the different types offer different levels of respiratory protection. It must be accepted that in some situations, high-efficiency respirators will not be available, and basic gauze masks may be all that can be used. Such masks should be changed every 4 hours.

- Individuals should select a particulate respirator that fits well. A user-seal check (fit check) should be performed each time a disposable particulate respirator is worn.
- Disposable particulate respirators, although similar in appearance to surgical masks, differ significantly from surgical masks because they are specifically designed to protect the wearer from exposure to airborne contaminants by sealing tightly to the face and filtering infectious particles from the air.
- If a particulate respirator is not available, a tightly fitting surgical or procedure mask should be used.
- Surgical and procedure masks do not provide protection against small-particle aerosols (such as droplet nuclei). Aerosol-generating procedures should not be performed if a particulate respirator is not available.

Particulate respirators (see photographs below) are lightweight and fairly comfortable to wear. Models with exhalation valves cannot be used when working in sterile areas (such as operating rooms) because the exhalation valve allows droplets and particles exhaled by the user to escape. Since air must be actively drawn into the mask, the mask will increase the work of breathing when used properly. In addition, it is almost impossible to prevent occasional leaks of contaminated air into the mask.



Disposable particulate respirators

with valves

and
without valves

Surgical mask

Disposable respirator
with valve



Disinfectants

Chlorine is one of the disinfectants used against influenza A (H5N1) contamination. Other disinfectants registered in Ukraine may also be used in accordance with the manufacturers' instructions.

Household bleach is the best compound for preparing chlorine solutions for disinfection. Household bleach is a solution of sodium hypochlorite, which generally contains 5 percent (50 g/liter or 50,000 ppm) available chlorine.

Note that:

- Different products may contain different concentrations of available chlorine. The concentration should be checked before use.
- Household bleach preparations can lose some of their chlorine over time. Use newly manufactured bleach if possible. If the bleach does not smell strongly of chlorine, it may not be sufficient and should not be used.
- Thick bleach solutions should never be used for disinfection purposes (other than cleaning toilet bowls), as they contain potentially poisonous additives.

When preparing chlorine solutions for use, note that:

- Chlorine solutions gradually lose strength. Freshly diluted solutions must be prepared daily.
- Clear water should be used because organic matter destroys chlorine.
- 1:10 bleach solution is caustic. Avoid direct contact with skin and eyes.
- Bleach solutions give off chlorine. Prepare them in a well-ventilated area.
- Use plastic containers for mixing and storing bleach solutions, as metal containers corrode rapidly.

Two different dilutions of bleach are used for disinfection:

- **1:10 bleach solution** (which contains 0.5 percent chlorine concentration) is a strong disinfectant that is used to disinfect:
 - Excreta.
 - Bodies.
 - Spills of blood/body fluids.
 - Vehicles and tires.

It is also used to prepare 1:100 bleach solution.

- **1:100 bleach solution** (which contains 0.05 percent chlorine concentration) is used to disinfect:
 - Surfaces.
 - Medical equipment.
 - Bedding.
 - Reusable protective clothing before it is laundered.

It is also recommended for:

- Rinsing gloves between contacts with different patients (if new gloves are not available).
- Rinsing gloves, aprons, and boots before leaving a patient's room.
- Disinfecting contaminated waste before disposal.

To prepare 1:10 bleach solution, add 1 volume (e.g., 1 liter) of household bleach to 9 volumes of clean water (e.g., 9 liters).

To prepare 1:100 bleach solution, add 1 volume (e.g., 1 liter) of 1:10 bleach solution to 9 volumes of clean water (e.g., 9 liters).

Note: 1:100 bleach solution can also be prepared directly from household bleach by adding 1 volume of household bleach to 99 volumes of clean water (e.g., 100 mL of bleach to 9.9 liters of clean water). Preparing it from 1:10 bleach solution is much easier.

Disinfection

All objects that have come in contact with potentially infectious materials should be decontaminated.

Decontamination of surfaces. Wear an apron, heavy-duty gloves, and other barrier protection if needed. Disinfect surfaces by wiping clean with 1:100 chlorine solution, then dispose of all absorbent material in heavy-duty garbage bags. The surfaces must be rinsed with clean water after disinfection.

Disinfection of surfaces in laboratories where PCR work is undertaken. Disinfection is carried out by special disinfectants that do not affect the course of laboratory reaction and do not damage the equipment.

Decontamination of blood or body fluid spills. For spills, use 1:10 chlorine solution to inactivate pathogens before soaking up the fluid with absorbent materials. These absorbent materials must then be disposed of.

Disinfection of hands. The principal means for disinfecting hands is by washing with soap and water. If available, a commercial hand disinfectant containing alcohol, chlorhexidine, or polyvidone iodine can be used. The use of strong chlorine solutions (such as 1:100 chlorine solution) should be avoided, as they are dangerous.

Sterilization and reuse of instruments and materials. In field outbreaks, sterilization and reuse of any instruments or materials are not generally advisable. However, if it is necessary to reuse instruments, these should first be disinfected and cleaned, then sterilized.

Vehicles. Vehicles driven into potentially infected poultry farms should be rigorously disinfected because influenza viruses may survive for weeks in cool, moist, dark conditions and can easily be spread via mud or fecal contamination on vehicle tires or subframes. All gross contamination must be removed from vehicles with a power washer, and then all surfaces that may have been splashed by mud or feces on the farm must be sprayed down with 1:10 chlorine solution. Use of a tire bath with 1:10 chlorine for disinfection of tires is ideal. (The chlorine solution should be replaced after every two or three vehicles, as it will rapidly become depleted.) Operators of power washers must be very well-protected due to the high risk of their being sprayed with contaminated material.

Monitoring Medical or Veterinary Personnel

If an incident that could lead to infection occurs during a sampling procedure (such as a breakdown of protective procedures), the staff members involved should be monitored for signs of illness (including daily temperature) for the following week. Post-exposure chemoprophylaxis with a neuraminidase inhibitor should be considered.

All staff working with human or animal cases of avian influenza should monitor their own health, and any evidence of ILI within 7 days of exposure to a confirmed or suspected human case or to a potential avian source should be viewed as suspected avian influenza and treated appropriately by a medical doctor.

Annex 2

Social Mobilization: Delivering Community Education Messages

Social mobilization involves planned actions and processes to reach, influence, and involve all relevant segments of society across all sectors, particularly at the community level.

This section presents community education messages that should be delivered by public health care workers and medical professionals to help the population know:

1. How to recognize avian influenza in animals and humans.
2. How to prevent its transmission.
3. When to seek treatment.

It should also help the population prevent a panic in the case of a confirmed animal or human infection in the area in which they live.

These messages should be delivered by appropriate communication methods, such as:

- Newspapers.
- Television, radio.
- Presentations at schools.
- Meetings with health care personnel and trusted and respected religious and political leaders.
- Individual consultation of residents seeking advice or recommendation.

Relevant printed education materials (such as leaflets and brochures) should be disseminated during meetings and presentations for future reference.

Several sample questions and answers are presented below. Public health care workers and medical professionals should be prepared to adapt these materials to address beliefs about the disease and the needs of specific populations.

Q: What is bird flu? Will it cause the next influenza pandemic?

A: Avian influenza (“bird flu”) is a disease of wild and farm birds caused by avian influenza viruses. Bird flu viruses do not usually infect humans, but since 1997, there have been a number of confirmed cases of human infection from bird flu viruses. Most of these resulted from direct or close contact with infected birds. The spread of bird flu viruses from an infected person to another person has been very rarely reported; it has not been reported to continue beyond one person. A worldwide pandemic could occur if a bird flu virus were to change so that it could be easily passed from person to person. Experts around the world are watching for changes in bird flu viruses that could lead to an influenza pandemic.

Q: What types of birds can be infected with bird viruses?

A: Avian influenza viruses can infect chickens, turkeys, pheasants, quail, ducks, and geese, as well as a wide variety of other birds, including migratory waterfowl.

Each year, there is a flu season for birds just as there is for humans, and as with people, some forms of the flu are worse than others, depending on how strong the virus is. A weak virus may cause only mild illness in infected poultry and birds, but a strong virus could cause severe and extremely contagious illness—and even death—among infected poultry and birds.

Q: What are the signs and symptoms of bird flu in birds?

A: Infection causes a wide spectrum of symptoms in birds, ranging from mild illness to a highly contagious and rapidly fatal disease resulting in severe epidemics. Specific symptoms include:

- Decrease in activity.
- Drastic decline in egg production.
- Facial swelling with swollen and bluish-violet colored combs and wattles.
- Hemorrhages on internal membrane surfaces.
- Gasping for breath.
- Muscle weakness/paralysis.
- Diarrhea.
- Sudden death.

Virus isolation is needed for definitive diagnosis.

Q: Is it safe to eat poultry?

A: Yes, it is safe to eat properly cooked poultry. Cooking destroys germs, including bird flu viruses. Be sure to:

- Cook thoroughly: Ensure that poultry meat reaches 70°C or that the meat is not pink; egg yolks should not be runny.
- Separate raw meat from cooked or ready-to-eat foods; do not use the same knife or the same chopping board; do not use raw or soft-boiled eggs in food preparations that will not be heat-treated/cooked.
- Keep clean and wash your hands after handling frozen or soft raw chicken or eggs; thoroughly wash surfaces and utensils that have been in contact with raw meat.

Q: What else can I do to reduce my risk of becoming ill?

A: 1. **Avoid contact with chickens, ducks, and other poultry unless absolutely necessary**, particularly on any farm where animals have been ill, slaughtered, or are thought to harbor avian influenza. Do not let poultry into your house. Discourage children from playing with birds or keeping them as pets.

Note that birds that are infected can spread the disease before they show signs of illness. Some birds, such as ducks, can get and spread the disease and never show signs of illness.

If there is contact with poultry: Do not rub your eyes or eat, drink, or smoke before washing your hands with soap and water.

2. **Avoid close contact with people who are sick.** When you are sick, stay home and/or keep your distance from others; cover your nose and mouth with a tissue when you cough or sneeze to protect others from catching a virus.
3. **Wash your hands with soap and water often**, especially:
 - After going to the toilet.
 - After changing a child's diaper.
 - Before preparing or eating food or feeding a child/infant.
 - After handling raw foods.
 - After blowing your nose, coughing, or sneezing.
 - After handling garbage.
 - Before and after treating a cut or wound.
 - After handling animals or animal waste.
 - After visiting markets.
4. **Regularly clean the areas where poultry are kept.** Clean or sweep feces and unconsumed feed from the yard every day. Burn or bury feathers and other waste away from the farm. Bury the waste deep and with lime so that scavengers do not dig it up.
5. **Take precautions in preparing and consuming poultry, meat, or eggs as specified above.**
6. **Take precautions if you are visiting a farm or other area where poultry are kept.** After leaving the area, wash your hands with soap and water, brush and disinfect your clothing, shoes, and the wheels of bicycles, motorcycles, or other vehicles.

Home slaughtering

- Sick birds (or birds from flocks in which one or more birds are sick) should never be slaughtered for consumption. Eggs for human or animal consumption should never be marketed.
- The slaughter should take place in a confined area away from birds. Children and animals should be kept away.
- The person performing the slaughter should wear personal protective equipment and observe strict hygiene. After slaughter, the area should be cleaned and disinfected and feathers and animal remains safely disposed of.

Buying poultry or eggs

- Purchase only poultry and poultry products from shops with evident high food-hygiene standards.
- Avoid buying live poultry, as bird flu can spread through close contact with infected live poultry.
- Select fresh poultry with no signs of illness (such as unusually dark color, hemorrhage, etc.).
- Select fresh eggs without feces stains on the shells. Avoid buying eggs with cracked shells.
- Remember that canned poultry products can be safely consumed, as all processed foods undergo a heat treatment process that effectively destroys viruses.

Q: What additional measures should I take if there is avian influenza in poultry in the area?

A: 1. Do not bring in contamination from other farms or markets.

- Brush or wash off your shoes and the wheels of your bicycle/motorcycle or other vehicle and change clothing immediately after returning from farms or live-bird markets (so you do not carry the virus home on your clothing, shoes, or equipment).
- Clean or disinfect anything coming into the farm that may have contacted poultry or poultry droppings outside the farm. This includes clothing, tools, and equipment such as cages and bicycle or vehicle tires.
- Do not borrow equipment or vehicles from other farms.
- Do not transport live or dead chickens, ducks, or other poultry from one place to another—even if you think the birds are healthy.
- Do not bring other animals, such as chicks, ducklings, or piglets, from another farm.
- Do not buy or accept animals, eggs, or manure from other farms.

2. Separate your poultry from wild birds and any domestic birds that roam free.

- Keep poultry brought to the farm/homestead from another location separate from your flock for at least 14 days.
- Keep all your poultry fenced or caged away from other animals, wild birds, and any source of water that could have been contaminated by wild birds.

3. If recommended by authorities, bring your birds to be vaccinated.

4. Remember that hunting is prohibited in the 10-km zone surrounding any place where H5N1 virus has been found.

If you have had contact with the carcass of any chicken that has died from avian influenza, the feces of the chicken, or an environment that has had sick or dead chickens in it:

- Wash your hands thoroughly.
- Report any sick or dead bird(s) to the rayon veterinary office immediately.
- Monitor your temperature for 7 days. If you develop a high fever ($\geq 38^{\circ}\text{C}$), respiratory complaints, or an eye infection, immediately consult your doctor.

If poultry have died in your back yard, decontaminate the yard and immediately report the case to the rayon veterinary office.

- Wear personal protective equipment. At a minimum, cover your face and wear gloves or plastic bags over your hands.
- If authorities cannot come promptly, bury the dead poultry at a depth of at least 2.5 meters. This must be away from water supplies.
- Clean the area of all chicken droppings. Scrape or use a rake and bury the chicken droppings.
- Clean the chicken shed or area where the droppings have been with soap (or bleach) and water.

Note: Avian flu looks like other poultry diseases, especially Newcastle disease. Even if you think you know what is making your birds sick or die, still tell authorities, just to be safe.

Note: If your poultry or your neighbor's poultry are sick or have died from avian influenza, it is important to protect your community by culling any surviving birds and disinfecting your farm. Do not kill birds yourself—wait for the people sent by the government, who will do it properly. After your birds have been culled, follow the government authority's instructions about obtaining compensation and about disinfecting your farm.

Q: What should I do if I think someone else has avian influenza?

- A:**
- Take the person to a health care provider immediately.
 - Until you bring the person to the health care provider, take specific protective actions: wash your hands frequently, wear a mask or cover your mouth and nose with a cloth, have the person who is ill wear a mask or cover their mouth and nose with a cloth, and limit the number of people who come within a meter of the sick person.
 - Contact the nearest rayon hospital or ambulatory facility for additional guidance.

Q: Will the seasonal flu shot protect me against pandemic influenza?

A: No, it will not. But flu shots can help you avoid seasonal flu.

Q: Is there a special vaccine to protect me against pandemic influenza?

A: No, currently there is no vaccine to protect humans against avian viruses. Even though vaccine-development efforts are under way, there are a number of constraints to development and mass production. Because viruses change over time, a specific pandemic influenza vaccine cannot be produced until a pandemic influenza virus emerges and is identified. If a pandemic influenza virus is identified, it will likely take an additional 4 to 6 months to develop, test, and begin producing a vaccine.

Annex 3

Seasonal Influenza Vaccination Recommendations

The Justification for Vaccine Use

Influenza virus types A and B are common causes of acute respiratory illnesses, and influenza A viruses are the principal cause of large epidemics as well as pandemics. Influenza viruses undergo frequent changes in their surface antigens. Immunity resulting from infection by one influenza virus does not protect fully against antigenic variants of the same subtype (influenza A viruses) or type (influenza B viruses). As a consequence, influenza outbreaks occur every year.

Influenza poses a considerable economic burden both on society and the individual in terms of consumption of health care resources and lost productivity.

During influenza epidemics, attack rates of 5 to 10 percent are commonly observed, and they may reach 20 to 30 percent in children. While attack rates are highest among children, rates of serious complications, such as pneumonia, are highest among persons aged 65 or older, children younger than 2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza. In the United States, the majority of influenza-related deaths occur in persons older than 70 years. The average annual excess mortality among all age groups during influenza epidemics is estimated to be 7 to 23 per 100,000.

Economic considerations cannot be ignored, either. Indirect costs of influenza epidemics can include those associated with lost days of work and education, the need to increase the number of hospital beds for those needing supportive care, the increased use of antibiotics for actual or suspected cases of secondary bacterial infection (which may accelerate the development of resistance), and general social disruption. Recent estimates from France, Germany, and the United States indicate that the total annual cost of influenza outbreaks vary from US\$1 to \$6 million per 100,000 inhabitants.

Influenza vaccination is the primary and single most cost-effective method of preventing influenza and its severe complications. Antiviral agents used for chemoprophylaxis or treatment of influenza are adjuncts to vaccine, but they are not substitutes for annual vaccination. Most of the widely licensed influenza vaccines are manufactured according to the quality requirements defined by the World Health Organization (WHO) and have proven to be efficacious and safe. New influenza vaccines must be designed annually to match the circulating viruses that are expected to cause the next epidemic. Current influenza vaccines contain antigens from two influenza A virus strains (an H3N2 and an H1N1 strain) and one B strain, according to the annual recommendation of WHO. This recommendation is based on intensive surveillance of new influenza strains around the globe to ensure optimal antigenic match between the virus strains in the vaccine and the viruses circulating in the subsequent influenza season.

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. Vaccines containing strains that match the predominant circulating strains have been reported to be 70 to 90 percent efficacious for preventing (laboratory-confirmed) illness in healthy adults. Retrospective studies of people with predisposing medical conditions have found reductions of up to 50 percent in the rates of severe respiratory illness and death. In such persons, the main benefit of vaccination may be to prevent severe consequences of infection rather than preventing uncomplicated illness.

Types of Influenza Vaccine

Inactivated and live attenuated influenza vaccines are available and can be used to reduce the risk of influenza virus infection and its complications. Although both types of vaccines are effective, they differ in several aspects.

Inactivated influenza vaccine contains killed viruses and thus cannot produce signs or symptoms of influenza virus infection. In contrast, live attenuated influenza vaccine contains live, weakened viruses and therefore has a potential to produce mild signs or symptoms related to influenza virus infection.

Only inactivated vaccine is currently registered and available in Ukraine.

There are three types of inactivated influenza vaccine that show comparable efficacy but differ in terms of reactogenicity.

- *Whole-virus vaccines* often cause local reactions in children lasting for 1 to 2 days. Transient systemic reactions such as fever, malaise, and myalgias may occur in a minority of vaccine recipients within 6 to 12 hours of vaccination.
- *Split vaccines* are vaccine formulations consisting of disrupted viral particles.
- *Subunit vaccines*, specifically the ones containing hemagglutinin and neuraminidase surface glycoproteins purified from other viral components, show reduced systemic reactogenicity both in children and adults as compared to whole-virus preparations. Consequently, they are more attractive, particularly for use in children.

Whole-virus vaccines are being replaced by less reactogenic split virus and subunit vaccines.

Recommendations for Using Inactivated Influenza Vaccines

The primary objective for the prevention of influenza is to reduce the incidence of severe illness and premature death in groups at increased risk of severe disease and, as a consequence, to reduce the need for specialized health care services and pharmacological supplies, in particular antibiotics.

The inactivated vaccine is approved for persons 6 months of age and older, including those with high-risk conditions. Annual influenza vaccination is recommended for the following groups:

TARGET GROUPS	
Persons at increased risk for complications	Residents of institutions for the elderly or disabled
	All individuals ≥6 months of age with one or more of the following chronic conditions: chronic cardiovascular, ⁹ pulmonary, metabolic (such as diabetes mellitus or renal dysfunction), or immunodeficiency (caused by medications or HIV)
	Persons >60 years of age
	Children aged 6–23 months
	Women who will be pregnant during the influenza season
	Individuals who are receiving long-term aspirin therapy and therefore might be at risk of experiencing Reye's syndrome after influenza virus infection
Persons at increased risk for influenza-associated clinic or hospital visits	Children aged 24–59 months
	Persons aged 50–59 years
Persons who live with or care for persons at high risk for influenza-related complications	Health care workers
	Healthy household contacts and caregivers of children aged 0–59 months and persons at high risk for severe complications from influenza

The Ministry of Health (MoH) of Ukraine and WHO recommend increasing vaccination of high-risk individuals and aiming at vaccination coverage of elderly people of at least 50 percent by 2007 and 75 percent by 2010.

Notes

General population: In addition to the groups for which annual influenza vaccination is recommended, vaccination providers should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza or retransmitting influenza to others should they become infected. In this case, the cost of vaccination can be covered by local budgets or other sources permitted by law (funds of companies, organizations, or individuals).

Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students and other persons in institutional settings (e.g., those who reside in dormitories) should be encouraged to receive the vaccine to minimize the disruption of routine activities during epidemics.

Breastfeeding mothers: Inactivated influenza vaccine is safe for mothers who are breastfeeding and their infants.

Use of Seasonal Influenza Vaccines in Humans at Risk of H5N1 Infection

Targeted vaccination with the current seasonal influenza vaccine is now recommended as one of several measures for reducing opportunities for the simultaneous infection of humans with avian and human influenza

⁹Hypertension is not considered a high-risk condition.

viruses. Minimizing the opportunities for dual infections reduces the chance for viral reassortment and for the eventual emergence of a novel influenza virus with pandemic potential.¹⁰

In addition to the above target groups, the following populations should be considered for current seasonal influenza vaccination:

1. All persons who are expected to be in contact with poultry or poultry farms potentially being affected by highly pathogenic avian influenza (HPAI), especially cullers involved in destruction of poultry; people living and working on poultry farms where HPAI has been reported or is suspected or where culling takes place; and hunters, zoo workers, vendors in live animal markets, and others having direct contact with animals.
2. Health care workers involved in the daily care of strongly suspected or confirmed human cases of HPAI, collection of specimens for laboratory investigation, and personnel of laboratories investigating H5N1 virus or material from suspected cases.
3. Health care workers in emergency care facilities in areas where there is confirmed occurrence of HPAI in birds.
4. Close contacts of HPAI human cases.

Other Aspects of Influenza Vaccine Use

STORAGE	IN A REFRIGERATOR AT +2–8°C
Dosage	Usually 1 dose (consult the manufacturer's package insert). Two doses administered at least 1 month apart are recommended for children aged 6 months to 9 years who are receiving influenza vaccine for the first time.
Route	Intramuscular. Adults and older children should be vaccinated in the deltoid muscle; infants and young children should be vaccinated in the anterolateral aspect of the thigh.
Contra-indications	1. Persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine. 2. Persons with moderate to severe acute febrile illness.
Timing	The optimal time for vaccination efforts is usually during November–December but can often be extended into January. Providers should routinely offer influenza vaccine throughout the influenza season, even after influenza activity has been documented in the community. People have peak antibody protection against influenza virus infection 2 weeks after vaccination.

Role of Physicians in Increasing Vaccination Levels

Vaccination rates among target populations in Ukraine are not in line with WHO recommendations despite the well-established safety and efficacy of current inactivated influenza vaccines. Clearly, influenza vaccines are still seriously underutilized, which is often due to perceptions related to influenza and influenza vaccinations that are based on insufficient or inappropriate information among the general population. Too often, influenza is viewed as a comparatively mild disease that does not pose a serious threat. At the same time, influenza vaccination is frequently considered ineffective or even a cause of the flu. In addition, the current mode of the vaccine administration by injection represents a barrier for individuals with a fear of needles.

Health care professionals are in a key position to share information regarding influenza vaccine effectiveness, cost-effectiveness, and safety and explain the favorable risk-benefit ratio of influenza vaccination to people in

¹⁰This vaccination does not protect against infection with bird flu. This fact must be understood by those exposed so that they are still aware of the need for general protective measures.

target groups and, thus, to motivate them to receive the vaccine. *The single most important factor influencing the use of influenza vaccine is a trust in the doctor's recommendation.*

Current inactivated influenza vaccines have an excellent safety record. About 300 million vaccine doses are being administered annually around the globe, and the overall rate of adverse reactions is extremely low. The most frequently occurring side effects are local reactions at the site of vaccination, which usually do not last more than 1 to 2 days. Generally, the reactions are mild and transient. When educating patients regarding potential side effects, clinicians should emphasize that inactivated influenza vaccine contains non-infectious killed viruses or their fragments and cannot cause influenza.

Possible actions by primary-care physicians to encourage vaccine uptake in target populations may include:

- Making/updating the records of people recommended for vaccination.
- Sending invitation letters together with information leaflets to people recommended for vaccination.
- Organizing polyclinics to administer the vaccine to as many target subjects as possible in a time-efficient way.
- Promoting vaccination of family members of at-risk patients and health care personnel.
- Displaying appropriate information in patient waiting rooms and in offices.

Increased use of influenza vaccines is expected to significantly reduce epidemics and improve our preparedness for potential new pandemic outbreaks.

Use of Vaccines in the Private Sector

Beyond government programs, physicians may prescribe influenza vaccine to any person wishing to reduce the risk of influenza, except where it is medically contraindicated. Private practitioners should ensure that their use of vaccines is consistent with national guidelines.

Some Aspects of Developing a Human Vaccine Against Pandemic Influenza

H5N1 is presently considered the most likely virus to ignite the next influenza pandemic. The increasing spread and evolution of H5N1 viruses in Asia have brought the world closer to another pandemic than at any time since 1968, when the last of the previous century's three pandemics began.

Data from initial clinical trials of a vaccine being developed to protect humans against infection with H5N1 avian influenza indicate that the experimental vaccine evoked an immune response in a small group of healthy adults. Although more trials are needed, the findings reconfirm the feasibility of developing an H5N1-specific vaccine.

Vaccines are the principal medical intervention for protecting individuals against pandemic influenza. If available rapidly and in sufficient quantities, they can reduce the morbidity and mortality that have traditionally made pandemics so socially disruptive as well as deadly.

However, many problems need to be resolved before vaccines can assume such a role in mitigating the effects of the next pandemic. Pandemic vaccine production faces two major challenges: first, two doses would almost certainly be required to compensate for the lack of existing immunity within the world population and, second, at least based on current trials of pandemic vaccines, much higher concentrations of antigen¹¹ may be needed to achieve an immune response, further limiting the number of people who can be vaccinated.

¹¹Antigen is the component of the vaccine that elicits an immune response.

Strategies for stretching limited antigen supplies—by adding an adjuvant to the vaccine formulation or by injecting the vaccine into the skin rather than into muscle—have been proposed. Adjuvants are chemicals that can be added to the vaccine formulation to boost the immune response, theoretically allowing the use of smaller doses of antigen to achieve an immune response. Such antigen-sparing strategies using adjuvants are currently being tested by several manufacturers.

At present, 90 percent of production capacity for all influenza vaccines is concentrated in Europe and North America, in countries that account for only 10 percent of the world's population. Current global manufacturing capacity (estimated at 300 million doses of regular trivalent influenza vaccine per year) is inadequate to meet the expected global needs during a pandemic and cannot be rapidly augmented.

Because the present total global manufacturing capacity for influenza vaccine is limited, any decision to manufacture a pandemic vaccine in large quantities prior to the start of a pandemic would, if necessary, compromise the capacity to produce vaccines for seasonal influenza. Seasonal epidemics of influenza predictably cause an estimated 250,000 to 500,000 deaths each year. In the current situation, the capacity to respond to seasonal influenza must be balanced against preparations for pandemic influenza. However, once a pandemic has been declared, all manufacturers would stop production of seasonal vaccines and produce only the pandemic vaccine.

Even with the use of an adjuvant, however, it is important to remember that current production technologies can take up to six months to produce the seasonal vaccine supply. Therefore, it is doubtful at this time that enough H5N1 vaccine could be produced to meet global needs during the first wave of a pandemic.

Preparedness Planning for Vaccination Against a Pandemic Influenza Virus

The primary goal of a pandemic response is to decrease health impacts, including severe morbidity and death, and minimize societal and economic impacts.

The MoH of Ukraine has submitted a request to WHO to take into account the need of Ukraine's high-risk populations in a pandemic in the case of a threat of pandemic influenza virus spread or if other complications of avian influenza arose.

Initial pandemic vaccine stocks will be used to vaccinate designated high-priority groups. After vaccination of these groups, vaccination of all those who desire it will be phased in depending on available supplies.

Vaccination of high-priority groups

A provisional list of high-priority groups for receiving vaccination and rationale for prioritization is provided in the table on the following pages. To prepare for vaccination of high-priority groups, the MoH and regional sanitary-epidemiological stations (SES) and health administrations should:

- Identify a process for finalizing national recommendations for pandemic influenza vaccination and develop region-specific modifications for priority groups, depending on local circumstances.
- Develop specific priority groups and their definitions, identifying occupational categories as needed.
- Estimate the size of relevant priority groups.
- Develop a plan for how persons in priority groups will be identified at polyclinics and how vaccine would be most efficiently provided to these groups.
- Educate medical professionals and other stakeholders about the need for priority groups and the rationale for selecting them.

The recommendations summarized in the following table are based on the following assumptions:

- The greatest risk of hospitalization and deaths will be in infants, the elderly, and those with underlying health conditions.
- The health care system may be overwhelmed due to the large number of illnesses and complications from influenza requiring hospitalization and critical care. (The demand may increase by 25 percent or more.)
- During a pandemic, 25 to 30 percent of people will become ill during a 6- to 8-week wave. At the peak of pandemic disease, 10 percent of the workforce will be absent due to illness or caring for an ill family member.
- The amount of pandemic vaccine needed will be updated, taking into consideration regional needs based on the above recommended priority groups.

Vaccine priority-group recommendations

The recommendations are based on the US Department of Health and Human Services' 2005 *Pandemic Influenza Plan*. They are currently being debated in the United States and other countries because of numerous ethical implications. They may be revised in the near future.

TIER	VACCINE PRIORITY-GROUP RECOMMENDATIONS	RATIONALE
1	Manufacturers/suppliers of antiviral medications and vaccine	The health community needs to ensure maximum availability of antiviral drugs and pandemic vaccine
	Medical workers involved in direct patient care and vaccinations	Health care workers are required for good-quality medical care
2	Persons >60 years old with one or more influenza high-risk conditions ¹²	These groups are at high risk of hospitalization and death
	Persons 6 months to 59 years old with two or more influenza high-risk conditions	
	Persons 6 months or older with a history of hospitalization for pneumonia or influenza or other influenza high-risk condition in the past year	
3	Pregnant women	In past pandemics and for annual influenza, pregnant women have been at high risk; vaccination will also protect the infant who cannot receive vaccine
	Household contacts of severely immunocompromised persons who would not be vaccinated due to likely poor response to vaccine	Vaccination of household contacts of immunocompromised and young infants will decrease the risk of exposure and infection among those who cannot be directly protected by vaccination
	Household contacts of children <6 months old	
4	Public health emergency response workers critical to pandemic response	It is critical to implement pandemic response measures, such as providing vaccinations and managing/monitoring response activities
	Key government leaders	Preserving decision-making capacity is critical for managing and implementing a response

¹²See an earlier section on recommendations for using influenza vaccine.

TIER	VACCINE PRIORITY-GROUP RECOMMENDATIONS	RATIONALE
5	Healthy persons ≥60 years old	These groups are also at increased risk, but not as high as the population in tier 2
	Persons 6 months to 59 years old with one high-risk condition	
	Healthy children 6–23 months old	
6	Other public health emergency responders	This group includes critical infrastructure groups that have an impact on maintaining health, implementing a pandemic response, and maintaining societal functions
	Public safety workers, including police, fire, 01-02-03-04 telephone dispatchers, and correctional facility staff	
	Utility workers essential for maintenance of power, water, and sewage system functioning	
	Transportation workers transporting fuel, water, food, and medical supplies, as well as public transportation workers	
	Telecommunications/information technology workers for essential network operations and maintenance	
7	Other key government health decision-makers	These are other important societal groups for a pandemic response, but they are of a lower priority
	Funeral directors	
8	Healthy persons 2–59 years old not included in the above categories	All persons not included in other groups based on the objective to vaccinate all those who want protection

Vaccine procurement and distribution

Each regional and rayon SES (hospital) will receive available vaccine in proportion to the size of its population in defined priority groups.

Local SES and health administrations should:

- Identify organizations that will provide vaccinations to the individuals in priority groups.
- Obtain written commitments from the heads of each clinic or facility responsible for vaccinating a priority group.
- Work with the heads of these facilities to develop strategies for rapid distribution and administration of vaccines, taking into account vaccine security issues, cold-chain requirements, and transport and storage issues.
- Estimate the size of the priority groups that will be vaccinated based on extrapolation from national data or on local data where available.
- Develop procedures for collecting, removing, and disposing of used syringes, needles, and other vaccination supplies.
- Develop a plan for training vaccinators and other staff responsible for mass vaccination.
- Develop strategies for vaccinating hard-to-reach populations.

A vaccine against pandemic influenza will likely require two doses, administered at least a month apart, to provide a level of immunity comparable to that obtained with seasonal influenza vaccines. If two doses are

required to achieve immunity, it will be necessary to ensure that vaccinated persons return for the second dose. Regional and district SES and health administrations should do the following:

- Arrange for information about the need for a second dose to be provided at the time of administration of the first dose.
- Ensure that planning for vaccine procurement and distribution to clinics and other facilities accounts for the need to use portions of future shipments for second doses, thus reducing the number of available first doses.
- Consider implementing a call-back system, immunization registry, or other management information system that would help accomplish the goals of pandemic vaccination.

Vaccine monitoring and data collection

Vaccine effectiveness will be assessed by comparing rates of influenza-related illness, hospitalization, and/or death among vaccinated and unvaccinated persons.¹³ Vaccine tracking will be implemented by regional and local health authorities who will have the major responsibility for allocation decisions. Vaccine tracking may be used by decision-makers at the central and other levels to estimate adverse event rates and to determine if vaccine is being administered according to established priority groups for pandemic vaccine. Data will be collected from individual providers, collated at the district and regional levels, and reported to the MoH on a scheduled routine basis. At a minimum, tracking data should include:

- Number of doses administered, by date, age, priority group, and district.
- Number of doses that represent second doses, as applicable.

The MoH is working on the development of a system for monitoring vaccination rates and for reporting and investigating adverse effects following immunization with a pandemic vaccine.

Public health communications

The provision of vaccine information will be an important component of ongoing public health communication during a pandemic.

- Regional and local SES and health departments should work with the Ministry of Health to disseminate accurate, useful, and consistent public health messages on:
 - Rationale for prioritization and list of priority groups.
 - Phasing of vaccination, if any, after priority groups have been vaccinated.
 - When and where vaccination is available.
 - Importance of vaccination given the likelihood of subsequent pandemic waves.

In addition, all vaccine providers will need vaccine information sheets that describe the vaccine's risks, benefits, and contraindications.

Training

Regional and district SES and health departments can assist health care partners in conducting training exercises to facilitate rapid and effective delivery and use of vaccines. Exercises and drills are essential to ensure that emergency procedures are in place and that roles and responsibilities are well understood. It may be useful, for example, to practice emergency implementation of mass vaccination (e.g., receiving large quantities of vaccine; storing and handling vaccine; setting up and staffing polyclinics; administering vaccine; testing information management systems; educating the public, media, and health care providers; targeting specific priority groups).

¹³Since influenza-related illnesses have non-specific clinical definitions, this needs to be supplemented with some type of laboratory surveillance, so at least a subset of cases are laboratory-confirmed and reasonable estimates can be made.

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