



INTERIM REFERENCE DOCUMENT

Avian Influenza Tool Kit

Responding to human cases of A/H5N1

Public health management of human avian influenza outbreaks in Europe

Beta-testing Version

November 2007

Comments to influenza@ecdc.europa.eu

Table of Contents

Acknowledgements.....	1-4
1. Introduction	1-5
1.1. Background.....	1-5
1.2. Purpose – When should this be used.....	1-6
1.3. Audience.....	1-6
1.4. Documents development	1-6
2. Human avian influenza disease	Error! Bookmark not defined.
3. Case definitions for influenza A/H5N1 in humans in the European Union.....	2-8
3.1. Case definitions for use in surveillance	2-8
3.1.1. Clinical criteria.....	2-8
3.1.2. Laboratory criteria.....	2-8
3.1.3. Epidemiological criteria	2-8
3.1.4. Surveillance case classification	2-9
3.2. Other definitions	2-10
3.2.1. Case definition for use in outbreak.....	2-10
3.2.2. Exposed persons to influenza A/H5N1	2-10
3.2.3. Persons under investigation.....	2-10
4. Initial assessment of potential human highly pathogenic avian influenza A/H5N1 cases in the European Union	3-11
4.1. Who is at risk of getting avian influenza A/H5N1?.....	3-11
4.2. Communication about persons under investigation for avian influenza A/H5N1.....	3-11
4.3. Who is at risk of getting “Bird Flu” - Highly pathogenic A/H5N1 avian influenza?	3-12
5. Outbreak investigation of human A/H5N1 cases	4-13
5.1. Definition of a A/H5N1 outbreak in humans.....	4-13
5.2. Purpose and objectives	4-13
6. Key roles and responsibilities in the public health management of human avian influenza outbreaks 5-15	
6.1. Clinical professionals	5-15
6.1.1. Initial assessment, admission and referral of persons requiring investigation for avian influenza (Person under investigation).....	5-15
6.1.2. Management of avian influenza exposed persons	5-16
6.1.3. Management of possible avian influenza cases	5-17
6.1.4. Discharge of avian influenza cases	5-17
6.1.5. Management of persons that do not meet the definition of exposed person or possible case.....	5-18
6.2. Hospital infection control / occupational health professionals	5-18
6.2.1. Hospital infection control procedures	5-18
6.2.2. Health care workers tracing and monitoring	5-18

6.3.	<i>Laboratory professionals</i>	5-19
6.3.1.	Receipt of samples	5-19
6.3.2.	Processing of samples	5-19
6.3.3.	Communication of results	5-19
6.4.	<i>Public Health Professionals</i>	5-19
6.4.1.	Confirm outbreak and diagnosis.....	5-19
6.4.2.	Ascertain clinical history, exposure history and how diagnosis was made:	5-19
6.4.3.	Re-assess the notified person	5-20
6.4.4.	Establishing a case definition	5-20
6.4.5.	Convening an Outbreak Control Team (OCT).....	5-20
6.4.6.	Identify cases and obtain information	5-21
6.4.7.	Determining the likely source of infection or contamination.....	5-21
6.4.8.	Risk assessment and management of exposed persons	5-23
6.4.9.	Active case finding.....	5-26
6.4.10.	Describing any clustering / assessing human-to-human transmission.....	5-26
6.4.11.	Public health department and agency reporting and liaison	5-27
7.	Avian influenza algorithms	6-29
8.	Avian influenza forms and line lists	7-30
8.1.	<i>Clinical professionals</i>	7-30
8.2.	<i>Hospital infection control / occupational health professionals</i>	7-30
8.3.	<i>Laboratory professionals</i>	7-30
8.4.	<i>Public health professionals</i>	7-30
9.	Avian influenza resources	8-33
9.1.	<i>ECDC avian influenza guidelines</i>	8-33
9.1.1.	Risk assessments	8-33
9.1.2.	Advice to European Union citizens.....	8-33
9.1.3.	Technical advice to European Union public health authorities	8-33
9.2.	<i>WHO resources</i>	8-34
9.2.1.	Ethics (Informed consent, confidentiality, respect for human rights and scientific integrity) and code of conduct.....	8-34
9.2.2.	Clinical	8-34
9.2.3.	Hospital infection control.....	8-34
9.2.4.	Laboratory	8-34
9.2.5.	Public health.....	8-35
9.2.6.	Social mobilization and communication	8-35
9.2.7.	Veterinary.....	8-35

Acknowledgements

This tool kit has drawn on the avian influenza work experience and produced documents from the WHO led international missions to Turkey (January and February 2006) and Iraq (February 2006) and on public health work experience. It is a reference document for European Union Member States.

We would like to acknowledge everyone who through discussions and comments have helped to shape this document both within ECDC and beyond.

Preparedness and Response Unit and ECDC Influenza Project Team

The intention now is that the Tool Kit should be beta-tested by national authorities in Member States and comments on its use returned to influenza@ecdc.europa.eu.

ECDC would welcome national authorities informing ECDC when the tool kit is used, through the 24h/7d duty system (E mail: support@ecdc.europa.eu; Phone: +46 841047878).

1. Introduction

1.1. Background

Confirmed A/H5N1 infections in wild birds have been detected in a number of European Union (EU) countries since early 2006. Some domestic poultry have been infected, as have a few companion animals (cats). Domestic poultry are found in all EU countries, and in many of these countries they are sometimes in close proximity with humans. Exposure to domestic poultry ill from highly pathogenic avian influenza (HPAI) has been associated with human H5N1 infections in ten countries worldwide, including those neighbouring Turkey, on the edge of Europe. In addition, other HPAI viruses (A/H7N7) have already resulted in human infections in Europe. There is therefore a small but significant risk of transmission to humans in the EU especially if more infections appear in domestic poultry. Therefore, preparations need to be made for that eventuality.

Equally, European Member States need to investigate people presenting with respiratory illness who are thought to have had contact with infected birds, wild or domestic, in Europe or abroad or with other human cases abroad.

ECDC's public health strategy for dealing with A/H5N1 has three components:

- **Control the infection in birds to reduce potential exposures for humans and domestic animals, including poultry.** That is supporting veterinary initiatives and ensuring they include backyard and domestic poultry;
- **Mobilise and educate communities to reduce risk of human exposure to infected birds.** There is model guidance on the messages that can support this component in some EU Member States¹. UNICEF has developed specific health education materials for this purpose²;
- **Strengthen Member States capacity** to detect, investigate and treat human cases, implement surveillance strategies, define procedures for laboratory confirmation and ensure proper infection control practices.

The highest priority from the public health point of view is the rapid detection of cases in order to start timely treatment if needed and to initiate follow-up of close contacts to determine if person-to-person transmission of A/H5N1 occurs. In addition, risk factors need to be identified, in order to target the public health interventions more effectively.

1 Avian influenza: guidance for National Authorities to produce messages for the public concerning the protection of vulnerable groups (February 2006)

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/National_authorities_awareness.pdf

2 <http://www.unicef.org/avianflu/index.html>

The main source of information for human infection with influenza A/H5N1 is the article “Current concepts Avian Influenza A/H5N1 Infection in Humans”³ and subsequent articles. At present the virus “*remains a not very infectious bird flu virus (not infectious for humans – very infectious for birds), poorly adapted to humans, but highly pathogenic in those few humans it infects, and then generally does not transmit on to others*”⁴.

1.2. Purpose – When should this be used?

The specific purpose of this document and its supporting annexes is to assist and guide those responsible for public health in EU countries who are confronted with reports of people who are suspected of having been infected with HPAI viruses including A/H5N1.

Elements of the document and its annexes will also be useful in the event of an outbreak of A/H5N1 (or another HPAI virus in poultry in the EU) where there needs to be case finding to ensure that there are no human cases

These documents will be of particular use when there are persons suspected of having acquired infections but they also contain components to be used pre-emptively when cases are yet to appear. These documents are not meant to replace documents already produced by Member States, but represent model documents that Member States can adapt, while ensuring an overall consistent approach across the EU.

The tool kit is a reference document that aims to represent an outline of the principles of public health management of an outbreak of human cases of avian influenza. It does not provide detailed guidance to European Union Member States on the operations of public health management nor does it cover research needs and opportunities.

1.3. Audience

The primary audience is public health professionals responsible for detecting, investigating and responding to the threat of A/H5N1 infection in humans. However, there is a wider range of professionals who will potentially find these documents useful, in particular those delivering front-line clinical services.

1.4. Documents development

These documents have drawn on examples of good practice in Member States (MS), World Health Organisation (WHO) documents and documents already developed in the field by

3 Avian Influenza A (H5N1) Infection in Humans 29 September 2005. The Writing Committee of the World Health Organisation (WHO) Consultation on Human Influenza A/H5, 2005
<http://content.nejm.org/cgi/content/full/353/13/1374>

4 ECDC The public health risk from highly pathogenic avian influenza viruses emerging in Europe with specific reference to type A/H5N1 (June 2006)
http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/060601_public_health_risk_HPAI.pdf

multi-agency around animal outbreaks and human cases in Turkey, Iraq and South-East Asia. They complement scientific and technical guidance documents produced by ECDC in relation with avian influenza infection (see section 8-33).

As they are living documents which will develop and improve with experience, comments, corrections and reflections are therefore welcomed and should come through influenza@ecdc.europa.eu

2. EU case definitions for influenza A/H5N1 in humans

2.1. Case definitions for use in surveillance

The following “Interim surveillance case definition for influenza A/H5N1 in humans in the EU” is derived from the WHO guidelines for global surveillance of influenza A/H5⁵ and is intended for EU Member States. It should be used, in the current situation (WHO, Pre-pandemic alert phase 3) for the purpose of undertaking surveillance for cases of influenza A/H5N1 infections in humans in the EU. This case definition is under revision; the latest interim case definition is from 10 November 2006.

The definition is not intended to be used for diagnosis or management of cases.

2.1.1. Clinical criteria

Any person with at least one of the following two:

- Fever AND signs and symptoms of acute respiratory infection;
- Death from an unexplained acute respiratory illness.

2.1.2. Laboratory criteria

At least one of the following three:

- Isolation of influenza A(H5N1) from a clinical specimen;
- Detection of influenza A(H5) nucleic acid in a clinical specimen;
- Influenza A(H5) specific antibody response (fourfold or greater rise or single high titre).

2.1.3. Epidemiological criteria

At least one of the following four epidemiological links within 7 days prior to onset of symptoms:

- Human to human transmission by having been in close contact (within one metre) to a person reported as probable or confirmed case;
- Laboratory exposure: where there is a potential exposure to influenza A/H5N1;
- Close contact (within one metre) with an animal with confirmed A/H5N1 infection other than poultry or wild birds (e.g. cat or pig);

⁵ http://www.who.int/csr/disease/avian_influenza/guidelines/globalsurveillance.pdf

- Reside in or have visited an area⁶ where influenza A/H5N1/ is currently suspected or confirmed as reported to the European Commission (SANCO) by the Animal Disease Notification System (ADNS), available at http://ec.europa.eu/food/animal/diseases/adns/index_en.htm#.

AND at least one of the following two:

- Having been in close contact with sick or dead domestic poultry or wild birds in the affected area;
- Having been in a home or a farm where sick or dead domestic poultry have been reported in the previous month in the affected area.

Incubation period is usually 7 days.

2.1.4. Surveillance case classification

Possible case

Any person meeting the clinical criteria and with an epidemiological link.

Probable case

Any person with a positive test for influenza A/H5 or A/H5N1 performed by a laboratory which is not a National Reference Laboratory participating in the EU Community Network of Reference Laboratories for human influenza (CNRL).

Nationally confirmed case

Any person with a positive test for influenza A/H5 or A/H5N1 performed by a National Reference Laboratory participating in the EU Community Network of Reference Laboratories for human influenza (CNRL).

WHO confirmed case

Any person with a laboratory confirmation by a WHO Collaborating Centre for H5 (e.g. Institut Pasteur, Paris or National Institute for Medical Research, Mill Hill, London).

To be reported to the EU level

Probable and confirmed cases, nationally and WHO confirmed, should be reported.

⁶ Definition of affected area within the EU will be further developed

2.1.5. Other definitions

Case definition for use in outbreak

The above case definitions were developed for surveillance purposes. However, in the event of an investigation of an existing outbreak of human cases, this case definition may be amended, in particular to include criteria of time and place of occurrence of the outbreak.

Exposed persons to influenza A/H5N1

Any individual, without clinical history or with clinical history different to the one defined above, meeting at least one of the epidemiological links (as defined above). The exposed persons to influenza A/H5N1 will be identified, risk assessed and managed.

Persons under investigation

A person whom public health authorities have decided to investigate for possible A/H5N1 infection (WHO)⁷.

⁷ http://www.who.int/csr/disease/avian_influenza/guidelines/case_definition2006_08_29/en/index.html

3. Initial assessment of potential human highly pathogenic avian influenza A/H5N1 cases in the European Union

3.1. Who is at risk of getting avian influenza A/H5N1?

In making an initial rapid risk assessment of any person that could possibly be considered to have influenza A/H5N1 infection, clinicians and public health professionals should consider the following five points:

- To date, the experience in EU countries with humans who have been evaluated, is that none have been infected with A/H5N1;
- It is important to remember that influenza A/H5N1 is at present “a not very infectious bird flu virus for humans, poorly adapted to humans, but highly pathogenic in those few humans it infects, and then generally does not transmit on to others⁸.”
- Risk groups for infection with A/H5N1 have quite specific characteristics (see section 3.3);
- The clinical presentation of the people confirmed to have A/H5N1 infections is in the majority of cases a severe febrile illness with respiratory symptoms rarely a diarrhoeal or encephalitic-like illness without clear respiratory symptoms which were found in very few patients⁹;
- To date, there have been no confirmed mild or asymptomatic infections. Seemingly, this is reflecting that at present A/H5N1 infection in humans is acting like a severe zoonosis.

Person under investigation are very unlikely to have A/H5N1 infection but rather another infectious condition and should be treated accordingly

3.2. Communication about persons under investigation for avian influenza A/H5N1

Given the extremely low probability of an A/H5N1 positive test result in, for example, a person with a mild febrile respiratory illness with only a vague exposure to infected birds, public health departments and/or agencies should be cautious to make such a situation proactively public.

8 ECDC The public health risk from highly pathogenic avian influenza viruses emerging in Europe with specific reference to type A/H5N1 (June 2006)

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/060601_public_health_risk_HPAI.pdf

9 Avian Influenza A (H5N1) Infection in Humans 29 September 2005

<http://content.nejm.org/cgi/content/full/353/13/1374>

Instead, a reactive statement should be prepared. Terminology is important: such cases should not be referred to as suspect A/H5N1 cases. More correctly, they are persons under investigation where A/H5N1 is being excluded and other diagnoses are much more likely. This is very important as otherwise people will start referring to them as, for example suspect or possible cases, with all the implications that follow.

3.3. Who is at risk of getting “Bird Flu” – HPAI A/H5N1?

For the majority of people who have no contacts with domestic or wild birds or their droppings, the risk of acquiring A/H5N1 is almost non-existent. However there are two groups of persons that have shown to be at increased risk of becoming infected with A viruses.

Group 1 - Low but real risk

The risk of infection is almost entirely confined to the small numbers of people who have close and intense contact with sick A/H5N1 infected domestic poultry (chickens, ducks, etc) or their droppings or sometimes wild birds, for example through having sick and A/H5N1 infected poultry in the house. Human cases have almost entirely been in this category. This includes people who have contact in markets where there are live chickens.

In these circumstances children may be at higher risk than adults. This probably represents behavioural rather than constitutional susceptibility. In these setting children are being more likely to play with or look after poultry and are less likely to practice good personal hygiene than adults.

People travelling to countries where A/H5N1 is prevalent can sometimes enter this category if they are staying with families with domestic poultry.

People who are at highest risk of acquiring A/H5N1 are the very small number of people living in the same household as cases of A/H5N1 in humans. It is thought that this result from shared exposure, though person to person transmission also occasionally happens. This is why early identification of human cases and early treatment of them and their household contacts is crucial.

Group 2 Theoretical risk – precautions required

There are also those at theoretical risk who may be exposed to the virus and should take appropriate precautions. This includes the following where A/H5N1 may be present:

- Health care workers caring for those with A/H5N1 infection though there have been no cases in this group for nearly a decade the risk is there and preventive measures should be taken. A related group are those working in laboratories with A/H5N1 viruses;

- Veterinarian and people involved in controlling outbreaks in birds (culling);
- People who work on industrial poultry farms;
- People who may have close contact with infected wild birds e.g. some ornithologists and hunters;
- People who deal with sewage which is contaminated with H5N1H5N1¹⁰.

4. Outbreak investigation of human A/H5N1 cases

Outbreak investigation and control should be led and coordinated by public health professionals.

4.1. Definition of a A/H5N1 outbreak in humans

A human avian influenza outbreak is defined as at least one probable or confirmed case of human A/H5N1 or a cluster of probable or confirmed cases related to the same exposure.

4.2. Purpose and objectives

The public health management of outbreaks of A/H5N1 human cases and other outbreaks involving HPAI, has the usual purposes and objectives of outbreak control.

Purpose includes controlling the current outbreak, preventing future outbreaks, conducting research to increase our knowledge of the disease, and training health professionals.

Objectives include;

- Caring for cases, ensuring rapid treatment and effective care of those who are infected;
- Investigating the case and/or cluster and determining its cause, extent and population at risk;
- Preventing new primary cases by identifying and controlling the source of infection or contamination;
- Educating those at risk so as to protect themselves and allow early detection of further cases;
- Identifying all potential cases by active case finding in the population at risk;
- Preventing new secondary cases by identifying cases and potential cases and giving prophylaxis antiviral treatment to those at risk so as to prevent further cases, interrupt transmission and prevent further spread;

¹⁰ Who is at risk of getting “Bird Flu” - Highly pathogenic A/H5N1 avian influenza in Europe?
http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/Table_Who_is_at_risk_H5N1.pdf

- Informing those who need to be aware and provide detailed, authoritative, timely and consistent information and advice to those involved in the events and the general public;
- Reviewing the progress of the event and control measures and respond accordingly;
- Describing and analysing the epidemiological features of the cluster according to international standards;
- Auditing the process and control, and ensuring any relevant lessons are learned, disseminated and when agreed, enacted.

5. Key roles and responsibilities in the public health management of human avian influenza outbreaks

The key roles and responsibilities in the public health management of human avian influenza outbreaks are presented for the following professional groups:

- Clinical professionals (see section 5.1);
- Hospital infection control /occupational health professionals (see section 5.2);
- Laboratory professionals (see section 5.3);
- Public health professionals (see section 5.4).

There are other professional groups involved, i.e. animal health professionals, communication professionals, logisticians, etc, but these groups are not addressed in this tool kit.

5.1. Clinical professionals

When making an initial assessment of patients who present with febrile respiratory illness to a health care centre, and in whom infection with avian influenza A/H5N1 has to be considered, it is important for physicians to start by determining the clinical history and epidemiological (exposure) link. Other differential diagnoses are much more likely and so need to be considered. Treatment has to be based on clinical judgment and not on surveillance case definitions. Appropriate samples should be taken. The initial diagnosis will be based on clinical and exposure history, and on laboratory results when received.

There is currently no formal obligation for notification of a person in whom infection with avian influenza A/H5N1 is considered. The European Centre for Disease Prevention and Control (ECDC) has an interim surveillance case definition for influenza A/H5N1 in humans in the EU. This case definition is not intended to be used for clinical diagnosis or management of cases (see section 2.1). Its purpose is for surveillance of human cases of influenza A/H5N1 infections in humans in the EU.

For further clinical information please refer to section 8.2.2.

The admission of persons for which avian influenza is a differential diagnosis can occur in any health centre, either a designated or not designated avian influenza health care centre.

5.1.1. Initial assessment, admission and referral of persons requiring investigation for avian influenza (person under investigation)

- Initial assessment of patient presenting with febrile respiratory illness, in whom infection with avian influenza A/H5N1 is considered, to a health care centre by health care worker (doctor, nurse, etc) to determine clinical history and epidemiological (exposure) link according to the avian influenza surveillance case definition;
- As soon as the patient mentions a febrile respiratory illness with an epidemiological link, staff should wear surgical mask, gown and gloves and patient should wear surgical mask;
- If the patient does not meet the definition for a possible case, but avian influenza is still considered a differential diagnosis, please contact the national communicable disease surveillance centre to review the case. Please note that the case definition is a surveillance case definition and not a clinical case definition.

If not designated avian influenza health care centre:

- Isolate the patient in side room as much as possible until referral;
- Refer the avian influenza case as soon as possible (depending on status of the case, distance to facility, etc) to the designated avian influenza referral facility with special ambulance and team which should be equipped with adequate PPE;
- Inform patient and family of referral and on avoidance of unprotected contact;
- Inform the designated avian influenza referral facility of the arrival of the patient, to allow for immediate case management;
- Register the patient according to the health facility register format, including full address of patient;
- Inform by phone to the local public health department that the avian influenza case is being referred to the designated avian influenza health care centre.

If designated avian influenza health care centre:

- Isolate the patient in side room unless A/H5N1 is ruled out in further investigation.

5.1.2. Management of avian influenza exposed persons**Clinical aspects**

- Treat patient according to clinical judgment;
- Monitor and reassess;
- Complete Form 5. Avian influenza exposed person investigation and monitoring

Laboratory aspects

- If applicable, inform laboratory team in charge of specimen collection

Infection control aspects: start protective and isolation measures

- If applicable, inform the hospital infection control / occupational health department;
- Inform and notify public health department;
- Inform laboratory team in charge of specimen collection;
- Complete Form 1. Notification of persons under investigation for avian influenza and email/fax to public health department.

Hospital management aspects

For management purposes, develop a line list and add case to hospital: Line list 1. Persons under investigation for avian influenza notified (Avian influenza case + exposed person).

5.1.3. Management of possible avian influenza cases

Clinical aspects: examine, confirm and treat

- Think of other differential diagnosis;
- Collect samples for avian influenza and other tests as per clinical history including chest X-ray. Treat samples as “high risk”. Complete Form 2. Avian influenza laboratory request;
- Start treatment with antiviral according to national protocols, once samples have been collected and other treatment as clinically indicated;
- Document the case through an avian influenza case clinical report;
- Monitor side effects of antivirals. Complete Form 6. Avian influenza antiviral side effects monitoring;
- Inform and reassure patient and family regarding disease;
- Provide psychological support as required.

Laboratory aspects

- Inform laboratory team in charge of specimen collection.

Infection control aspects: start protective and isolation measures

- Inform the hospital infection control / occupational health department;
- Staff to wear personal protective equipment (PPE) (FFP3, gown, gloves and goggles);
- Patient to be in strict respiratory isolation preferably in negative pressure room;
- Educate patient and family of procedure for infection control (isolation, PPE, hygiene, etc).

Public health aspects: inform and notify

- Notify the local public health department;
- Complete Form 1. Notification of persons under investigation for avian influenza and email/fax to public health department.

Hospital management aspects

- For management purposes, develop a line list and add case to Line list 1. Persons under investigation for avian influenza notified (Avian influenza case + exposed person).

5.1.4. Discharge of avian influenza cases

- Proceed to case re-evaluation at the end of the treatment;
- Decide on date of discharge according to national protocols;
- Inform and educate patient and family before discharge on personal hygiene, coughing etiquette and hand washing;

- Set up follow-up appointment for case reassessment and collection of convalescent serum after discharge;
- Check that all the clinical forms have been completed (in coordination with public health):
 - Form 1. Notification of persons under investigation for avian influenza and email/fax to public health department
 - Form 2. Avian influenza laboratory request
 - Form 6. Avian influenza antiviral side effects monitoring
- Update the line list 1. persons under investigation for avian influenza notified (avian influenza case + exposed person)

5.1.5. Management of persons that do not meet the definition of exposed person or possible case

Clinical aspects

- Treat patient according to clinical judgment;
- Contact the national communicable disease centre to discuss if needed.

5.2. Hospital infection control/occupational health professionals

5.2.1. Hospital infection control procedures

Hospital infection control professionals need to ensure that:

- Sufficient availability of personal protective equipment (PPE) according to recommended norms, for all health care workers (HCW) attending avian influenza patients, including health, cleaning, radiology, laboratory, ambulance and mortuary staff;
- Procedures and norms for infection control are respected in isolation and while attending to patient, including restriction and monitoring of visits and staff attendance;
- HCW treating patients under investigation for avian influenza do not attend other patients and that shift organization allows recuperation time.

5.2.2. Health care workers tracing and monitoring

Occupational health / hospital infection control staff should ensure:

- Respect of national protocols for antiviral prophylaxis in HCW;
- That HCW are traced and monitored twice daily for occurrence of fever or symptoms from the moment one of the possible cases they care for becomes a probable or confirmed case;
- Complete the following forms (in coordination with public health professionals):
 - Form 4. Avian influenza exposed persons tracing
 - Form 5. Avian influenza exposed person investigation and monitoring
 - Form 6. Avian influenza antiviral side effects monitoring

- For management purposes, develop a line list and add HCW to:
 - Line list 1. Persons under investigation for avian influenza notified (Avian influenza case + exposed person)
 - Line list 2. Avian influenza exposed persons monitored

For further hospital infection control information please refer to section 8.2.3.

5.3. Laboratory professionals

5.3.1. Receipt of samples

- Ensure safe sample collection;
- Sign the Form 2. Avian influenza laboratory request upon receipt indicating the date, time and condition of samples when received.

5.3.2. Processing of samples

- Analyse samples according to national guidelines;
- If necessary, prepare samples for shipment to the reference laboratory according to national protocols;
- Transport samples to the referral laboratory with a copy of Form 2. Avian influenza laboratory request

5.3.3. Communication of results

- Develop and add all laboratory results to Line list 3. Avian influenza laboratory results;
- Ensure results are communicated to the clinicians, public health professionals and others as per national guidelines using the Form 7. Avian influenza laboratory results.

For further laboratory information please refer to section 8.2.4.

5.4. Public Health Professionals

The following components and steps of an outbreak investigation are under the responsibility of public health professionals.

5.4.1. Confirm outbreak and diagnosis

The early phase of an outbreak investigation aims to confirm the existence of an outbreak and, if necessary, to institute, immediate control measures. The initial investigation should be carried out jointly by the clinician, public health professional and virologist. The objectives of the preliminary phase are to determine:

- Whether a problem exists;
- Nature and extent of outbreak;
- What immediate steps need to be taken.

5.4.2. Ascertain clinical history, exposure history and how diagnosis was made

- As soon as public health department receives a “Form 1. Notification of persons under investigation for avian influenza” by phone, fax or email, the validity of this information

should be assessed. The public health professional in consultation with the physician and virologist need to discuss the most likely diagnosis in the light of the clinical and laboratory findings;

- An initial visit by the public health professionals can be done at this stage especially to enquiry about exposure history and other relevant information. It is important to maintain contact with the clinicians who are caring for the cases to ensure the relevant clinical specimens are obtained and examined. Check that samples have been taken and sent using the “Form 2. Avian influenza laboratory request”;
- If cases were exposed to any items that may have been contaminated with A/H5N1 these should be collected immediately before anything is destroyed.

5.4.3. Re-assess the notified person

- If a possible human case of A/H5N1 as per surveillance case definition, complete the “Form 3. Avian influenza case investigation”;
- If the notified person is an avian influenza exposed person, contact the national communicable disease centre to discuss if needed and ask clinicians to:
 - Monitor and reassess clinically;
 - Monitor antiviral side effects if applicable.

5.4.4. Establishing a case definition

An outbreak case definition should be formulated with information about time, place and person. Please note that the case definitions in section 2-8 are surveillance case definitions. The cases that require public health action will need to be re-defined. In addition, the exposed persons to influenza A/H5N1 will be identified, risk assessed and managed (see sections 5.4.8).

5.4.5. Convening an outbreak control team (OCT)

The multidisciplinary outbreak control and investigation team needs to be set up, with terms of reference for team members, objectives of the investigation, etc. The team should be led and coordinated by a public health professional. The team can be further strengthened by national or external (international) experts called upon for their specific experience in dealing with such investigations. As a minimum, the following professionals should be mobilized:

- Epidemiologists / public health professionals;
- Virologists;
- Infectious disease clinicians;
- Public health veterinarians;
- Environmental health specialists;
- Social mobilization specialists;
- Logisticians / administrators;
- Media officer / public relations person;
- Medical anthropologists in certain settings.

5.4.6. Identify cases and obtain information

Descriptive epidemiology should be undertaken. For each case, data needs to be collected on:

- Identifying information;
- Demographic information;
- Clinical information;
- Suspected risk factors.

The descriptive analysis of the epidemiological data looks at time, place and person characteristics of the cases. The analysis of the epidemiological features of the outbreak is crucial in allowing proper management of the outbreak and the impact of control measures.

This involves:

Characteristics of time: describing the epidemic curve

- Plotting cases by date of onset (epidemic curve) provides insight on the potential mode of transmission of the infection. The characteristics of the epidemic curve may indicate:
 - A likely point source exposure event, when cases are clustered in time;
 - Sporadic apparition of cases when they occur over a period of time;
 - Potential human-to-human transmission when some cases having been exposed to human cases appear after a delay corresponding to the duration of the incubation period.

Characteristics of place

- Characteristics of place provide an insight on the spread of the potential exposure and disease.

Characteristics of person

- Characteristics of persons, such as age, sex or occupation may provide an insight on the nature of the exposure. The investigation should estimate epidemiological indicators such as:
 - Sex ratio;
 - Case-fatality ratio;
 - Attack rate among household members;
 - Transmission coefficient in case human-to-human transmission is suspected, etc

5.4.7. Determining the likely source of infection or contamination

This step should consist of investigating all potential exposures which resulted in the infection of the index case including possible human-to-human transmission.

The following potential exposures should be considered:

Exposure with human cases (probable and confirmed):

- Being a health care worker and having cared for patients presenting with severe respiratory infection;
- Being a laboratory worker and having handled samples potentially infected;
- Having been in close contact (share household, sleeping in same room) with patient presenting with severe respiratory infection.

Exposure with sick birds (wild or poultry):

- Close contact with sick or dead, wild or domestic birds;
- Defeathering sick or dead birds;
- Slaughtering sick birds;
- Attending/working in wet market;
- Having travelled in an area and been in contact with sick or dead birds;
- Having eaten dead or sick wild or domestic birds.

Determining the extent of the outbreak

The investigation of potential exposure in relation with the index case should determine whether this exposure represents a point source event (such as defeathering a sick or dead bird) or may be a persistent exposure in the community (e.g. attending/working in a wet market). This will be an important point to consider when attempting identifying other exposed community members.

Controlling the source of infection or contamination

Preventing further episodes of illness by identifying any continuing wider hazards in infected birds and eliminating them or minimising the risks they pose including through alerting other people and agencies especially those in the veterinary sector.

Determining the population at risk

The population at risk needs to be determined, specially the likelihood of an isolated incident vs. other members of the community sharing this exposure.

5.4.8. Risk assessment and management of exposed persons

The risk assessment and management of exposed persons includes:

- Identification of all those potentially exposed;
- Assessment and monitoring of identified exposed persons;
- Chemoprophylaxis.

Identification of all those potentially exposed

“Contact” should be considered in the human avian influenza context in a broad sense, exposure to a human case, probable or confirmed, and/or shared exposure with such a case or another epidemiological link to A/H5N1.

The traditional “contact tracing” will be referred to here as “exposed persons tracing”. See definition of “exposed persons to influenza A/H5N1”

The identification of all the exposed members of the community and additional cases needs a three-pronged approach (see table 1).

1. Identifying exposed members of the community in relation with the index case (A, B, C in table 1)

- This is traditionally referred to as “contact tracing”¹¹;
- This step aims to identify “contacts” or persons with exposure to a human case (probable or confirmed).

2. Identifying exposed members of the community in relation with the index case’s exposure (B and D in table 1)

- This step aims to identify persons with a shared exposure with a human case (probable or confirmed).

3. Identifying other members of the community, sharing similar exposures, but not in relation with the index case or his/her exposure (E in table 1)

- This step aims at identifying members of the community with an epidemiological link to A/H5N1 and therefore at risk of developing the infection.

11 Contact tracing is the process of finding who an individual was infected by and who the individual may have infected (Maxcy-Rosenau-Last, 1998)

Table 1. Exposure types to define criteria for contact and exposed persons tracing

Exposure to symptomatic case \ Other exposures ¹²	No	Yes	
	No exposure event	Shared exposure event with case	Other exposure event
No	Not exposed	D	E
Yes	A	B	C

As a result, five categories of exposed persons may be defined (see table 1 and figure 1):

A) Persons who had had contact within 1 meter with a probable or confirmed human case while symptomatic, but no other exposure event. This category is of particular importance as these people, if they develop the infection, are likely to have been infected through human-to-human transmission;

B) Persons who shared the exposure and had a subsequent contact within 1 meter with a probable or confirmed human case while symptomatic;

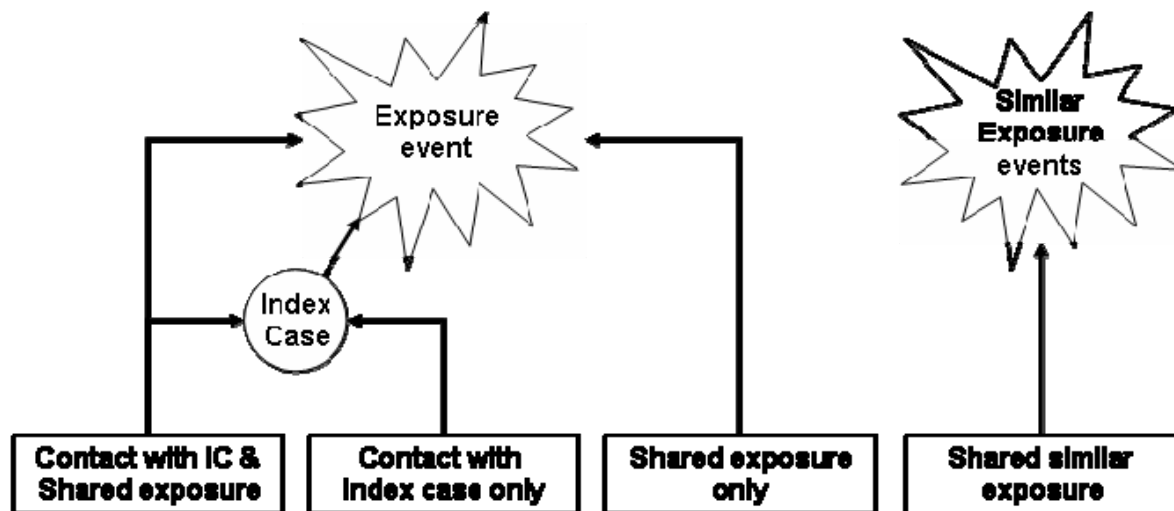
C) Persons who had other exposures (different from the human case) and had subsequent contact within 1 meter with a probable or confirmed case while symptomatic;

D) Persons who shared the exposure only, but did not have a contact within 1 meter with a probable or confirmed human case while symptomatic;

E) Persons who had other exposures (different from the human case), but did not have a contact within 1 meter with a probable or confirmed human case while symptomatic;

Figure 1: diagram showing possible exposures

¹² As defined in the epidemiological criteria (see section 2.1.3)



The assessment of the identified potentially exposed persons' health status at the time of their identification may result in detecting possible cases requiring to be managed accordingly (see section 5.1.3).

Identifying exposed members of the community in relation with the index case and/or his/her exposure

The traditional “contact tracing” has as starting point, the human case (probable or confirmed) for the identification of potentially exposed/sick contacts. The investigation team should initially focus on this case. Once the potential exposures identified (see section 5.4.7 and table 1), the investigation should list:

- All persons who had contact within 1 meter with the human case while he was symptomatic (exposure to symptomatic case): household members, health care workers having cared for the case, laboratory workers, etc;
- All persons who shared the potential exposures (shared exposure event as case);
- Once identified, these members of the community should be listed using “Form 4. Avian influenza exposed persons tracing”.

Identifying other members of the community, with other similar exposures, but not in relation with the index case or his/her exposure

Once the initial “contacts” have been traced (exposed members of the community in relation with the index case and/or his/her exposure), the community needs to be approached to detect additional people not related to the index case and the initial exposure event of that case, but to detect additional community members that are sharing the same risky behaviours or exposures.

The strategy for the identification of other exposed members of the community should consider whether the probable exposure of the index case is point event in time, or represents a persistent source in the community.

Point source event

- Potentially exposed members of the communities have been identified by interviewing the index case and/or his/her family. However, it is likely that similar events may have taken place in the community. Therefore, potentially exposed

members of the community may be identified and assessed through active finding of exposed persons (community survey) or through passive messages broadcasted through the media.

Persistent source event

- The identification of members of the community potentially exposed to a persistent source of infection, such as a wet market, may rely on an active strategy (visit to the site and listing of people) or a passive strategy (broadcasting media messages);
- Once identified, these members of the community should be listed using “Form 4. Avian influenza exposed persons tracing”.

Assessment and monitoring of identified exposed persons

Once identified, the health status of the identified exposed members of the community needs to be assessed and monitored. They should be enrolled in daily health monitoring and potentially be offered post-exposure prophylaxis, as defined by national protocols.

The exposed person assessment and monitoring can be recorded using “Form 5. Avian influenza exposed person investigation and monitoring”.

In the context of exposed persons tracing it is important to identify all possible cases who meet the clinical criteria of the case definition and had a contact within 1 meter with the probable or confirmed case prior to onset of symptoms or shared a common exposure with such a case (see section 5.4.9). These persons need to be assessed as described in previously (see section 5.1.1).

5.4.9. Active case finding

The case finding has two components:

- During the process of contact tracing, it is important to determine if the case was infected by an individual (this is important if human-to-human transmission has occurred);
- During the process of exposed persons tracing, the new concept of active exposed persons/case finding needs to be introduced. This consists of a community survey where exposed persons are found actively, in combination with the traditional “active case search”.

Different ways of active exposed/case finding depending on the potential exposures need to be considered:

- Persons in contact with the case since onset of symptoms;
- Persons having shared the suspected exposure event;
- Persons engaging in same exposures as the case but not related to the initial exposure or the case.

5.4.10. Describing clustering/assessing human-to-human transmission

This step is crucial in relation with an assessment of the emergence of a pandemic strain of influenza. Under the current alert level phase 3, limited human-to-human transmission may occur, but not in a sustained way. Therefore, the assessment of potential human-to-human transmission is essential to allow raising the alert level when necessary.

This assessment includes the following:

Assessing the nature of the exposure

- Very often human cases of avian influenza have been in contact with another symptomatic case but also have shared a common exposure to sick or dead birds. It is therefore very difficult in these instances to suspect human-to-human infection. However, when a person develops symptoms, after a contact with a confirmed case and without environmental exposure identified, human-to-human exposure should be considered. This is particularly true for health care workers, laboratory workers or relative visiting a confirmed case when symptomatic and without identifiable environmental exposure.

Assessing the delay between environmental exposure and onset of symptoms

- When the exposure was limited in time and persons exposed to an index case develop symptoms after a delay corresponding to 2 or more incubation periods, human-to-human transmission should be considered.

Sequencing and phylogenetic analysis of A/H5N1 viruses isolated from patients involved in the outbreak may contribute to assessment of human-to-human transmission by indicating how viruses are related to each other and provide insight on the potential chain of transmission.

5.4.11. Public health department and agency reporting and liaison

Local public health department should:

- Report cases to national public health agency;
- Provide support as necessary and maintain regular contact with national public health agency;
- Maintain regular contact with hospital professionals.

Clinicians should provide:

- Condition of patient;
- Detailed clinical history Avian influenza case clinical report;
- Monitoring of antiviral side effects using “Form 6. Avian influenza antiviral side effects monitoring”.

Laboratory should provide

- Results at local laboratory using “Form 7. Avian influenza laboratory results”.

Hospital infection control/occupational health should:

- Trace Exposed health care workers (HCW) using “Form 4. Avian influenza exposed persons tracing”;
- Monitor them using “Form 5. Avian influenza exposed person investigation and monitoring” and “Form 6. Avian influenza antiviral side effects monitoring”.

Hospital management (avian influenza) should provide:

- Line list 1. Persons under investigation for avian influenza notified (Avian influenza case + exposed person);

- Line list 2. Avian influenza exposed persons monitored.

National public health agency should:

- Report probable and confirmed cases to ECDC, according to surveillance case definition;
- Provide support as necessary and maintains regular contact with local public health department;
- Maintain regular contact with the national reference laboratory.

Public health department should

- Liaise with animal health authorities to:
 - Ensure that cullers and other workers exposed to animals are monitored for occurrence of fever and symptoms that they are informed regarding prevention measures and where to report in the event of fever.
- Complete all relevant forms:
 - “Form 4. Avian influenza exposed persons tracing”;
 - “Form 5. Avian influenza exposed person investigation and monitoring”;
 - “Line list 2. Avian influenza exposed persons monitored”.
- Ensure that antiviral is available for eligible workers exposed to animals, if recommended by national protocols;
- Monitor side effects of antiviral intake should be done and relevant form completed: “Form 6. Avian influenza antiviral side effects monitoring”.

For further public health information please refer to section 8.2.5.

6. Avian influenza algorithms

At least two EU Member States public health agencies have developed documents or algorithms for evaluating people who are considered to have avian influenza, see section:

France

http://www.invs.sante.fr/surveillance/grippe_aviaire/default.htm

United Kingdom

http://www.hpa.org.uk/infections/topics_az/influenza/avian/algorithm.htm

Applying these evidence-based algorithms to people with potential influenza A/H5N1 infection, health authorities have not missed any real cases to date. Indeed, most of those potential cases coming forward and being evaluated have not even been potential cases when above points 1 to 5 or national algorithms were applied. This is because exposures have been too slight and symptoms too mild to be consistent with real case presentations.

However, there is nothing wrong in initially managing the patient conservatively and undertaking A/H5N1 diagnostic tests if the clinician feels that it is appropriate and because of the considerable implications of a positive test result.

The list of avian influenza algorithms can be found below. These algorithms can be found in annex 1:

- Clinical professionals: algorithm for clinical professionals
- Laboratory professionals: algorithm for laboratory professionals
- Public health professionals: algorithm for public health professionals

7. Avian influenza forms and line lists

The list of avian influenza forms and line lists can be found below and in Table 2.

The forms can be found in Annex 2.

Clinical professionals

- Form 1. Notification of persons under investigation for avian influenza;
- Form 2. Avian influenza laboratory request;
- Form 6. Avian influenza antiviral side effects monitoring;
- Line list 1. Persons under investigation for avian influenza notified (Avian influenza case + exposed person).

Hospital infection control / occupational health professionals

- Form 4. Avian influenza exposed persons tracing;
- Form 5. Avian influenza exposed person investigation and monitoring;
- Form 6. Avian influenza antiviral side effects monitoring;
- Line list 1. Persons under investigation for avian influenza notified (Avian influenza case + exposed person);
- Line list 2. Avian influenza exposed persons monitored.

Laboratory professionals

- Form 7. Avian influenza laboratory results;
- Line list 3. Avian influenza laboratory results.

Public health professionals

- Form 3. Avian influenza case investigation;
- Form 4. Avian influenza exposed persons tracing;
- Form 5. Avian influenza exposed person investigation and monitoring;
- Form 6. Avian influenza antiviral side effects monitoring;
- Line list 1. Persons under investigation for avian influenza notified (Avian influenza case + exposed person);
- Line list 2. Avian influenza exposed persons monitored.

- Human case of avian influenza A/H5N1 form for reporting to ECDC¹³.

¹³ http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/H5N1_Case_definition.pdf

Table 2. Avian influenza forms

Avian influenza forms	Clinical professionals	Hospital infection control / occupational health professionals	Laboratory professionals	Public health professionals
Form 1. Notification of persons under investigation for avian influenza	X			
Form 2. Avian influenza laboratory request	X			
Form 3. Avian influenza case investigation				X
Form 4. Avian influenza exposed persons tracing		X		X
Form 5. Avian influenza exposed person investigation and monitoring	X	X		X
Form 6. Avian influenza antiviral side effects monitoring	X	X		X
Form 7. Avian influenza laboratory results			X	
Human case of avian influenza A/H5n1 form for reporting to ECDC14				X
Line list 1. Persons under investigation for avian influenza notified (Avian influenza case + exposed person)	X	X		X
Line list 2. Avian influenza exposed persons monitored		X		X
Line list 3. Avian influenza laboratory results			X	

¹⁴ http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/H5N1_Case_definition.pdf

8. Avian influenza resources

8.1. ECDC avian influenza guidelines

The documents produced by the ECDC on avian influenza are:

Risk assessments

The public health risk from highly pathogenic avian influenza viruses emerging in Europe with specific reference to type A/H5N1 (June 2006):

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/060601_public_health_risk_HPAI.pdf.

Avian influenza A/H5N1 in bathing and potable (drinking) water and risks to human health (June 2006):

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/H5N1_Bathing_water_060609.pdf.

Advice to European Union citizens

Health advice for people living in or travelling to countries where the A/H5N1 virus has been detected (April 2006):

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/travelling.pdf.

Minimise the risk of humans acquiring highly pathogenic avian influenza from exposure to infected birds or animals:

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/Guidelines-human_exposure_HPAI.pdf.

Avian influenza in cats ECDC advice for avoiding exposure of humans (March 2006):

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/ECDC_advice_cats_H5N1.pdf.

8.1.1. Technical advice to European Union public health authorities

Avian influenza: guidance for National Authorities to produce messages for the public concerning the protection of vulnerable groups (February 2006):

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/National_authorities_awareness.pdf.

Oseltamivir prophylaxis following suspected exposure of humans to highly pathogenic avian influenza (HPAI) with particular reference to HPAI type A/H5N1;

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/Post_exposure_oseltamivir.pdf.

Interim surveillance case definition for influenza A/H5N1 in humans in the EU:

http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/H5N1_Case_definition.pdf.

8.2. WHO resources

8.2.1. Ethics (Informed consent, confidentiality, respect for human rights and scientific integrity) and code of conduct

Ethics

Ethics and Health: <http://www.who.int/ethics/en/>.

Ethical standards and procedures for research with human beings:
<http://www.who.int/ethics/research/en/>.

Operational Guidelines for Ethics Committees That Review Biomedical Research:
<http://www.who.int/tdr/publications/publications/pdf/ethics.pdf>.

Code of conduct

Guiding principles for international outbreak alert and response:
<http://www.who.int/csr/outbreaknetwork/guidingprinciples/en/index.html>.

8.2.2. Clinical

Avian Influenza A (H5N1) Infection in Humans 29 September 2005:
<http://content.nejm.org/cgi/content/full/353/13/1374>;

WHO interim guidelines on clinical management of humans infected by influenza A(H5N1) 2 March 2004:
http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage/en/index.html;

WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus:
http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html

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8.2.3. Hospital infection control

Avian influenza, including influenza A (H5N1), in humans: WHO interim infection control guideline for health care facilities Revised 24 April 2006:
http://www.wpro.who.int/NR/rdonlyres/EA6D9DF3-688D-4316-91DF-5553E7B1DBCD/0/InfectionControlAIinhumansWHOInterimGuidelinesfor2b_0628.pdf

Infection control recommendations for avian influenza in health-care facilities:
http://www.who.int/csr/disease/avian_influenza/guidelines/EPR_AM_final1.pdf.

8.2.4. Laboratory

WHO recommendations on the use of rapid testing for influenza diagnosis July 2005:
http://www.who.int/csr/disease/avian_influenza/guidelines/rapid_testing/en/index.html.

Recommended laboratory tests to identify avian influenza A virus in specimens from humans June 2005: http://www.who.int/csr/disease/avian_influenza/guidelines/labtests/en/index.html.

WHO laboratory biosafety guidelines for handling specimens suspected of containing avian influenza A virus 12 January 2005:
http://www.who.int/csr/disease/avian_influenza/guidelines/handlingspecimens/en/index.html.

WHO guidelines for the storage and transport of human and animal specimens for laboratory diagnosis of suspected avian influenza A infection 12 January 2005:

http://www.who.int/csr/disease/avian_influenza/guidelines/transport/en/index.html.

WHO guidelines for the collection of human specimens for laboratory diagnosis of avian influenza infection 12 January 2005:

http://www.who.int/csr/disease/avian_influenza/guidelines/humanspecimens/en/index.html.

WHO reference laboratories for diagnosis of influenza A/H5 infection 23 March 2004:

http://www.who.int/csr/disease/avian_influenza/guidelines/referencelabs/en/index.html.

8.2.5. Public health

WHO pandemic influenza draft protocol for rapid response and containment:

http://www.who.int/csr/disease/avian_influenza/guidelines/protocolfinal30_05_06a.pdf.

WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus:

http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html

:

WHO case definitions for human infections with influenza A(H5N1) virus 29 August 2006:

http://www.who.int/csr/disease/avian_influenza/guidelines/case_definition2006_08_29/en/index.html.

WHO guidelines for global surveillance of influenza A/H5 6 February 2004:

http://www.who.int/csr/disease/avian_influenza/guidelines/globalsurveillance/en/index.html.

8.2.6. Social mobilization and communication

WHO Outbreak Communication Guidelines: <http://www.who.int/infectious-disease-news/IDdocs/whocds200528/whocds200528en.pdf>,

http://www.who.int/csr/resources/publications/WHO_CDS_2005_32web.pdf.

WHO handbook for journalists: influenza pandemic:

http://www.who.int/csr/don/Handbook_influenza_pandemic_dec05.pdf.

8.2.7. Veterinary

WHO manual on animal influenza diagnosis and surveillance:

http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_NCS_2002_5/en/index.html.