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Prevention and Control of Influenza
due to
Avian Influenza Virus A (H5N1)



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1. Introduction

Influenza virus can infect both human beings and animals notably pigs and birds. Three types of influenza viruses viz A, B and C are known. Only influenza A viruses have been reported to cause natural infections of birds. Type A influenza viruses are further divided into subtypes based on the antigenic relationships in surface glycoproteins haemagglutinin (HA) and neuraminidase (NA). At present 15 HA subtypes (H1-H15) and nine neuraminidase subtypes (N1-N9) have been recognized. Each virus has one H and one N antigen, apparently in any combination. The subtypes of influenza virus demonstrate species specificity and those, which infect animals, do not usually cause infection and disease in human beings. Fifteen subtypes of influenza virus are known to infect birds; some of these are highly pathogenic. To date, all outbreaks of the highly pathogenic form have been caused by influenza A viruses of subtypes H5 and H7. This "highly pathogenic avian influenza" is characterized in birds by sudden onset, severe illness, and rapid death, with a mortality that can approach 100%. Infections to human beings from poultry infected with H9 subtype have also been documented.

1.1 Spread of avian influenza

Migratory waterfowl – most notably wild ducks – are the natural reservoir of avian influenza viruses, and these are also the most resistant to infection. These birds excrete virus in their respiratory secretions and faeces. Spread of avian influenza virus is related chiefly to the excretion of high concentrations of virus in the faeces of the infected birds. Domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza.

Direct or indirect contact of domestic flocks with wild migratory waterfowl has been implicated as a frequent cause of epidemics. Epidemiological evidence of higher prevalence of infection in poultry on routes followed by migratory waterfowls supports this hypothesis which is further strengthened by the fact that most of the commercial poultry farms are concentrated in some countries on precisely the flyways of migratory waterfowls. The absence of poultry farms or poultry congregations on the flyways of the migratory birds may also explain the non-occurrence of avian influenza in some countries in spite of their geographical location.

Avian influenza outbreaks have been reported from Australia and the USA because of the presence of natural or artificial lakes or ponds near the poultry farms. The lakes always attract migratory waterfowls because of the availability of surface drinking water.

Influenza outbreaks also show a seasonal occurrence in high risk areas, which coincides with the migratory activity. In most documented specific outbreaks evidence has been obtained of probable waterfowl contact at the initial site.

Live bird markets may also played an important role in the spread of epidemics and so does the transport of infected chickens across borders, both legally as well as illegally. Man-driven movement of poultry within the country, mainly for commercial purposes, has the potential to cause secondary spread among poultry.

Avian influenza usually does not make wild birds sick, but can make domesticated birds very sick and kill them. Avian influenza A viruses do not usually infect humans; however, several instances of human infections and outbreaks have been reported since 1997. When such infections occur, public health authorities monitor the situation closely because of concerns about the potential for more widespread infection in the human population if the virus mutates and mixes with human-flu viruses, and suddenly starts spreading as swiftly and devastatingly among people as it has among chickens.

Avian Influenza Infections in Humans

The first documented infection of humans with an avian influenza virus occurred in Hong Kong in 1997, when the H5N1 strain caused severe respiratory disease in 18 humans, of whom 6 died. The infection of humans coincided with an epidemic of highly pathogenic avian influenza, caused by the same strain, in Hong Kong's poultry population.

Extensive investigation of that outbreak determined that close contact with live infected poultry was the source of human infection. Studies at the genetic level further determined that the virus had jumped directly from birds to humans. Limited transmission to health care workers occurred, but did not cause severe disease.

Rapid destruction – within three days – of Hong Kong's entire poultry population, estimated at around 1.5 million birds, reduced opportunities for further direct transmission to humans, and may have averted a pandemic.

The Hong Kong episode alarmed public health authorities, as it marked the first time that an avian influenza virus was transmitted directly to humans and caused severe illness with high mortality. Confirmed instances of avian influenza viruses infecting humans since 1997 have been summarized in Table 1. In all these cases close contact with poultry was incriminated.

Table 1: Confirmed cases of avian influenza in human beings 1997-2003

Year	Country	Cases	Deaths	Type of Influenza A Virus
1997	Hong Kong	18	6	H5N1
1999	Hong Kong	2	0	H9N2
1999	Mainland China	Several	?	H9N2
2003	Hong Kong	2	1	H5N1
2003	Netherlands	80	1	H7N7
2003	Hong Kong	1	1	H9N2

The importance of H5N1 subtype of Influenza virus type A

Of the 15 avian influenza virus subtypes, H5N1 is of particular concern for several reasons. H5N1 mutates rapidly and has a documented propensity to acquire genes from viruses infecting other animal species. Its ability to cause severe disease in humans has now been documented on two occasions. In addition, laboratory studies have demonstrated that isolates from this virus have a high pathogenicity and can cause severe disease in humans. Birds that survive infection excrete virus for at least 10 days, orally and in faeces, thus facilitating further spread at live poultry markets and by migratory birds

2. Genesis of Current Outbreak

The most recent cause for alarm occurred in January 2004, when laboratory tests confirmed the presence of H5N1 avian influenza virus in human cases of severe respiratory disease in the northern part of Viet Nam. The epidemic of highly pathogenic avian influenza caused by H5N1, is presumed to have begun in mid-December 2003 in the Republic of Korea and is now being seen in other Asian countries, is therefore of particular public health concern. H5N1 subtype has already demonstrated a capacity to directly infect humans in 1997, and have done so again in Viet Nam and Thailand in January 2004. The spread of infection in birds increases the opportunities for direct infection of humans. If more humans become infected over time, the likelihood also increases that humans, if concurrently infected with human and avian influenza strains, could serve as the "mixing vessel" for the emergence of a novel subtype with sufficient human genes to be easily transmitted from person to person. Such an event would mark the start of an influenza pandemic.

Till date, WHO has reported 20 laboratory-confirmed cases of H5N1 avian influenza in Vietnam (15) and Thailand (5) of whom 16 (Five in Thailand and 11 in Vietnam) have died. Infection with this virus has been confirmed in poultry in Republic of Korea, Vietnam, Japan, Thailand, Cambodia, China, Laos and Indonesia. Infections in poultry in Delaware state of USA and in Pakistan due to H7 subtype of influenza A virus has also been reported recently.

Human to human transmission?

WHO has investigated a family in Vietnam for possible instance of limited human-to-human transmission of the H5N1 avian influenza strain. Virus genetic materials from two fatal cases in this cluster – sisters aged 23 and 30 years – have now been fully sequenced by the Government Virus Unit of Hong Kong's Department of Health. Both viruses are of avian origin and contain no human influenza genes.

This finding, which indicates that the virus has not changed to a form easily transmitted from one person to another, is consistent with earlier findings from epidemiological investigations. No illness has been reported in other family members, in the local community, or in health workers involved in care of these patients.

3. Epidemiology

Like SARS, epidemiology of avian influenza is complex and not fully understood. Influenza A viruses can infect human beings as well as many different animals, including ducks, chickens, pigs, whales, horses, and seals. Influenza B and C viruses circulate widely only among humans.

Wild birds are the primary natural reservoir for all subtypes of influenza A viruses and are thought to be the source of influenza A viruses in all other animals (not human beings). Most influenza viruses cause asymptomatic or mild infection in birds; however, the range of symptoms in birds varies greatly depending on the strain of virus. Infection with certain avian influenza A viruses (for example, some strains of H5 and H7 viruses) can cause widespread disease and death among some species of wild and especially domestic birds such as chickens and turkeys.

Pigs can be infected with both human and avian influenza viruses in addition to swine influenza viruses. Infected pigs get symptoms similar to humans, such as cough, fever, and runny nose. Because pigs are susceptible to avian, human and swine influenza viruses, they potentially may be infected with influenza viruses from different species (e.g., ducks and humans) at the same time. If this happens, it is possible for the genes of these viruses to mix and create a new virus. For example, if a pig were infected with a human influenza virus and an avian influenza virus at the same time, the viruses could mix (reassort) and produce a new virus that had most of the genes from the human virus, but a hemagglutinin and/or neuraminidase from the avian virus. The resulting new virus would likely be able to infect humans and spread from person to person, but it would have surface proteins (hemagglutinin and/or neuraminidase) not previously seen in influenza viruses that infect humans. This type of major change in the influenza A viruses is known as antigenic shift. Antigenic shift results when a new influenza A subtype to which most people have little or no immune protection infects humans. If this new virus causes illness in people and can be transmitted easily from person to person, an influenza pandemic can occur.

While it is unusual for people to get influenza infections directly from animals, sporadic human infections and outbreaks caused by certain avian influenza A viruses have been reported. The exact epidemiology of avian influenza and precise mechanisms of transmission of these viruses to human-beings need to be fully elucidated.

Once influenza virus is established in domestic poultry, it is a highly contagious disease and wild birds are no longer an essential ingredient for spread. Infected birds excrete virus in high concentration in their faeces and also in nasal and ocular discharges. Once introduced into a flock, the virus is spread from flock to flock by the usual methods involving the movement of infected birds, contaminated equipment, egg flats, feed trucks, and service crews, to mention a few. The disease generally spreads rapidly in a flock by direct contact, but on occasions spread is erratic.

In virulent (or highly pathogenic avian influenza) of the type traditionally associated with fowl plague, the disease appears suddenly in a flock and many birds die either without premonitory signs or with minimal signs of depression, inappetence, ruffled feathers and fever. Other birds show weakness and a staggering gait. Hens may at first lay soft-shelled eggs, but soon stop laying. Sick birds often sit or stand in a semi-comatose state with their heads touching the ground. Combs and wattles are cyanotic and oedematous, and may have petechial or ecchymotic haemorrhages at their tips. Profuse watery diarrhoea is frequently present and birds are excessively thirsty. Respiration may be laboured. Haemorrhages may occur on unfeathered areas of skin. The mortality rate varies from 50 to 100%.

Airborne transmission may occur if birds are in close proximity and with appropriate air movement. Birds are readily infected via instillation of virus into the conjunctival sac, nares, or the trachea. Preliminary field and laboratory evidence indicates that virus can be recovered from the yolk and albumen of eggs laid by hens at the height of the disease. The possibility of vertical transmission is unresolved; however, it is unlikely infected embryos could survive and hatch. Attempts to hatch eggs in disease isolation cabinets from a broiler breeder flock at the height of disease failed to result in any avian influenza -infected chickens. This does not mean that broken contaminated eggs could not be the source of virus to infect chicks after they hatch in the same incubator. The hatching of eggs from a diseased flock would likely be associated with considerable risk.

4. Aetiology

Influenza viruses are members of the family Orthomyxoviridae. These are classified into types A, B or C based on differences between their nucleoprotein and matrix protein antigens. Influenza viruses are further categorised into subtypes according to the antigens of the haemagglutinin (H) and neuraminidase (N) projections on their surfaces. There are 15 haemagglutinin subtypes and 9 neuraminidase subtypes of influenza A viruses. While all subtypes can be found in birds, only 3 subtypes of HA (H1, H2 and H3) and two subtypes of NA (N1 and N2) are known to have circulated widely in humans.

Influenza A, B, and C viruses

Influenza types A or B viruses cause epidemics of disease in human beings almost every winter. Influenza type C infections cause a mild respiratory illness and are not thought to cause epidemics. Influenza type A viruses are divided into subtypes based on two proteins on the surface of the virus. These proteins are called hemagglutinin (H) and neuraminidase (N). The current subtypes of influenza A viruses found in people are A(H1N1) and A(H3N2). Influenza B and C viruses are not divided into subtypes. Influenza A(H1N1), A(H3N2), and influenza B strains are included in each year's influenza vaccine.

5. Provisional Case Definitions for Avian Influenza

For clinical management and reporting within a country or territory, case definitions with a hierarchy of case categories will need to be developed according to the epidemiological situation. The case-definition being followed in Vietnam is reproduced below. However, the countries may need to adapt these to match their epidemiological situation. In general, countries with reported highly pathogenic avian influenza (HPAI) in animal populations need to adopt more sensitive case definitions to initiate laboratory testing than countries without reported outbreaks of avian influenza.

Patient under investigation

Any individual presenting with fever (temperature $\geq 38^{\circ}\text{C}$)

AND one or more of the following symptoms:

- cough;
- sore throat;
- shortness of breath;

who is under clinical observation and laboratory investigations are under way.

Possible influenza A/H5 case

i. Any individual presenting with fever (temperature $\geq 38^{\circ}\text{C}$)

AND one or more of the following symptoms:

- cough;
- sore throat;
- shortness of breath;

AND one or more of the following:

- a. laboratory evidence for influenza A by a test that does not sub-type the virus;
- b. having been in contact during the 7 days prior to the onset of symptoms with a confirmed case of Influenza A/H5 while this case was infectious*;
- c. having been in contact during the 7 days prior to the onset of symptoms with birds, including chickens, that have died of an illness;
- d. having worked in a laboratory during the 7 days prior to the onset of symptoms where there is processing of samples from persons or animals that are suspected of having highly pathogenic avian influenza (HPAI) infection.

OR

ii. Death from an unexplained acute respiratory illness

AND one or more of the following

- a. residing in area where HPAI is suspected or confirmed;
- b. having been in contact during the 7 days prior to the onset of symptoms with a confirmed case of Influenza A/H5 while this case was infectious*.

Probable influenza A/H5 case

Any individual presenting with fever (temperature $\geq 38^{\circ}\text{C}$)

AND one or more of the following symptoms:

- cough;
- sore throat;
- shortness of breath;

AND limited laboratory evidence for Influenza A/H5 (H5 specific antibodies detected in a single serum specimen).

Confirmed influenza A/H5 case

An individual[§] for whom laboratory testing demonstrates one or more of the following

- a. positive viral culture for Influenza A/H5;
- b. positive PCR for Influenza A/H5;
- c. immunofluorescence antibody (IFA) test positive with A/H5 monoclonal antibodies;
- d. 4-fold rise in Influenza A/H5 specific antibody titre in paired serum samples.

* Individuals infected with Influenza A/H5 virus are considered to be infectious starting from one day before the onset of symptoms up to 7 days after onset of symptoms.

[§] Laboratory investigations for Influenza A/H5 may also be undertaken on deceased individuals and in the context of targeted epidemiological studies. Laboratory confirmed cases identified under these circumstances should also be reported.

6. Clinical Picture

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 eye infections, pneumonia, acute respiratory distress, viral pneumonia, and other severe and life-threatening complications.

Published information about the clinical course of human infection with H5N1 avian influenza is limited to studies of cases in the 1997 Hong Kong outbreak. In that outbreak, patients developed symptoms of fever, sore throat, cough and, in several of the fatal cases, severe respiratory distress secondary to viral pneumonia. Previously healthy adults and children, and some with chronic medical conditions, were affected.

7. Laboratory Diagnosis

Laboratory diagnosis depends upon the demonstration of the virus and or a rising antibody titre. Following tests are available (kits for these are being developed and may be available soon):

1. Virus culture
2. RT-PCR
3. Immunofluorescence using monoclonal antibody to H5N1
4. Serological tests (ELISA and IFAT) for detection of specific antibody

Of these, virus culture can be done in laboratories with infrastructure, skills and reagents for isolation of influenza virus and confirmation of H5N1 subtype. These facilities are available only in a limited number of laboratories. A list of some of the reference laboratories that can provide diagnostic services can be seen at Annex 1.

Primers for performing RT-PCR tests are being developed and expected to be available shortly. The information on these primers shall be made available on websites of WHO, CDC, Atlanta, Ga and other institutes which may develop these.

Direct immunofluorescence test can be used to ascertain presence of virus using H5N1 specific monoclonal antibody conjugated with a fluoresceing dye.

The laboratory tests for the diagnosis of influenza A/H5 infection included in the case definition are considered the standard for the identification of these viruses. WHO recommends that laboratory results for influenza A/H5 are corroborated by a national influenza centre or other national reference laboratory. Any sample or isolate that is a non-typable influenza A (i.e. non-H3 or non-H1 subtype) should be sent immediately to a WHO collaborating centre on influenza or other WHO-recommended reference laboratory (see Annex 1). WHO also recommends that the first positive laboratory identification of influenza A/H5 virus in humans in any country or territory be confirmed by one of the WHO reference laboratories for diagnosis of influenza A/H5 infection. In addition, and until further notice, WHO requests that all human influenza A/H5 virus isolates or samples be sent to one of the WHO reference laboratories for diagnosis of influenza A/H5 infection.

Tests for diagnosing all influenza strains of animals and humans are rapid and reliable. Many laboratories in the WHO global influenza network have the necessary high-security facilities and reagents for performing these tests as well as considerable experience. Rapid bedside tests for the diagnosis of human influenza are also available, but do not have the precision of the more extensive laboratory testing that is currently needed to fully understand the most recent cases and determine whether human infection is spreading, either directly from birds or from person to person

Rapid tests for diagnosis of influenza type A

Commercial rapid diagnostic tests are available that can be used by to detect influenza viruses within 30 minutes. These rapid tests provide information upto type level. Which means that by using rapid kits one can obtain a fairly reliable indication about the presence of Influenza A virus. Confirmation of H5N1 subtype can be done only in a well equipped laboratory with all facilities and adequate biocontainment measures (details given in annex 1). Since most of the rapid tests have good specificity, a negative test can give broad indication about absence of influenza virus in specimen. As of now no commercial kit is available that can diagnose infection due to H5N1 subtype. The types of specimens acceptable for use (i.e., throat swab, nasal wash, or nasal swab) also vary by test.

Despite the availability of rapid diagnostic tests, collecting clinical specimens for viral culture is critical, because only culture isolates can provide specific information regarding circulating influenza subtypes and strains. This information is needed to establish diagnosis of avian influenza.

Keeping their limitations in mind, rapid diagnostics for influenza have proven to be valuable in early diagnosis which enables treatment in a timely fashion. Anti-influenza treatments must be administered within 48 hours of onset of symptoms in order to be effective. Some of the rapid

kits appear to be quite sensitive (mean of 87.4%; range of 74-100%) for detection of virus in nasopharyngeal specimens and is preferred for screening for influenza.

7.1 Collection of human specimens

General information

Respiratory virus diagnosis depends on the collection of high-quality specimens, their rapid transport to the laboratory and appropriate storage before laboratory testing. Virus is best detected in specimens containing infected cells and secretions. Specimens for the direct detection of viral antigens or nucleic acids and virus isolation in cell cultures should be taken during the first 3 days after onset of clinical symptoms.

Type of specimens

A variety of specimens are suitable for the diagnosis of virus infections of the **upper respiratory tract**:

- nasal swab
- nasopharyngeal swab
- nasopharyngeal aspirate
- nasal wash
- throat swab.

In addition to swabs from the upper respiratory tract, invasive procedures can be performed for the diagnosis of virus infections of the lower respiratory tract where clinically indicated:

- transtracheal aspirate
- bronchoalveolar lavage
- lung biopsy
- post-mortem lung or tracheal tissue.

Specimens for the laboratory diagnosis of highly pathogenic avian influenza A/H5 should be collected in the following order of priority :

1. nasopharyngeal aspirates
2. acute serum
3. convalescent serum.

Specimens for direct detection of viral antigens by immunofluorescence staining of infected cells should be refrigerated and processed within 1–2 hours. Specimens for use with commercial near-patient tests should be stored in accordance with the manufacturer's instructions. Specimens for virus isolation should be refrigerated immediately after collection and inoculated into susceptible cell cultures as soon as possible. If specimens cannot be processed within 48–72 hours, they should be kept frozen at or below -70°C .

Respiratory specimens should be collected and transported in virus transport media. A number of media that are satisfactory for the recovery of a wide variety of viruses are commercially available. Procedure for specimen collection is described in Annex 2.

7.2 Storage and transport of specimens

To preserve the viral integrity in specimens for inoculation, specimens should be placed in appropriate viral transport medium and stored at recommended temperatures: for respiratory samples and frozen tissues -70°C , for serum $4-8^{\circ}\text{C}$ for 24-48 hrs, or at -20°C for longer periods. Expert advice should be sought when in doubt about storage conditions related to the type of test to be done. Details of storage and transportation can be seen at Annex 3

Labelling and documentation

Specimen labeling : Each specimen should be labeled with the patient ID number and date collected.

Accompanying documentation : The package should include a linelist for all specimens including patient name and ID number, date collected, samples collected, clinical contact name and phone number, and submitter contact name and phone number (Annex 2).

7.3 Biosafety guidelines

1. The laboratories must apply good laboratory practices and standard precautions.
2. The virology work, PCR as well as preparations for transportation of infectious material should be performed in Biosafety Level (BSL) 2 facilities using BSL-3 practices
3. The following activities require BSL-3 facilities and BSL-3 work practices :
 - Culture-based attempts to isolate the agent, including inoculation onto cell culture, and eggs.
 - Initial characterization of agents recovered in cultures of specimens.
 - Any procedure that may generate aerosols or droplets and these should be performed in a biosafety cabinet.
4. Laboratory workers should wear following personal protective equipment
 - Protective clothing, preferably coveralls plus impermeable apron or long cuffed sleeves surgical gowns plus impermeable apron;
 - Disposable examination gloves;
 - Masks: the minimum requirement are well-fitted surgical masks. Where available the use of N95 masks is recommended.
 - Goggles.
 - Boots or some protective foot cover that can be disinfected
 - Frequent hand washing

When a procedure or process cannot be conducted within a biological safety cabinet, then appropriate combinations of personal protective equipment (e.g. respirators, face shields) and physical containment devices (e.g. centrifuge safety cups or sealed rotors) must be used.

In cases where laboratory facilities do not meet at least basic laboratory BSL2 containment conditions, consideration should be given to referral of specimens to suitably equipped reference laboratories (link to the list of reference labs) for primary diagnostic tests.

For laboratories that meet BSL3 containment standards and are operated by staff trained in the use of appropriate BSL3 work practices the following procedures can be undertaken:

- Performance of diagnostic tests that involve propagation of viral agents *in vitro* or *in vivo*
- Work involving the replication of influenza H5 virus in cell culture and/or storage of cell culture isolates
- Recovery of viral agents from cultures of influenza H5 specimens
- Manipulations involving growth or concentration of influenza H5 virus

8. Management of Case

The management of a case with avian influenza does not differ from that of influenza due to a primarily human pathogenic virus. Antiviral drugs, some of which can be used for both treatment and prevention, should be theoretically effective against influenza A virus strains in otherwise healthy adults and children. However, preliminary studies with Hong Kong isolates of 1997 have shown resistance to amantadine and rimantadine. It is believed that oseltamivir may be an effective drug for which reliable evidence is awaited.

Aspirin and Influenza

Children or teenagers who have flu-like symptoms – and particularly fever – should not be given aspirin as it may cause a rare but serious illness called Reye syndrome. Children or teenagers with the flu should get plenty of rest, drink lots of liquids, and take medicines that contain no aspirin to relieve symptoms. Paracetamol or ibuprofen given orally or by suppository will generally be sufficient.

8.1 Infection control and prevention of nosocomial spread

Isolate the patient to a single room. If a single room is not available, cohort confirmed and suspect cases separately in designated multi-bed rooms or wards. In such a case, the distance between beds should be at least 1m and preferably separated by a physical barrier (e.g.curtain, partition).

Reinforce implementation of standard precautions with droplet and contact precautions*. Appropriate personal protective equipment (PPE) on patient visit/care consists of: mask (high efficiency masks, surgical masks as a second alternative), gown, face shield or goggles and gloves.

Transmission of human influenza is mostly by droplets. Direct or indirect contact and airborne transmissions are also recognized, the latter can involve fine-droplet nuclei suspended in the air for considerable duration of time. However, during the last Hong Kong H5N1 outbreak in humans in 1997, droplet and contact precautions successfully managed patients without nosocomial spread of the disease. So far there is no evidence suggesting airborne transmission of the disease from the current outbreak in Viet Nam, but because of the high mortality of the disease and possibility of mutation of the virus to cause efficient human-to-

human transmission, WHO is currently recommending the use of high efficiency masks in addition to droplet and contact precautions for care of human cases of H5N1. For same reason, a negative pressure room may be preferred if available.

Limit the number of the HCWs who have direct contact with the patient(s) and they should not look after other patients. Designated HCWs should be properly trained on infection control precautions. Other hospital employees (e.g. cleaners, lab personnel) and visitors should also be restricted and provided with appropriate PPE.

HCWs with direct patient contact should monitor their temperature twice daily and report the hospital authority on every ill event. HCWs who had potential contact with droplets under circumstances without adequate personal protective equipment should be considered for post-exposure prophylaxis with oseltamivir 75 mg / day, 7days for single exposure.

All HCWs who are unwell in particular with fever and/or respiratory symptoms should not come to work. They should remain at home and report their symptoms to the hospital authority to seek further advice.

Waste should be discarded properly in a sealed impermeable bag clearly labelled as 'Biohazard' and incinerated. Linen and reusable materials that have been in contact with suspect or confirmed AI patients should be handled separately and disinfected properly.

8.2 Medical treatment

Treat with a neuraminidase inhibitor such as oseltamivir (75mg twice orally for 5 days) as early in the clinical course as possible. For paediatric patients, see standard dosage information. Provide supportive care as required. Monitor oxygen saturation and treat desaturation with supplemental oxygen as required

Amantadine and rimantadine should not be used because this may increase the selective pressure for an amantadine/rimantadine resistant pandemic reassortant virus if the patient is co-infected by H5N1 and currently circulating human influenza A viruses. Ribavirin should not be used for treatment of suspected H5N1 virus infections, since there is substantial first pass hepatic metabolism and therefore no clinical benefit is expected; furthermore, anemia associated with ribavirin is an adverse reaction that is not infrequent.

Respiratory specimen and blood specimen should be taken on admission and checked serially to look for possible bacterial infection. Consider antibiotic IV therapy to cover secondary bacterial infections as required.

8.3 Discharge policy

Further studies on viral excretion in the current outbreak is required. For the time being, infection control precautions should remain in place for 7 days after resolution of fever. For

children younger than 12 years, infection control measures should remain in place for 21 days after the onset of illness. Where this discharge policy is not applicable due to local resources and should full recovered patients within 21 days after the onset of illness discharged, the family will need to be educated on personal hygiene and infection control measures and not attend school during this period.

8.4 Public health measures

Report all suspect and confirmed cases to the local health authority and seek advice. Identify the contacts and person who were exposed to the common source of infection and put them under observation. They should be followed up for 1 week. Persons under observation should be asked to check the temperature twice daily and report all ill health events.

If such a person developed (i) sudden onset of fever over 38 degrees, and/or (ii) other respiratory symptoms, immediately prescribe oseltamivir 75mg bid for 5 days. Hospitalize the person and manage under appropriate infection control precautions. Take respiratory and blood samples and the samples should be sent to the designated laboratory for further testing on H5N1. If a case should be managed at home, the family will need to be educated on personal hygiene and infection control measures.

9. Prevention and Control

9.1 Strategy

- **Remove animal reservoir**
 - Control outbreaks by safe slaughter of poultry
 - Restrict movement of poultry from infected areas

- **Understand the extent of problem in humans**
 - Enhanced surveillance
 - Epidemiological investigations (human to human transmission)
 - Laboratory support

- **Reduce the risk of human infections from occupational exposures**
 - Protection of occupationally exposed persons
 - Infection control in health care settings

The above mentioned strategy can be implemented by following mechanisms:

9.2 Control in poultry

- Early identification
- Destruction of the entire infected cohort as per the guidelines of FAO/OIE

- Vaccination of uninfected flocks
- Proper disposal
- Early notification
- Close coordination with health department

FAO/OIE/WHO has recommended that stamping out is the preferred control option for an outbreak of HPAI and should be used on all flocks exhibiting clinical disease. It has been highly effective in controlling confined outbreaks of HPAI where there is limited spread and low risk of re-introduction. At the same time there is no justification to recommend the systematic elimination of wildlife or swine for the management of HPAI outbreaks.

Role of vaccination of birds

FAO/OIE/WHO recommend that countries may consider vaccination as an option in those situations where massive culling is either not feasible or not desirable. Vaccination reduces susceptibility to infection and shedding and hence reduces incidence of new cases and viral load. It, thus, complements other control measures. The vaccination must be carried out with quality vaccines which comply with international standards as referred in OIE Manual of Standards.

Stamping-out and vaccination are not mutually exclusive, and the mix or sequence of measures may differ between vaccine production systems and stages of a control programme.

9.3 Control in human beings

The essential components to control an outbreak in human beings include:-

- Early identification
- Isolation of both suspect and probable cases
- Tracing and monitoring close contacts of all suspect / probable cases identified,
- Barrier nursing
- Public information

Several measures can help minimize the global public health risks that could arise from large outbreaks of highly pathogenic H5N1 avian influenza in birds. An immediate priority is to halt further spread of epidemics in poultry populations. This strategy works to reduce opportunities for human exposure to the virus. Vaccination of persons at high risk of exposure to infected poultry, using existing vaccines effective against currently circulating human influenza strains, can reduce the likelihood of co-infection of humans with avian and influenza strains, and thus reduce the risk that genes will be exchanged. Workers involved in the culling of poultry flocks must be protected, by proper clothing and equipment, against infection. These workers should also receive antiviral drugs as a prophylactic measure.

When cases of avian influenza in humans occur, information on the extent of influenza infection in animals as well as humans and on circulating influenza viruses is urgently needed to aid the assessment of risks to public health and to guide the best protective measures. Thorough investigation of each case is also essential. While WHO and the members of its global influenza network, together with other international agencies, can assist with many of these activities, the successful containment of public health risks also depends on the epidemiological and laboratory capacity of affected countries and the adequacy of surveillance systems already in place.

Protection of human beings involved in mass slaughter of potentially infected animals

WHO recommends that

A. Cullers and transporters should be provided with appropriate PPE

- Protective clothing, preferably coveralls plus an impermeable apron or surgical gowns with long cuffed sleeves plus an impermeable apron
- Heavy duty rubber gloves that may be disinfected
- N95 respirator masks are preferred. Standard well-fitted masks should be used if N95 respirators are not available
- Goggles
- Rubber or polyurethane boots that can be disinfected or protective foot covers that can be discarded

B. All persons who have been in close contact with infected animals should wash their hands frequently with soap and water. Cullers and transporters should disinfect their hands after the operation.

C. Environmental clean-up should be carried out in areas of culling, using the same protective measures as above

D. All persons exposed to infected chickens or to farms under suspicion should be under close monitoring by local health authorities and provided medical care as described earlier, if needed

E. They should be vaccinated with the current WHO recommended vaccine to avoid simultaneous infection with human influenza and avian influenza and to minimize the possibility of a re-assortment of the virus's genes

While all these activities can reduce the likelihood that a pandemic strain will emerge, the question of whether another influenza pandemic can be averted cannot be answered with certainty.

9.4 Vaccination

Vaccination of human beings is possible with currently available vaccines against influenza with the objective of limiting the risk of reassortment and emergence of an influenza virus with pandemic potential that readily spreads from human to human. However, it must be made clear to the vaccinee as well as the health authorities that human vaccination with current inter-

pandemic vaccine will not protect humans from infection with avian H5N1 influenza. The vaccine may be administered to cullers who are involved in destruction of poultry, people living and working on poultry farms where H5N1 infection is reported or suspected and health care workers involved in daily care of known or confirmed human cases of influenza due to H5N1 subtype. A specific vaccine is under development and may become available within 6-12 months.

10. Potential for an Influenza Pandemic

All influenza viruses have the potential to can change. It is possible that an avian influenza virus could change so that it could infect humans and could spread easily from person to person. Because these viruses do not commonly infect humans, there is little or no immune protection against them in the human population. If an avian virus were able to infect people and gain the ability to spread easily from person to person, an "influenza pandemic" could begin. An influenza pandemic is a global outbreak of influenza and occurs when a new influenza virus emerges, spreads, and causes disease worldwide. Past influenza pandemics have led to high levels of illness, death, social disruption and economic loss. There were 3 pandemics in the 20th century. All of them spread worldwide within 1 year of being detected. They are:

Period	Common name	Virus subtype	Deaths
1918-1919	Spanish flu	H1N1	20 million-50 million
1957-58	Asian flu	H2N2	70,000 deaths in USA alone
1968-1969	Hong Kong flu	H3N2	34,000 deaths in USA alone

The Spanish Flu is considered the most severe of all influenza outbreaks till date. Though the identification of aetiology of the pandemic was not possible at that time, modern day molecular biological techniques have tried to unravel its mystery. Modern techniques have permitted a reconstitution of some parts of the genome of the 1918 agent by amplifying fragments of viral RNA obtained from different sources. One of them was anatomopathologic samples of lungs from patients who died of the disease in 1918. Other samples were obtained after the exhumation of victims of Spanish flu in Alaska and in Svalberg whose bodies had been buried in permafrost ground. Genetic sequences were obtained by genic amplification of viral RNA extracted from the lung fragments and were compared to recent human and animal viruses. The comparison showed that the hemagglutinin of the 1918 virus was of the H1 subtype belonging to a subgroup of strains infecting human and pigs, but also sharing avian determinants. Sequence analysis indicates that many avian characteristics are present in critical locations of the hemagglutinin gene such as receptor, antigenic and glycosylation sites suggesting an avian relationship. However, the virus is closely related to human and swine viruses. Equivalent findings were obtained from the study of the neuraminidase gene : the enzymatic site is preserved but avian characteristics are found in antigenic and glycosylation sites. These results suggest that the 1918 virus borrowed determinants from avian strains but was already present in mammals for a prolonged period before the pandemic started

11. Advice to International Travellers

So far WHO has not issued any travel alerts or advisories for the region in response to the H5N1 outbreak. However, travellers to countries in Asia with documented H5N1 outbreaks are advised to avoid poultry farms, contact with animals in live food markets and any surfaces that appear to be contaminated with faeces from poultry or other animals.

12. Infection Control Practices

These are similar to those required for infectious respiratory pathogens and were practised for SARS containment during 2002-2003.. Management of avian influenza cases will depend on assigning proper isolation areas in the hospital, barrier nursing and stocking PPE and availability of other essential supplies and materials. This will require advance planning.

13. Personal Protective Equipment (PPE) and their use

In all cases, following principles apply:

- PPE reduces but does not completely eliminate the possibility of infection.
- PPE is only effective if used correctly and at all times where contact may occur.
- Any contact between contaminated (used) PPE and surfaces / clothing / people outside the isolation area must be avoided.
- Used PPE must be sealed in appropriate disposal bags and sterilized or decontaminated. If staff temporarily leave the isolation area, a complete change of PPE and hand washing required.
- The use of PPE does not replace basic hygiene measures such as hand-washing, washing is still essential to prevent transmission.
- Exposure to the infected patient should be kept to an absolute minimum necessary for the level of care required.

Who should use PPE?

The staff team assigned to care for the patient should be kept to a minimum. Staff should be strictly supervised and be experienced in infection control. PPE should be used by:

- All those who are handling infected or suspected to be infected poultry and poultry products. These include cullers and animal husbandry/veterinary staff.
- All doctors, nurses and health care workers who provide direct patient care to avian influenza cases (keep to minimum necessary for patients' condition);

- All support staff including medical aides, X-ray technicians, cleaners, transport staff, laundry staff (keep staff to the minimum necessary, designate avian influenza laundry staff, etc.);
- All laboratory staff who handle patient specimens from suspect cases (keep to the minimum the staff necessary for laboratory procedures);
- Family members who care for avian influenza patients (visits should be avoided where possible);
- The patient(s) should wear a mask (N95 preferable) when other people are in the isolation area.
- Contacts and international travellers during home isolation/quarantine must wear a mask (N95 preferable).

Personal Protective Equipment

The items included are:

- Masks (N-95; N/P/R-100, If not available N80 or surgical masks as last resort)
- Gloves
- Gloves and aprons
- Hair Covers
- Eye protective ware (goggle)
- Boots or shoe covers

Storage / positioning of the supplies

- The PPE stock should be stored where it can be readily accessed at all times (24 hours a day), and is available for despatch to a facility/transport where suspected influenza patients are involved.
- The stock must be accessible after hours and on weekends.

Hand washing

It is the single most important and effective component for preventing the transmission of infection. Running water and soap with friction should be ideally used for 15 to 20 seconds. It is important to dry hands after washing. A 70% alcohol-based hand rub solution after hand washing can be used.

Hand washing should be done:

- After removing gloves
- Before and after patient contact or contact with potentially infected material
- After contact with blood and body fluids
- After taking samples
- After taking blood pressure or vital signs from patient
- After using bath room
- After blowing/wiping nose

- Before eating and preparing food.
- When leaving the isolation unit.

Linen handling

- Designated laundry staff should put patient's linen in bags and seal in the isolation room itself.
- Laundry staff should wear full PPE.
- Washing should be done in laundry with hot water and detergent, bleach may be added if compatible with the detergent being used.

Waste disposal

The practices as approved by the Hospital Infection Control Committee or hospital authorities must be followed. Some of these are:

- Puncture proof and leak proof containers should be used for sharps.
- Waste should be collected in designated colour coded plastic bags for sterilization and disposal.
- Double bag system for transport should be used.

Cleaning and disinfection of hospital environment and equipment

The practices as approved by the Hospital Infection Control Committee or hospital authorities must be followed. Some of these are:

- Cleaning staff should wear full PPE
- Cleaning should be done thoroughly to be followed by disinfection
- Isolation, X-ray and changing rooms should be cleaned and disinfected
- Items and areas requiring cleaning and disinfection are:
 - Bedside table, bed stand, accessible areas of bed and floors (Use 0.1% sodium hypochlorite as disinfectant)
- If any surface is grossly contaminated, pour 1% sodium hypochlorite first and leave it for 10-15 minutes to be followed by cleaning and usual disinfection (0.1% sod. hypochlorite).
- Basins and bedpans should be cleaned and disinfected before being used for another patient.
- Spray disinfectant is prohibited.

14. Patient, Family and Community Education

Education for the patient, their family, contacts at home isolation and the community is essential for control and prevention of avian influenza.

Education should be imparted on

- What avian influenza is and how it is transmitted.
- Why isolation is required for a case/contact of influenza
- Precaution required including PPE and how to wear N-95 mask.
- Hand washing procedure

15. IEC and Role of Media

Avian influenza is a disease that has raised a lot of concern and even panic in the population. The prevention and containment of avian influenza cannot be done without acting at the community level besides the steps taken in hospitals and laboratories. To be effective the prevention and control of any infectious disease is dependant upon the understanding, cooperation and partnership of the community. For this reason it is essential that effective and widespread awareness about avian influenza is propagated in the community with an explanation of the steps necessary to contain the disease. The media can be of great assistance in these objectives and also in getting cooperation without generating panic. An attitude of transparency and sharing will generally get media cooperation and help.

Food and HPAI

Previous outbreaks have shown that close contact of human beings with live infected poultry is the source of human infection. Therefore, the practice of marketing of live poultry directly to consumers should be discouraged in areas currently experiencing influenza outbreaks among poultry. In general, good hygiene practices during handling of raw poultry meat and usual recommended cooking practices for poultry products would lower any potential risk to insignificant levels. Eggs from infected poultry could also be contaminated with the virus and therefore care should be taken in handling shell eggs or raw egg products.

To date there is no epidemiological information to suggest that the disease can be transmitted through contaminated food or that products shipped from affected areas have been the source of infection in humans.

WHO also recommends that foods should be cooked to reach an internal temperature of 70°C since at this temperature influenza viruses are inactivated.

While trade restriction have been put in place by some countries to protect animal health, on the basis of presently available data, WHO does not at present conclude that any processed poultry products (whole refrigerated or frozen carcasses and products derived from these) and eggs in or arriving from areas currently experiencing outbreaks of avian influenza H5N1 in poultry pose a risk to public health. WHO recommends the importance of good hygiene practices during handling including hand washing, prevention of cross-contamination and thorough cooking of poultry products.

16. Country Preparedness

To ensure preparedness, the country is advised to set up a response structure at the national level and set up a contingency plan including the designation of a health care facility trained and equipped to deal with avian influenza. It is urgent that this is done as soon as possible. In summary the following actions are needed:

- Establish National Task Force with senior officials of animal husbandry departments
- Designate Focal Point
- Establish Expert Committee
- Establish Surveillance Unit and forge linkages with animal husbandry departments
- Put into place a national surveillance
- Designate at least one hospital and one laboratory
- Develop an inventory of supplies and equipment
- Provide accurate and timely information to public by efficient utilization of mass media
- Establish a mechanism of monitoring and supervision

Surveillance and reporting to WHO

For close global monitoring of the situation and coordination of the global response, the World Health Organization (WHO) is recommending enhanced surveillance for influenza A/H5 with following objectives:

1. To monitor the global occurrence of influenza A/H5 viral infection in humans.
2. To identify and characterize any emergent influenza strain so as to inform control strategies.
3. To monitor changes in transmission patterns of influenza A/H5 viruses and to detect potential human-to-human transmission of influenza A/H5 viruses;
4. To monitor unusual morbidity and mortality due to acute respiratory illness.
5. To contribute to the monitoring of outbreaks of HPAI in animal populations.

For the purposes of global surveillance, Member States are requested to report to WHO all laboratory confirmed cases of influenza A/H5 fulfilling the case definition. WHO requests that Member States immediately report the first identified individual fulfilling the confirmed case definition to the relevant WHO country office, WHO regional office, and WHO headquarters by e-mail or fax (see Annex 4: *Contact details for reporting to WHO*).

Once the first case has been identified, WHO requests that an aggregate report of confirmed cases is sent daily to the relevant WHO country office, WHO regional office, and WHO headquarters (see Annex 5: *Template for daily country summary*). Member States are requested to report summary case data daily by e-mail or fax or through the secure password-protected WHO Global Atlas web site. Any Member State wishing to report daily summary data via the WHO Global Atlas web site should contact outbreak@who.int to obtain the url address and their own specific password.

WHO requests that case-based information is sent weekly in a line-listing format (see Annex 6: *Template for line-listing* and Annex 7: *Data dictionary for line-listing*). The line-listing should include confirmed cases, all persons for whom the diagnosis of influenza A/H5 is being considered, and any discarded cases. A form to assist in data collection is also provided (see Annex 8: *Template for case report form*) and includes all variables requested in the line-listing. WHO additionally requests Member States to send documentation of their case definitions, and any subsequent revisions of these definitions, to the relevant WHO country office, WHO regional office, and WHO headquarters, by e-mail or fax.

Only information regarding confirmed cases will be made available in the public domain.

Following the confirmation of a case of influenza A/H5 infection, genetic and antigenic characterization of virus strains should be performed. WHO requests that Member States forward aliquots of original specimens and the viral isolates to one of the WHO reference laboratories for diagnosis of influenza A/H5 infection (see Annex 1) to complete these genetic and antigenic analyses.

A case report form should be completed for every individual for whom a diagnosis of influenza A/H5 viral infection is being considered (see Annex 8: *Template for case report form*). This will provide preliminary information about exposure history to help target further in-depth investigations. All individuals should be assigned a case classification according to the locally implemented case definitions.

WHO recommends a thorough field investigation of the first confirmed case of influenza A/H5 viral infection occurring in a public health district in any country or territory, to assess the exposures and the likelihood of human-to-human transmission. Subsequent confirmed cases should also be similarly investigated.

WHO recommends that Member States continue with their existing surveillance for influenza like illness and acute respiratory illness. WHO recommends that Member States with an existing early warning system for communicable disease or a surveillance system for severe or emerging acute respiratory illnesses, such as severe acute respiratory syndrome (SARS), actively investigate any unusual event and ensure that laboratory investigations for influenza are undertaken as appropriate.

WHO reference laboratories for diagnosis of influenza A/H5 infection

Department of Microbiology

Faculty of Medicine
University of Hong Kong
University Pathology Building
Queen Mary Hospital

Hong Kong

Fax: + 852 2855 1241

National Influenza Centre

Government Virus Unit
382 Nam Cheong Street
Shek Kip Mei
Kowloon

Hong Kong

Fax: +852 2319 5989

Unité de Génétique Moléculaire des Virus Respiratoires

Institut Pasteur
25 rue du Docteur Roux
75724 Paris, Cedex 15

France

Fax: +33 1 4061 3241

WHO Collaborating Centre for Reference and Research on Influenza

National Institute of Infectious Diseases
Gakuen 4-7-1, Musashi-Murayama,
Tokyo 208-0011

Japan

Fax: +81 42 561 0812 or +81 42 565 2498

WHO Collaborating Centre for Reference and Research on Influenza

National Institute for Medical Research,
The Ridgeway
Mill Hill
London NW7 1AA

England

Fax: +44 208 906 4477

WHO Collaborating Center for Studies on the Ecology of Influenza in Animals

Virology Division
Department of Infectious Disease
St. Jude Children's Research Hospital
332 North Lauderdale Street
Memphis

TN 38105-2794

USA

Fax: +1 901 523 2622

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza

Centers for Disease Control and Prevention

1600 Clifton Road, Mail Stop G16

Atlanta

GA 30333,

USA

Fax: +1 404 639 2334

Procedures for specimen collection from human cases

Materials required

- Sputum/mucus trap
- Polyester fibre-tipped applicator
- Plastic vials
- Tongue depressor
- 15-ml conical centrifuge tubes
- Specimen collection cup or Petri dishes
- Transfer pipettes

Virus transport medium

(A) *Virus transportation medium* for use in collecting throat and nasal swabs

1. Add 10 g veal infusion broth and 2 g bovine albumin fraction V to sterile distilled water (to 400 ml).
2. Add 0.8 ml gentamicin sulfate solution (50 mg/ml) and 3.2 ml amphotericin B (250 µg/ml)
3. Sterilize by filtration.

(B) *Nasal wash medium*

1. Sterile saline (0.85% NaCl).

Preparing to collect specimens

Clinical specimens should be collected as described below and added to transport medium. Nasal or nasopharyngeal swabs can be combined in the same vial of virus transport medium. When possible, the following information should be recorded on the **Field Data Collection Form** (see attached form): general patient information, type of specimens, date of collection, and contact information of person completing the form, etc

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 2–3 ml of virus transport medium and the applicator stick is broken off.

Nasopharyngeal swab

A flexible, fine-shafted polyester swab is inserted into the nostril and back to 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 2–3 ml of virus transport medium and the shaft 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 physiological saline) is applied to the nostril. With a transfer pipette, 1–1.5 ml of washing fluid is instilled 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 10–15 ml of washing fluid has been used. Dilute approximately 3 ml of washing fluid 1:2 in transport medium.

Throat swab

Both tonsils and the posterior pharynx are swabbed vigorously, and the swab is placed in transport medium as described above.

Sera collection for influenza diagnosis

An acute-phase serum specimen (3–5 ml of whole blood) should be taken soon after onset of clinical symptoms and not later than 7 days after onset. A convalescent-phase serum specimen should be collected 14 days after the onset of symptoms. Where patients are near death, a second ante-mortem specimen should be collected.

Although single serum specimens may not provide conclusive evidence in support of an individual diagnosis, when taken more than 2 weeks after the onset of symptoms they can be useful for detecting antibodies against avian influenza viruses in a neutralization test.

Field Data Collection Form

General patient information

Name:
 Address:
 Country:
 County:
 City/town/village:

Tracking record number

Date of Birth (dd/mm/yyyy):
 Sex: M [] F []
 Nationality:
 Occupation:

Date of onset of illness (dd/mm/yyyy):

Clinical specimens

Unique ID No.	Type	Date of collection	Clinical diagnosis	Health status when specimens collected	Remarks

Post-mortem specimens

Date of death(dd/mm/yyyy): ___/___/___

Name of person completing form: _____

Institutional affiliation: _____

Contact details: _____

Date(dd/mm/yyyy): ___/___/___

WHO guidelines for the storage and transport of human and animal specimens for laboratory diagnosis of influenza A/H5 infection

Specimen storage

Specimens in viral transport medium for viral isolation should be kept at 4 °C and transported to the laboratory promptly. If specimens are transported to the laboratory within 2 days, they may be kept at 4 °C; otherwise they should be frozen at or below –70 °C until they can be transported to the laboratory. Repeated freezing and thawing must be avoided to prevent loss of infectivity. Sera may be stored at 4 °C for approximately one week, but thereafter should be frozen at –20 °C.

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.

Specimen transport

Transport of specimens should comply with *WHO guidelines for the safe transport of infectious substances and diagnostic specimens* (WHO, 1997), available at http://www.who.int/emc/pdfs/emc97_3.pdf.

The receiving laboratory should be notified *before* shipment of specimens.

Transport of specimens within national borders should comply with the procedures detailed within each country's regulations.

International air transport of human specimens from suspect or probable highly pathogenic avian influenza (HPAI) H5 cases, or of specimens from HPAI H5 infected animals must follow the current edition of the International Air Transport Association (IATA) Dangerous Goods Regulations.

- [Dangerous goods index](#)
- [Consignment of diagnostic specimens 2003](#)

The IATA Regulations of 2003 (available at http://www.iata.org/NR/ContentConnector/CS2000/SiteInterface/pdf/cargo/dg/Consignment_diagnostic_specimens_2003.pdf) allow specimens known or suspected to contain the HPAI H5 agent to be transported as UN 3373 “diagnostic specimens” when they are transported for diagnostic or investigational purposes.

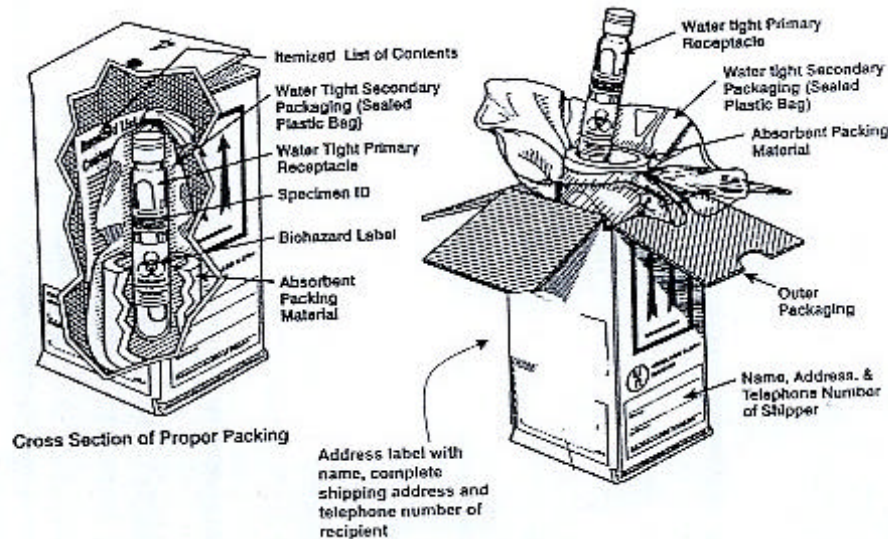
Specimens transported for any other purposes, and cultures (as defined in the IATA Regulations) prepared for the deliberate generation of pathogens, must be transported as UN 2814 or UN 2900, as appropriate.

All specimens to be transported (UN 3373, UN 2900, or UN 2814) must be packaged in triple packaging consisting of three packaging layers (see <http://www.iata.org/dangerousgoods/index>).

UN 3373, Diagnostic Specimens, shall be packed in good quality packaging, which shall be strong enough to withstand the shocks and loads normally encountered during transport. Packaging shall be constructed and closed so as to prevent any loss of contents that might be caused under normal conditions of transport, by vibration or by changes in temperature, humidity or pressure.

- Primary receptacle(s) must be water tight, e.g., if screw cap seal with parafilm or similar.
- Multiple primary receptacles must be wrapped individually to prevent breakage.
- Use enough absorbent material to absorb the entire contents of all primary receptacles in case of leakage or damage

Proper packing and labeling of the secondary container for shipping of diagnostic



The labeling for contents should include the words:
“UN 3373 Diagnostic Specimens”

In order to minimise possible loss of usefulness in specimens for further assays during the transportation period, it is advised to ship samples packed preferably with dry ice, or alternatively with enough amount of frozen ice packs/refrigerant. Detail packing, documentation, and handling requirements for the international transport of infectious materials

as contained in the regulations of the International Air Transport Association (IATA) and in documentation of the International Health Regulations (IHR).

For liquids

The primary receptacle(s) shall be leakproof and shall not contain more than 500 ml. There shall be absorbent material placed between the primary receptacle and the secondary packaging; if several fragile primary receptacles are placed in a single secondary packaging, they shall be either individually wrapped or separated so as to prevent contact between them. The absorbent material shall be in sufficient quantity to absorb the entire contents of the primary receptacles and there shall be a secondary packaging that shall be leakproof. The primary receptacle or the secondary packaging shall be capable of withstanding without leakage an internal pressure producing a pressure differential of not less than 95 kPa (0.95 bar). The outer packaging shall not contain more than 4 litres.

For solids

The primary receptacle(s) shall be sift-proof and shall not contain more than 500 g. If several fragile primary receptacles are placed in a single secondary packaging, they shall be either individually wrapped or separated so as to prevent contact between them and there shall be a secondary packaging which shall be leakproof. The outer packaging shall not contain more than 4 kg.

For air transport, the smallest overall external dimension of a completed package must be at least 10 cm.

Packaging must conform to certain performance standards.

For further information about definitions, packaging requirements, markings and labels, accompanying documentation, and refrigerants, please refer to the competent authority, current IATA shipping guidelines, commercial packaging suppliers, or available courier companies.

Annex 4

Contact details for reporting to WHO

WHO Headquarters, Geneva

Global Alert and Response Team

Mobile: +41 79 500 6540

Fax: +41 22 791 1397

E-mail: outbreak@who.int

Global Influenza Programme

Tel: +41 22 791 3004

Fax: + 41 22 791 4878

E-mail: influenza@who.int

Regional Offices

WHO Regional Office for Africa-**AFRO**

Dr Paul Lusamba-Dikassa

Regional Adviser, Communicable Disease Surveillance and Response

Tel: +263 4 746 000/011/070

Fax +263 4 746 867/127

E-mail: lusambap@whoafr.org

Regional Office for the Americas/Pan American Health Organization-**AMRO/PAHO**

Dr Marlo Libel

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Regional Office for the Eastern Mediterranean-**EMRO**

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Dr M.V.H. Gunaratne

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Regional Office for the Western Pacific-**WPRO**

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Regional Adviser in Communicable Disease Surveillance and Response

Tel: +632 528 9730/9964

Fax: +632 521 1036

E-mail: oshitanih@wpro.who.int and outbreak@wpro.who.int

Annex 7: Data dictionary for line-listing

Variable name	Information	Format	Specifications	Comments
01_country	Full name of reporting Country	Text		Full name of reporting country or territory
02_id	Case unique identifier	Any format		Provide case unique identifier being used in the Country
03_geo01	First Administrative Level	Text		Name of first administrative level from where person was reported, defined as first public health jurisdictional level below the national level
03_geo02	Second Administrative Level	Text		Name of second administrative level from where person was reported, defined as second public health jurisdictional level below the national level
03_geo03	City/Town/Village from where case was reported	Text		Name of city/town/village from where person was reported
04_d_rep	Date case identified	Date format	dd-mm-yyyy	Date that the person first came to the attention of local public health authorities
05_sex	Sex	Text	M=Male F=Female U=Unknown	Sex
06_dob	Date of birth	Date format	dd-mm-yyyy	Date of birth
06_age	Age	Numerical		Age either in years or in months using 06_unit to indicate the relevant time unit
06_unit	Age unit	Text	Y=Years M=Months	Indicate time unit used to indicate age in 06_age
07_d_ons	Date of onset of symptoms	Date format	dd-mm-yyyy	Date of onset of symptoms
08_adm01	Admitted to hospital	Text	Y=Yes N=No U=Unknown	Admitted to hospital
08_d_adm01	Date of admission to hospital01	Date format	dd-mm-yyyy	If Yes to 08_adm01, date of admission. If the person became ill while in hospital the date of admission should precede the date of onset of symptoms.
08_d_dis	Termination date of hospital stay	Date format	dd-mm-yyyy	If Yes to 08_adm01, date of discharge from final hospital where person was admitted or date of death. To be completed ONLY once
08_iso	Isolated or cohorted	Text	Y=Yes N=No U=Unknown	If Yes to 08_adm01, person isolated or cohorted during any of hospital admission
08_d_iso	Date of isolation in final hospital	Date format	dd-mm-yyyy	If Yes to 08_iso, date of isolation or cohorted in final hospital. To be completed ONLY once
08_vent	Ventilated	Text	Y=Yes N=No U=Unknown	Ventilated during any hospital admission
09_abroad	Travel abroad	Text	Y=Yes N=No U=Unknown	During the 7 days prior to the onset of symptoms, travel to or reside outside reporting country/territory. Detailed travel history should be made available on request
10_occ_an	At-risk animal-related occupation	Text	Y=Yes N=No U=Unknown	Person involved in at-risk animal-related occupation during the 7 days prior to the onset of symptoms. At-risk animal-related occupations include occupations such as: domestic fowl or swine farm worker, domestic fowl processing plant worker, domestic fowl culler (catching birds, bagging birds, transporting birds, disposing of dead birds), worker in live animal market, chef working with live or recently killed domestic fowls, dealer or trader of pet birds
10_occ_lab	Laboratory worker	Text	Y=Yes N=No U=Unknown	Worker in laboratory where samples are tested for influenza A/H5 viruses
10_occ_hcw	Health care worker	Text	Y=Yes N=No U=Unknown	Health care worker
11a_fowl	Contact with domestic fowl	Text	Y=Yes N=No U=Unknown	During the 7 days prior to the onset of symptoms contact (within 1 metre) with any live or dead domestic fowl. Domestic fowl are birds that are commonly reared for their flesh, eggs, or feathers, and kept in a yard or similar enclosure, including chickens, ducks, geese, turkeys, guinea-fowls
11b_fowl	Contact with domestic fowl setting	Text	Y=Yes N=No U=Unknown	During the 7 days prior to the onset of symptoms, entered settings where domestic fowls were confined or had been confined in the previous six weeks
11c_fowl01	Country where contact with domestic fowl	Text		If Yes to 11a_fowl or 11b_fowl, list countries/territories, excluding reporting country/territory, where exposure occurred. Create as many fields as needed to accommodate the names of all countries/territories
11a_wild	Contact with wild bird	Text	Y=Yes N=No U=Unknown	During the 7 days prior to the onset of symptoms contact (within 1 metre) with any live or dead wild bird
11b_wild	Contact with domestic wild bird	Text	Y=Yes N=No U=Unknown	During the 7 days prior to the onset of symptoms, entered settings where wild bird were confined or had been confined in the previous six weeks
11c_wild01	Country where contact with wild bird	Text		If Yes to 11a_wild or 11b_wild, list countries/territories, excluding reporting country/territory, where exposure occurred. Create as many fields as needed to accommodate the names of all countries/territories
11a_swine	Contact with swine	Text	Y=Yes N=No U=Unknown	During the 7 days prior to the onset of symptoms contact (within 1 metre) with any live or dead swine
11b_swine	Contact with domestic swine	Text	Y=Yes N=No U=Unknown	During the 7 days prior to the onset of symptoms, entered settings where swine were confined or had been confined in the previous six weeks
11c_swine01	Country where contact with swine	Text		If Yes to 11a_swine or 11b_swine, list countries/territories, excluding reporting country/territory, where exposure occurred. Create as many fields as needed to accommodate the names of all countries/territories
12_cont_c	Contact with confirmed case	Text	Y=Yes N=No U=Unknown	During the 7 days prior to onset of symptoms contact (within touching or speaking distance) with a laboratory confirmed case of influenza A/H5
12_cont_id	Unique identifier of confirmed case identified in 12_cont_c			Unique identifier of confirmed case identified in 12_cont_c
12_cont_dth	Contact with unexplained deaths	Text	Y=Yes N=No U=Unknown	During the 7 days prior to onset of symptoms contact (within touching or speaking distance) with a person with an acute unexplained respiratory illness which then resulted in death
12_cont_x	Contact with any other person for whom diagnosis of influenza A/H5 is being considered	Text	Y=Yes N=No U=Unknown	During the 7 days prior to onset of symptoms contact (within touching or speaking distance) with a person for whom diagnosis of influenza A/H5 viral infection is being considered. Include all case categories that are not confirmed and excludes unexplained deaths. To be updated if the classification of the case with whom the case has been in contact changes
13_clus	Person part of cluster	Text	A=Applicable NA=Not applicable	If Yes to 12_cont_c or 12_cont_dth or 12_cont_x, then person is part of a cluster, 13_clus=Applicable. Cluster is defined as two or more persons for whom the diagnosis of influenza A/H5 is being considered (including those persons who have died of an unexplained acute respiratory illness) with onset of symptoms within the same two-week period and who are associated with a specific setting such as a household, extended family, hospital, other residential institution, military barracks, or recreational camp ,either already identified or newly assigned

13_clus_id	Cluster identifier	Any format		If Applicable to 13_clus, indicate cluster unique identifier, either already identified or newly assigned. Suggest to use the unique identifier of the first identified case in the cluster as cluster identifier
13_clus_sett	Cluster setting	Text	HH=Household F=extended family H=Hospital I=other residential institution M=Military barracks R=Recreational camp O=Other	Defined setting in which cluster is occurring/occurred
14_no_an	No animal and no lab exposure	Text	A=Applicable NA=Not applicable	If No to (10_occ_an, and 10_occ_lab, and 11a_fowl, and 11b_fowl, and 11a_wild, and 11b_wild, and 11a_swine, and 11b_swine) then 14_no_an=Applicable; else then 14_no_an=Not applicable. This variable should be used to provide daily the number of confirmed cases with no reported at-risk animal exposure and no laboratory occupational exposure
14_ukn	Exposure history unknown or undetermined	Text	A=Applicable NA=Not applicable	If Unknown or blank to (10_occ_an, and 10_occ_lab, and 10_occ_HCW, and 11a_fowl, and 11b_fowl, and 11a_wild, and 11b_wild, and 11a_swine, and 11b_swine, and 12_cont_c, and 12_cont_dth, and 12_cont_x) then 14_ukn=Applicable; else then 14_ukn=Not applicable. This variable should be used to provide daily the number of confirmed cases for which exposure history is unknown or undetermined
15_cultH5	Positive viral culture for influenza A/H5	Text	Y=Yes N=No U=Unknown P=Pending	Positive viral culture for influenza A/H5
15_pcrH5	Positive PCR for influenza A/H5	Text	Y=Yes N=No U=Unknown P=Pending	Positive PCR for influenza A/H5
15_ifaH5	Positive IFA for influenza A/H5 monoclonal antibodies	Text	Y=Yes N=No U=Unknown P=Pending	Positive IFA for influenza A/H5 monoclonal antibodies
15_seroh5	4-fold rise in H5-specific antibody titre in paired serum samples	Text	Y=Yes N=No U=Unknown P=Pending	4-fold rise in H5-specific antibody titre in paired serum samples
15_subtype	Influenza H5 subtype	Text		Influenza H5 subtype
15_reflab	Samples sent for confirmation to WHO reference laboratory	Text	Y=Yes N=No U=Unknown	Samples sent for confirmation to WHO reference laboratories for diagnosis of influenza A/H5 infection
16_disp	Final disposition	Text	R=Recovered D=Deceased F=Lost to follow-up	R (=Recovered) includes persons discharged from hospital; L (=Lost to follow-up) includes persons lost to follow-up whilst still infectious. To be completed ONLY once
16_d_disp	Date of final disposition determined	Date format	dd-mm-yyyy	Date of final disposition determined
17_d_dead	If deceased, date of death	Date format	dd-mm-yyyy	If deceased, date of death
18_i_class	Interim case classification	Text	Confirmed Probable Possible Investigated Discarded	If 18_i_class=Confirmed then 19_fin_class=Confirmed. If 18_i_class=Discarded then 19_fin_class=Discarded. Case classification to be updated as appropriate. This variable provides the daily profile of current cases
19_fin_class	Final case classification	Text	Confirmed Probable Possible Investigated Discarded	To be completed ONLY once. Discarded cases should remain in the data set
19_d_fin_class	Date final case classification assigned	Date format	dd-mm-yyyy	Date final case classification assigned

Annex 8: Template for case report form

Case report form - Influenza A/H5

Case unique identifier (02_id)

1. Reporting details

Name of reporting Country or Territory (01_country)

Date of report to National Health Authorities (dd/mm/yyyy)

___/___/___

Contact details of person submitting the report

Name

Institution/Organization

Address

Telephone

Fax

E-mail

First administrative level from where person was reported (03_geo01)

(defined as first public health jurisdictional level below the national level)

Second administrative level from where person was reported (03_geo02)

(defined as second public health jurisdictional level below the national level)

City/town/village from where person was reported (03_geo03)

Date that person first came to the attention of local public health authorities

(dd/mm/yyyy) (04_d_rep)

___/___/___

2. Demographic details

Sex (05_sex)

Male Female

Unknown

Date of birth (dd/mm/yyyy) (06_dob)

___/___/___

Age (06_age)

expressed in (06_unit)

Years

Months

Current contact details

Full address

Country

Telephone

Fax

Nationality

Ethnicity

3. Signs and symptoms

Date of onset of illness (dd/mm/yyyy) (07_d_ons)

___/___/___

Body temperature higher than 38°C

Yes No Unknown

Cough

Yes No Unknown

Sore throat

Yes No Unknown

Shortness of breath

Yes No Unknown

4. History of admission to hospital

Has the person been admitted to hospital (**08_adm01**) Yes No Unknown

If Yes, complete table¹ below

Note: If the person became ill while in hospital, include these details of this hospital stay under Hospital 01 in the table. Under these circumstances the date of admission should precede the date of onset of symptoms.

	Name of the hospital or hospital identifier	Second administrative level where hospital is located	Date of admission to hospital (dd/mm/yyyy)	Has the person been isolated or cohorted	Date of isolation or cohorted (dd/mm/yyyy)	Date person discharged from hospital ² (dd/mm/yyyy)
Hospital 01			(08_d_adm01)	Yes No Unknown		
Hospital 02				Yes No Unknown		
Hospital 03				Yes No Unknown		
Hospital 04				Yes No Unknown		
Hospital 05				Yes No Unknown		

To be completed ONLY once

Termination date of hospital stay (correspond to date of discharge from **final** hospital, or date of death) (dd/mm/yyyy) (**08_d_dis**)

___/___/___

During any of the hospital admissions was the person:

Isolated or cohorted (**08_iso**) Yes No Unknown

If Yes, date of isolation in **final** hospital (dd/mm/yyyy) (**08_d_iso**)

___/___/___

Mechanically ventilated (**08_vent**) Yes No Unknown

Admitted to an intensive care unit Yes No Unknown

¹ Add as many lines as needed to accommodate all hospitals in which the case was admitted

² Date case discharged from hospital: this corresponds to the date of discharge OR date of transfer OR date of death

5. Travel history

During the 7 days prior to the onset of symptoms, did the person travel to or reside **outside** the reporting country or territory (**09_abroad**) Yes No Unknown
 If Yes, complete itinerary in table³ below

Place of departure	Country/territory of departure	HPAI outbreak reported in the animal populations of country/territory of departure	Date of departure (dd/mm/yyyy)	Primary means of transport 1. Plane 2. Boat 3. Train 4. Bus 5. Other	Place of arrival	Country/territory of arrival	HPAI outbreak reported in the animal populations of country/territory of arrival	Date of arrival (dd/mm/yyyy)
		Yes No Unknown					Yes No Unknown	
		Yes No Unknown					Yes No Unknown	
		Yes No Unknown					Yes No Unknown	
		Yes No Unknown					Yes No Unknown	
		Yes No Unknown					Yes No Unknown	
		Yes No Unknown					Yes No Unknown	

Note: Although detailed information contained in this table is not included in the line listing, WHO may request for it to be made readily available should it be needed for international outbreak control purposes.

³ Add as many lines as needed to accommodate all places visited

During the 7 days prior to the onset of symptoms, did the person travel to or reside in areas **within** the reporting country or territory? Yes No Unknown

If Yes, complete itinerary in table⁴ below

Area of departure (Second administrative level)	HPAI outbreak reported in the animal populations of area of departure	Date of departure (dd/mm/yyyy)	Primary mean of transport 1. Plane, 2. Boat, 3. Train, 4. Bus, 5. Other	Area of arrival (Second administrative level)	HPAI outbreak reported in the animal populations of area of arrival	Date of arrival (dd/mm/yyyy)
	Yes No Unknown				Yes No Unknown	
	Yes No Unknown				Yes No Unknown	
	Yes No Unknown				Yes No Unknown	
	Yes No Unknown				Yes No Unknown	
	Yes No Unknown				Yes No Unknown	
	Yes No Unknown				Yes No Unknown	

⁴ Add as many lines as needed to accommodate all places visited

6. Occupational exposure

During the 7 days prior to the onset of symptoms, has the person been working:

6a In an at-risk animal-related occupation ⁵ (10_occ_an)	Yes	No	Unknown
6b As a worker in laboratory where samples are tested for influenza A/H5 viruses (10_occ_lab)	Yes	No	Unknown
6c As a health care worker (10_occ_hcw)	Yes	No	Unknown

7. History of exposure to animal populations

During the 7 days prior to the onset of symptoms, has the person:

	<i>7a</i>	<i>7b</i>	<i>7c</i>
	Contact (within 1 metre) with any live or dead animal of species listed	Entered settings where animal species were confined or had been confined in the previous six weeks	If Yes to <i>7a</i> or <i>7b</i> , and exposure occurred outside the reporting country/territory, list all countries/territories where these exposures occurred
Domestic fowl ⁶	Yes No Unknown (11a_fowl)	Yes No Unknown (11b_fowl)	(11c_fowl) _____ _____ _____
Wild birds	Yes No Unknown (11a_wild)	Yes No Unknown (11b_wild)	(11c_wild) _____ _____ _____
Swine	Yes No Unknown (11a_swine)	Yes No Unknown (11b_swine)	(11c_swine) _____ _____ _____

⁵ At-risk animal-related occupations include occupations such as: domestic fowl or swine farm worker, domestic fowl processing plant worker, domestic fowl culler (catching birds, bagging birds, transporting birds, disposing of dead birds), worker in live animal market, chef working with live or recently killed domestic fowls, dealer or trader of pet birds.

⁶ Domestic fowl are birds that are commonly reared for their flesh, eggs, or feathers, and kept in a yard or similar enclosure, including chickens, ducks, geese, turkeys, guinea-fowls.

9. Laboratory investigation results

Positive influenza A by rapid test	Yes	No	Unknown
High influenza A/H5 specific antibodies detected in a single serum specimen	Yes	No	Unknown
If Yes, indicate titre _____			
Positive viral culture for influenza A/H5 (15_cultH5)	Yes	No	Unknown
Positive polymerase chain reaction (PCR) for influenza A/H5 (15_pcrH5)	Yes	No	Unknown
Positive immunofluorescence antibody (IFA) test for H5 antigen using H5 monoclonal antibodies (15_ifaH5)	Yes	No	Unknown
4-fold rise in H5-specific antibody titre in paired serum samples (15_seroH5)	Yes	No	Unknown
Has influenza A/H5 virus subtype been identified	Yes	No	Unknown
If Yes, specify (15_subtype) _____			
Were samples or isolates sent for further confirmation to a WHO reference laboratories for diagnosis of influenza A/H5 infection ¹⁰ (15_reflab)	Yes	No	Unknown
If Yes, indicate laboratory:			
National Institute of Infectious Diseases, Japan	Yes	No	Unknown
Centers for Disease Control and Prevention, US	Yes	No	Unknown
National Institute for Medical Research, UK	Yes	No	Unknown
St. Jude Children's Research Hospital, US	Yes	No	Unknown
National Influenza Center - Government Virus Unit			
Hong Kong - SAR China	Yes	No	Unknown
The University of Hong Kong, Queen Mary Hospital			
Hong Kong - SAR China	Yes	No	Unknown
Institut Pasteur, France	Yes	No	Unknown
Other	Yes	No	Unknown
If Yes , specify _____			

¹⁰ See Annex 6: WHO reference laboratories for diagnosis of influenza A/H5 infection

10. Prophylaxis against influenza

Was the person vaccinated against influenza in the 6 months prior to the onset of symptoms

Yes No Unknown

If Yes, in which country _____

During the 7 days prior to the onset of symptoms has the person been taking any of the following medications

	Medication		Was the medication taken every day during this 7 day period
Oseltamivir phosphate (Tamiflu®)	Yes No Unknown	If Yes,	Yes No Unknown
Zanimivir (Relenza®)	Yes No Unknown		Yes No Unknown
Amantadine (Symadine®, Symmetrel®)	Yes No Unknown		Yes No Unknown
Rimantadine (Flumadine®)	Yes No Unknown		Yes No Unknown

11. Final disposition (16_disp) To be completed ONLY once

Recovered (Recovered includes persons discharged from hospital)
Deceased
Lost to follow-up (Lost to follow-up includes persons lost to follow-up whilst still infectious)

Date final status was determined (dd/mm/yyyy) (16_d_disp) ____/____/____

For deceased persons ONLY

If person deceased, date of death (dd/mm/yyyy) (17_d_dead) ____/____/____

12. Case classification

Initial case classification Date initial case classification (dd/mm/yyyy) ____/____/____
Confirmed
Probable
Possible
Under investigation

Interim Case Classification (18_i_class)

Date case classification assigned (dd/mm/yyyy)
Confirmed ____/____/____
Probable ____/____/____
Possible ____/____/____
Under investigation ____/____/____
Discarded ____/____/____

Final case classification (19_fin_class)

Confirmed
Probable
Possible
Under investigation
Discarded (Discarded cases should remain in the data set)
Date final case classification (dd/mm/yyyy) (19_fin_class) ____/____/____