

WHO guidelines for investigation of human cases of avian influenza A(H5N1)

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This revised document replaces the version published in October 2006 and includes the following changes:

- Revision of considerations for initiating an investigation
- Revision of the section on contact tracing, including the time frames for tracing
- Monitoring of health-care workers
- Revision and addition of technical references.



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Introduction

The initial outbreak of highly pathogenic avian influenza A(H5N1) among poultry and people in Hong Kong SAR in 1997 increased awareness of our vulnerability to a global pandemic. Since late 2003 the accelerated geographical spread of A(H5N1) among birds in Asia, Europe, the Middle East and Africa has heightened concerns. As of January 2007, more than 250 confirmed cases of human infection with A(H5N1) in 10 countries have been reported to WHO.

Associated investigations have underscored the importance of timely identification of cases and contacts to rapidly implement disease control and prevention measures, strong linkages between human and animal health sectors, advance planning and preparedness in anticipation of outbreaks of avian influenza, rapid assessment to determine if the risk for pandemic influenza has increased, and communication of findings to advance understanding of the evolution of A(H5N1) — the most visible, albeit not sole, pandemic threat.

Purpose and scope of the document

This document provides a framework and approach for public health authorities and investigators at all levels to plan for and conduct investigations of human cases of A(H5N1) (or other novel influenza viruses of pandemic potential). The document focuses on the key steps that should be undertaken in an investigation.

The document reflects and incorporates the practical field experience gained by investigators working at international, national and sub-national levels during investigations of A(H5N1). Together with other key resources, the *Guidelines* can provide all levels of public health investigators with the essential information on how to conduct an investigation of human cases of A(H5N1). Using the *Guidelines* as a foundation, localities can develop operational plans and procedures tailored to their specific needs. The document will be updated as necessary to reflect increased understanding of A(H5N1) transmission and control and if the current pandemic threat situation changes.

The *WHO guidelines for investigation of human cases of avian influenza A (H5N1)* is not intended to be a comprehensive compendium of all the measures that need to be instituted in response to the identification of human cases of A(H5N1) influenza. This document should be read in conjunction with other detailed guidance referenced in the text.

Objectives for investigations of human cases of A(H5N1)

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

- Confirm the diagnosis of recent infection with influenza A(H5N1).
- Reduce morbidity and mortality through rapid identification, isolation, treatment and clinical management of cases and follow-up of contacts.
- Reduce further spread through 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 of vulnerable flocks, environmental decontamination, communication and social mobilization activities.
- Determine if the risk for pandemic influenza has increased as evidenced by increased efficiency of human-to-human transmission.
- Determine key epidemiological, clinical, and virological characteristics for cases including the mode(s) of transmission and disease diagnosis, manifestations and responses to treatment.
- Ensure timely exchange of information among clinicians, investigators of public and animal health, and government officials to facilitate critical and informed decision-making at sub-national, national and international levels during the investigation.

Initiating an investigation

Clinicians and public health officials at all levels need to be alert to possible human cases of A(H5N1) infection. National and sub-national systems of surveillance and reporting for influenza need to be in place as appropriate.

Laboratory-confirmation of a human case (i.e. an A(H5N1) positive test as determined by a laboratory using WHO standards for confirmation or a WHO H5 Reference Laboratory) is an immediate trigger to launch a thorough investigation (1,2). However, because collection, shipment, and testing of specimens often require several days or longer, the investigation will need to begin before laboratory test results are available for persons suspected of having A(H5N1) infection.

Investigation of ill persons will usually be undertaken in the context of established or highly suspect A(H5N1) infection in domestic or wild bird populations. The likelihood of A(H5N1) infection for ill persons is increased if exposure to birds or environments contaminated with bird droppings or consumption of uncooked poultry products occurred. However, it is important to note that human cases of A(H5N1) infection have been diagnosed in some locations where illness or death in bird populations had not been reported previously (e.g. agriculture surveillance did not detect poultry outbreaks or vaccination resulted in asymptomatic infection in poultry).

In the setting of confirmed or highly suspect A(H5N1) infection in domestic or wild bird populations, the urgency of initiating an investigation is increased when:

- two or more persons presenting with manifestations of unexplained acute lower respiratory illness¹ with fever (>38°C) (or who died of an unexplained respiratory

¹ Manifestations of acute lower respiratory illness include cough, shortness of breath, or difficulty breathing and clinical or radiographic findings of pneumonia.

illness) are detected with onset of illness in a two-week period and in the same geographical area and/or are epidemiologically linked;

- health-care workers with only occupational exposure risks develop unexplained acute lower respiratory illness with fever after providing care to patients with either known A(H5N1) infection or unexplained acute respiratory illness with fever;
- people working with birds/animals present with unexplained acute lower respiratory illness with fever;
- routine seasonal influenza surveillance detects influenza-like illness with an unusual distribution by age group, high frequency of pneumonia, or unexplained acute moderate-to-severe respiratory illness in previously healthy adults or adolescents.

Key steps for investigation of human cases of A(H5N1)

A number of critical activities must be undertaken as part of every A(H5N1) investigation. The order in which they are done may vary depending on local circumstances and often multiple activities are undertaken in parallel.

1. Prepare for the investigation

A multi-disciplinary team should be assembled. Team members should have experience in field epidemiology, clinical assessment, laboratory specimen collection, infection control, and social mobilization. Other additional team members could include logisticians, public health veterinarians, and environmental health specialists. The size and composition of the initial investigation team may vary depending in part on the size and complexity of the anticipated investigation. Designation of a team leader and attribution of roles and responsibilities is critical to the success of the investigation.

Before deploying, the team should gather preliminary background information (e.g. a description of the area where the investigation will take place including a description of the health infrastructure and the agricultural sector), assemble the necessary materials and supplies (e.g. personal protective equipment (PPE), antiviral drugs, specimen collection and transport materials) and inform relevant local public health and animal health authorities.

2. Confirm the diagnosis, interview the case patient and visit the patient's home

The case patient and/or family members (if the patient is too ill to be interviewed or has died), should be interviewed within the first 24–48 hours of the investigation to collect basic demographic, clinical, and epidemiological information. First, the date of the case patient's illness onset needs to be ascertained. Exposures to potential sources of A(H5N1) in the 7 days before illness onset² should then be sought. If the diagnosis of A(H5N1) infection has not been

² Based on currently available information and for purposes of conducting investigations, 7 days is considered to be the usual upper limit of the incubation period for human cases of A(H5N1).

confirmed, collection and testing of appropriate clinical samples from the case patients(s) is an immediate priority (see section 4).

Information that is essential for local and national authorities to manage the investigation should be collected including:

- Patient ID number/cluster number (if applicable)
- Date of illness onset
- Date of initial report
- Date of initial WHO notification
- Patient details (e.g. name, home address, home/mobile telephone numbers)
- Demographic information (e.g. date of birth/age, sex)
- Travel history in 7 days before the onset of symptoms
- Occupation (note if health-care worker or laboratory worker)
- H5 laboratory diagnosis
 - date of sampling
 - name of national laboratory: type of test, type of sample
 - name of WHO reference laboratory (if applicable): type of test, type of sample
 - test results
- Contact with confirmed or suspect human H5 cases in the 7 days before symptom onset
 - relationship with contact (first/last date of contact)
 - type of contact (speaking distance, slept in same room, touched, provided bedside care, other)
- Exposure history to animals (chickens and other animals) and their environment in the 7 days before symptom onset
 - setting (e.g. farm, backyard, household, visit of live/wet market, hunting, traditional medicine, other)
 - type of animal exposure (e.g. de-feathered, slaughtered, butchered, prepared, cleaned cages, shared living space, handled/used droppings as fertilizers, handled, played with, other)
 - occupational exposure to animal and/or animal products (e.g. slaughterer, farm worker, factory worker, poultry seller, veterinarian, culler, laboratory worker)
 - consumption of raw or undercooked animal products (e.g. meat, eggs, blood, liver)
 - H5N1 outbreak in animals in the area
 - first/last date of contact
- Clinical data
 - symptoms on day of onset
 - days of illness before initial presentation
 - symptoms at initial presentation
 - illness onset during antiviral prophylaxis
 - hospitalization, including first date of admission and duration
 - pre-existing conditions
- Laboratory data
 - white blood cell count and differential
 - haemoglobin/platelets
 - Aspartate amino transferase (AST) /Amino alanine transferase (ALT) and creatinine
 - chest radiograph results
- Antiviral treatment

- Other treatment (e.g. oxygen, intubation, antibiotics, steroids)
- Secondary complications (e.g. bacteraemia, bacterial pneumonia, shock, renal failure, coagulopathy)
- Outcome (dead/alive).

It is important that investigators obtain and verify first-hand as much information as possible. This usually includes visiting the case patient's home during which a number of key actions should be undertaken:

- Confirm the family/household composition and identify contacts of the case patient (see section 3) including:
 - Household and other contacts in work, school, and community settings who had close³ unprotected (i.e., not wearing PPE) contact in the 1 day before⁴ through 14 days⁵ after the case patient's symptom onset
 - Contacts in traditional and non-traditional in- and out-patient health-care settings before initiation of appropriate infection control measures.
- Inquire about possible bird/animal exposures for the case patient in the 7 days before illness onset including exposure⁶ to ill or dead poultry, wild birds, contaminated environments (e.g. exposure to poultry droppings including fertilizers or contaminated sewage, bathing in ponds/canals where domestic or wild birds can be found, etc.), and other animals regardless of their clinical status, especially those that may have consumed dead poultry (e.g. cats, dogs, and civets).
- Inquire about illness or deaths in birds, cats, swine, or other animals in the household and neighbouring area.
- Examine the house and its surroundings for evidence of domestic poultry (e.g. feathers, scratch marks on the floor or furniture, bird droppings, cages, poultry bones/carcasses). Note if poultry and other animals were allowed to enter the house, had access to household water and food storage areas, and if persons, especially children, were exposed to poultry or interior or exterior environmental surfaces potentially contaminated by poultry.
- Map or photograph the house and its surroundings. Indicate its location with respect to homes of other relatives or neighbours, farms (backyard and commercial), markets and nearby bodies of water that birds could inhabit.
- Collect animal and/or environmental samples and map/note locations (see section 7).

The use of PPE by investigators during home visits should be guided by the overarching priority to protect the health of investigators. Decisions can be guided by the health status of household members (e.g. asymptomatic versus actively coughing) and activities that are undertaken (e.g. collection of human or animal specimens). Investigators may elect to interview persons outdoors and not in a closed interior setting, avoid direct face-to-face contact, etc. Appropriate

³ Examples of close contact (within 1 metre) with a person include providing care, speaking with, or touching.

⁴ Based on seasonal influenza studies which indicate virus shedding typically begins the day before symptom onset; comparable data are not available for H5N1.

⁵ H5N1 virus is commonly detected in respiratory specimens during the first 2 weeks after illness onset (3,4,5). Although virus can be detected during the third week of illness for some patients with H5N1-related pneumonia, such patients would likely be hospitalized and isolated.

⁶ Examples of exposure to birds/animals include handling, slaughtering, de-feathering, preparation for consumption, consumption of raw or undercooked poultry products (including blood) in an affected area; or playing, cleaning, or touching surfaces contaminated with bird faeces.

PPE should be worn when in contact with symptomatic persons and in situations where human-to-human transmission is suspected (6,7).

3. Define a case and actively search for cases and their contacts

Information obtained from the interview and home visit of the case patient can be used to develop a working case definition. WHO has developed surveillance case definitions for tabulation and classification of human cases of A(H5N1) that can be adapted for this purpose (8). However, it will be necessary to develop a locally implemented case definition that incorporates time periods, localities, illness characteristics, exposure and other information that is specific to the investigation. Simple and objective criteria should be used whenever possible to facilitate application of the definition in a consistent and unbiased manner by field investigators. As the investigation evolves and more information is obtained it may be desirable to refine the definition to increase its sensitivity and specificity.

Contact tracing

Tracing efforts should focus on persons who had close unprotected (i.e., were not wearing PPE) contact with the case patient in the 1 day before through 14 days after the case patient's illness onset. Information about close contacts can be obtained from interviews of the patient, family members, workplace or school associates, or others with knowledge about the patient's recent activities and travels.

Prioritization of contact tracing activities may be necessary if a large number of contacts are eligible for tracing or personnel resources are limited. In such situations it may be necessary to focus on those contacts with the highest risk of infection or exposure. Factors that can be used to prioritize among contacts include:

- probability of A(H5N1) infection in the case patient (e.g. contacts of confirmed or probable cases);
- duration, spatial proximity, and intensity of exposure to the case patient (e.g. health-care workers (see section 5), household contacts sharing the same sleeping or eating space, persons providing bedside care);
- Likelihood that human-to-human transmission has resulted from contact with the case patient.

A line-listing of all contacts and co-exposed persons (see **Active case-finding** below) that records demographic information, date of last common exposure or date of contact with the case patient, daily temperature check, date of onset if fever or respiratory symptoms develop, and receipt of antiviral prophylaxis should be maintained.

- For symptomatic persons:
 - Refer persons with fever and respiratory illness for collection and laboratory testing of specimens and appropriate medical care including antiviral therapy (3,9,10). Depending on the severity of illness, acceptability, and the availability of hospital beds, contacts that are ill may be isolated at a health-care facility or at home while awaiting test results.
- For asymptomatic contacts:
 - Initiate active monitoring (e.g. daily visits or telephone calls) for the development of fever or respiratory symptoms for 7 days after the last exposure to the case patient.

Administration of antiviral chemoprophylaxis should be guided by an exposure risk assessment detailed in *WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus (10)*.

Active case-finding

Efforts to identify additional cases beyond close contacts are critical for prevention and control of infection. Active case-finding should focus on:

- persons who may have been co-exposed to the same source as the case patient
- persons with bird and animal exposures (see section 2)
- persons with unexplained acute lower respiratory infection with fever or persons who died of an unexplained respiratory illness with fever

Cases should be sought in the area under investigation using house-to-house searches and visits to and/or telephone surveys of health-care facilities, private practitioners, and laboratories.

Simple algorithms or a sequential series of direct questions (e.g. presence of a febrile respiratory illness, date of onset, date of possible exposures, etc.) will need to be developed for use by investigators at the local level (e.g. community health workers/volunteers) during contact tracing and active case-finding efforts. This will help ensure that systematic and consistent procedures are used to identify and triage cases and contacts.

4. Collect specimens

Rapid collection and testing of appropriate specimens (9) from case patients and symptomatic contacts is the highest priority. Under certain circumstances and if resources permit, specimens can be collected from asymptomatic contacts or asymptomatic persons exposed to another source of A(H5N1) for complimentary study purposes (see section 9).

It is critical that specimens be appropriately labelled with a unique identifier that can be linked to case patient demographic and epidemiological data. Assignment of identifiers must be able to distinguish multiple specimens obtained from the same patient.

Investigators need to be familiar with the type and the recommended number of specimens to be collected, optimal timing of specimen collection, which varies for respiratory and blood specimens, correct collection techniques, including the appropriate use of PPE, and standards for specimen storage, packaging and transport (9). Adequate laboratory capacity for processing and testing of specimens for A(H5N1) must also be identified.

The use of commercially available rapid diagnostic tests for the detection of human A(H5N1) infections is in general not recommended (11). The diagnostic accuracy of commercially available rapid tests for human A(H5N1) infections is unknown, and if the test result is positive, differentiation between influenza A subtypes is not possible and confirmatory tests must be done. If rapid tests are used for screening and treatment purposes, test results need to be interpreted carefully based on the epidemiological situation (i.e. circulation of human influenza A/H1, A/H3 or B) and the patient's clinical findings and exposure history. Samples should be sent for appropriate laboratory testing if A(H5N1) infection is suspected.

Collection of specimens for detailed genetic and antigenic characterization by designated WHO Reference Laboratories is especially critical if the investigation suggests that human-to-human

transmission may be occurring. WHO has provided guidance regarding timely sharing of influenza viruses/specimens with the potential for causing an influenza pandemic (12).

5. Visit hospitals and other sites of health care

All locations where the patient received traditional or non-traditional care should be visited. Visits should be undertaken regardless of whether the patient has died or been discharged in order to:

- Obtain information about the case patient:
 - interview the physician and other care providers about the patient's illness, clinical course, treatment, epidemiological/exposure information;
 - review medical records and obtain copies if possible;
 - obtain additional specimens from the patient for testing if needed; identify and secure any stored specimens previously collected from the patient.
- Review registers (e.g. admission, laboratory, consultation) to identify other possible case patients with acute febrile respiratory illness both prospectively and retrospectively (see section 6). Retrospective review of registers can be extended as needed to a longer period of time (e.g. months/years) to establish a "baseline" rate of influenza or acute respiratory illness.

Identify any health-care workers, patients, or others who were close contacts, especially those who may require chemoprophylaxis. Health care workers who have provided care for case patients should be monitored for fever and symptoms of influenza-like illness (cough, sore throat, difficulty in breathing), irrespective of the use of PPE (6,7).

- Conduct site visits and review procedures in key areas of the facility including the isolation unit/area, outpatient area for triage of persons with acute respiratory illness, and laboratory facilities.
- Provide guidance regarding:
 - medical management of persons with A(H5N1) (3,10)
 - infection control procedures (6,7).
- Inquire if there are adequate supplies of:
 - PPE
 - antiviral drugs for treatment of ill patients, chemoprophylaxis for health-care workers and others as guided by the country's protocol;
 - supportive therapy (e.g. antipyretics, antibiotics);
 - specimen collection equipment, cold chain storage, and transport material.

6. Initiate enhanced surveillance

In addition to active case searches and contact tracing as part of the investigation, efforts should be undertaken to enhance routine surveillance systems in the area(s) where case patients(s) reside or where animal outbreaks are occurring. The geographical area that should be targeted for enhanced surveillance will need to be assessed on a case-by-case basis. Factors to consider include the endemicity of A(H5N1) in the bird population, the quality of animal health surveillance, implementation of stamping out procedures and rigorous biosecurity measures, and the movement of birds (e.g. through trade, smuggling, migration) and people who may have been exposed.

Enhanced surveillance should consider the health-care seeking behaviour of the population and can include a range of options such as active and passive approaches that are health-care- and community-based. For example, surveillance can be further enhanced by:

- Active surveillance in hospitals particularly targeting in-patient and emergency departments.
- Inclusion of other sources such as traditional healers, private practitioners, private laboratories.
- Active surveillance of groups that may be at higher occupational risk of exposure (e.g. health-care workers, persons exposed to live or dead birds/animals).

Enhanced surveillance should build on whatever systems are already in place using supplementary measures such as telephone hotlines, rumour tracking and verification, and radio or other emergency networks as needed for reporting suspect cases in the community. The success of enhanced surveillance efforts will be dependent on training of health professionals, local public health investigators and volunteers, and education of the community-at-large to be alert for possible cases. In particular, early self-reporting of illness and consultation with public health facilities (e.g. through establishment of “fever clinics”) should be encouraged so that prompt and appropriate testing and clinical care and treatment can be provided. In addition, the affected community should be provided with appropriate prevention and intervention measures to reduce the risk of acquiring infection from human and animal sources.

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

7. Undertake animal health and environmental investigations

Public health investigators should work with animal health investigators to assess the role of A(H5N1) infection in wild or domestic birds or other animals as sources of possible exposure for human cases. This is particularly important in localities where highly pathogenic avian influenza A(H5N1) has not previously been documented in bird or animal populations and/or the source of exposure for human cases is unclear.

Field visits to investigate the occurrence of illness among birds and animals that is qualitatively or quantitatively unusual (e.g. large numbers of bird deaths) can include:

- the patient's home and its surroundings, especially backyard poultry areas
- poultry farms (commercial or backyard farms) near the case patient's home
- poultry/live animal markets near the case patient's home
- places frequented by wild birds (e.g. lakes)
- any other place of significance that the patient visited in the 7 days prior to illness onset.

In addition to animal illness and death, information should be sought about local housing, feeding and bird handling practices, previous poultry vaccination for H5, recent poultry/bird movement (e.g. introduction of new poultry/birds into a flock), and migratory bird patterns.

Before any specimens are collected, it is critical for investigators to be familiar with the correct collection techniques, types and recommended number of specimens to collect and appropriate use of PPE. Adequate laboratory capacity for processing and testing of specimens must also be determined. Investigators of human and animal health should coordinate their activities so that human and animal specimens can be linked and compared.

FAO and OIE guidance should be consulted regarding technical issues related to surveillance, prevention, and control of disease in birds and animals, as well as diagnostic methods, use of vaccines, and the safety of poultry products.⁷

8. Analyse data

A descriptive analysis of cases should be performed in terms of person, place, and time. For investigations that yield multiple cases, graphical and/or tabular descriptions of cases by date of onset (i.e. epidemic curve), geographical location (e.g. maps of the locale, case patients' homes), relationship (i.e. transmission or family trees) and demographic characteristics (e.g. distribution by age) should be developed. Key epidemiological (e.g. estimation of an incubation period, description of transmission patterns, attack rates by age, occupation, blood relation, etc.) and clinical (e.g. spectrum of illness severity, proportion of cases who develop pneumonia, require hospitalization, die) parameters should be characterized to enhance understanding of the spectrum and dynamics of disease associated with A(H5N1) infection.

Another key objective of the investigation is to ascertain whether any evidence exists that the virus may have increased its ability to cause human disease or improved its transmissibility. Examples of situations that might indicate a change in the transmission pattern of A(H5N1) include:

- sharp increase in the number of A(H5N1) cases despite adequate control measures in the animal population;
- absence of exposures to bird or animals among confirmed/possible 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, etc.).

Assessment of possible human-to-human transmission

Detection of two or more cases of confirmed, probable or suspect A(H5N1) infection (8) with onset of illness in the same two-week period and who are in the same geographical area and/or are epidemiologically linked, requires careful and detailed investigation to assess if transmission was likely due to a common source exposure or to human-to-human transmission.

To date, there is little evidence of human-to-human transmission of A(H5N1). Settings where persons have direct, prolonged, and unprotected contact with a symptomatic person may facilitate human-to-human transmission such as households and extended families, health-care

⁷ see web links to FAO and OIE web pages on avian influenza (accessed December 2006)
http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/avian_recomm.html
http://www.oie.int/eng/info/en_influenza.htm

settings, schools, places of work, and residential institutions such as prisons, military barracks, recreational camps, refugee/displacement locations, or orphanages.

Evaluation of clusters of cases requires collection of extremely detailed information about how the cases are related in time and space (e.g. familial relationships, dates of contact with other cases, the location, circumstances and types of contact, the time interval between contact and onset of illness), as well as all other exposures cases may have had with infected animals or contaminated environments. If human-to-human transmission is suspected, secondary attack rates among household and other close contacts and the serial interval (i.e. number of days between the onset of illness for each case) should be calculated. It may be helpful to display data using graphs or transmission tree/cluster diagrams.

In practice it can be very difficult to differentiate between human-to-human transmission and a common source exposure. Human-to-human transmission may be indicated in the setting of:

- Well documented exposure to a confirmed, probable, or suspect human case (8)
and
The time interval between contact with a human case and illness onset is 7 days or less
and
Absence of an alternative source of exposure such as exposures to birds, animals, feathers, droppings, fertilizers made of fresh bird droppings, contaminated environments, or laboratory specimens
OR
- Several generations of transmission linked to a primary case

In line with the International Health Regulations (2005), WHO should be notified if the investigation suggests that human-to-human transmission is occurring as described above (13,14). If transition from inefficient and non-sustained human-to-human transmission of influenza to efficient and sustained transmission were to occur, consideration of more intensive “containment” procedures may be indicated (15).

9. Conduct complementary studies

Depending on the outcome of the field investigation, additional studies may be undertaken to advance the understanding of the epidemiological, virological, and clinical aspects of infection with the A(H5N1) virus, including:

- sero-incidence studies among close contacts of case patients to document the incidence of new infection using paired sera;
- seroprevalence surveys among persons in the affected area with possible occupational risk (e.g. health-care workers, veterinarians, cullers, farmers, zoo personal, live poultry market workers), residents of an area experiencing bird or animal and/or human outbreaks, blood donors, or persons enrolled in ongoing sentinel surveillance for influenza or encephalitis. Such surveys should include collection of appropriate epidemiological data to assess risk factors for infection;
- case-control or cohort studies to evaluate risk factors for infection;
- systematic evaluation of the safety and efficacy of antivirals or other treatment regimens.

Studies require considerable investment in time (e.g. protocol design including institutional review board and appropriate human subjects approval, logistics preparation, implementation, and data analysis) as well as human and financial resources. The outbreak investigation and related surveillance and control activities should not be compromised by the conduct of more specialized studies.

10. Implement prevention and control measures

Many of the standard prevention and control measures to reduce opportunities for further transmission of A(H5N1) have been previously noted and are listed below.

- Strict infection control, the use of PPE during the delivery of care, and isolation of cases.
- Administration of antiviral drugs for the treatment of cases and targeted prophylaxis of close contacts.
- Initiation of active case-finding and enhanced surveillance.
- Active monitoring of contacts for the development of fever and respiratory symptoms.
- Voluntary home quarantine of asymptomatic case contacts if human-to-human transmission is occurring.

Informing the public about the outbreak and initiating social mobilization strategies are critically important. Culturally sensitive and appropriate communication messages should be formulated about specific risk factors and behaviours and how such risks can be reduced (*16*). Early self-reporting of illness and consultation with public health officials should be encouraged so that prompt and appropriate testing and clinical care and treatment can be provided.

11. Report and notify

Detection of a possible human case(s) of A(H5N1) should trigger immediate notification of local, sub-national and national public health and agricultural authorities to make immediate decisions about the launching of an investigation. This in turn should result in notification of health-care providers (traditional and non-traditional), hospitals and outpatient facilities, community leaders in the area where the case patient resided and/or travelled as part of active case-finding efforts. In line with the International Health Regulations (2005), the national health authority must notify WHO of any human case of A(H5N1) or other new human influenza virus subtype (*13*) and should disseminate to WHO collaborating centres relevant information and biological materials in a timely and consistent manner (*14*).

During the investigation, daily situation reports and efficient and timely communication with relevant authorities at local, national and international levels and other stakeholders (e.g. the public and the media) are critical.

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