What is Avian Influenza?
Avian influenza (AI) is an RNA virus of the Orthomyxoviridae family. The influenza viruses are classified as A, B and C. Avian influenza belongs to type A. Avian influenza was first identified in birds in Italy in 1878. Avian influenza is commonly also known as “bird flu”.

Avian influenza viruses are further classified according to their pathogenicity, i.e., the ability to cause illness. There are the less harmful low pathogenic avian influenza (LPAI) strains and the more virulent and dangerous strains known as highly pathogenic avian influenza (HPAI). Low pathogenic avian influenza becomes highly pathogenic avian influenza through gene mutation and re-assortment. HPAI has numerous subtypes. The most pathogenic subtypes identified to date are the HPAI H5N1 and the HPAI H7N1 subtypes.

Avian Influenza and Birds and Other Animals
Avian influenza is naturally-occurring in birds and other animals, e.g., ducks, chickens, geese, turkeys, wild and migratory birds, especially waterfowl and shorebirds, pigeons, cats, horses, pigs, and sea mammals. Some of the bird species are carriers of the virus in their intestines and do not get sick or exhibit signs or symptoms. Bird flu is very contagious among domestic poultry such as chickens and ducks often resulting in serious illness and death.
Avian Influenza and Humans
Avian influenza virus strains have only recently been identified as the cause of human disease. Humans can also be infected by avian influenza although a vast majority of avian influenza viruses do not infect humans. The only avian influenza strain to repeatedly cause severe disease in humans is the H5N1 serotype, first diagnosed in humans in Hong Kong in 1997.

Pandemic Influenza
An influenza pandemic is a global outbreak of influenza among the human population, which can spread easily from person-to-person causing serious illness.

Global experts predict and fear the potential of the H5N1 virus evolving to form a new pandemic virus strain. Once this adaptation occurs, it will no longer be an avian/bird virus, it will be a new human influenza virus. The pandemic H5N1 strain will cause massive fatalities to occur as the virus inevitably spreads globally. As a result of this significant threat, national, regional and global preparedness & response plans are being developed for this possibility.

Difference Between Seasonal Influenza and Pandemic Influenza
Seasonal influenza outbreaks occur in a predictable pattern annually caused by subtypes of influenza viruses that already circulate among people who already have some immunity, and for which we have vaccines. The young, elderly, and sick are usually those most at risk of developing severe
complications from seasonal influenza. As a result, the impact of seasonal influenza every year is moderate. On the other hand, pandemic influenza is caused by new virus subtypes, which occur very rarely, and to which no, or extremely few, humans have immunity. Sufficient quantities of effective and commercially available vaccines will unlikely be available during the early stages of a pandemic. Everyone, including healthy adults, will be at risk of developing severe complications from pandemic influenza. As a result, significant morbidity and mortality would be expected, causing a major impact on national and global society.

Basic Virology

Influenza A and B viruses are enveloped viruses with a segmented genome made of eight single-stranded negative RNA segments. They are spherical or filamentous in structure, ranging from 80 to 120 nm in diameter. On the basis of the antigenicity of the surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), influenza A viruses are further divided into sixteen H (H1-H16) and nine N (N1-N9) subtypes. HA is the major antigen for neutralising antibodies, and is involved in the binding of the virus to host cell receptors. NA is concerned with the release of progeny virions from the cell surface.

H5N1 Transmission to Humans

So far, the number of human cases has fortunately been relatively low. The source of infection of confirmed cases of human H5N1 influenza so far around the
world have been identified as having a history of contact with infected poultry. There has been no confirmed human-to-human transmission. H5N1 infection transmission is considered to be through one or more of the following methods during 7 – 10 days before onset of symptoms:

- Direct and unprotected contact with birds:
  - Close contact (within 1 metre) with live, sick, or dead birds;
  - Preparing birds during slaughtering or for meals;
  - Playing with birds;
  - Having worked in a laboratory where samples from animals or humans suspected of having H5N1 are being tested.

- Indirect contact:
  - Exposure to settings where domestic poultry were or had been confined in the previous 6 weeks;
  - Infected materials, surfaces;
  - History of travel to a country or territory with reported HPAI due to H5N1 in animals;
  - Eating undercooked or raw infectious birds’ meat, eggs or blood.
  - Possible risk from contaminated water
  - Intake of contaminated water by swimming, drinking, or getting contaminated water in the eyes
  - Uncertain risk of person-to-person spread
    - Face-to-face contact without proper precautions;
    - Touching or within 1 metre of suspected or diagnosed H5N1 patient without proper precautions;
    - Touching or being within 1 meter (without proper precautions) of a person who has severe pneumonia or dies from an acute respiratory illness.

**H5N1 Incubation Period in Humans**

The precise incubation period is unknown, but is likely to be 2 – 8 days, but may be longer. The incubation period for H5N1 may be longer than for seasonal influenza – up to 17 days.
Period of H5N1 Communicability

The infectious period is 7 days after resolution of fever in adults and 21 days after onset of illness in children. Communicability increases with the severity of disease and degree of direct exposure.

The virus is known to survive in cold temperature and in contaminated manure of birds for up to three months. In water it may survive up to 4 days at 22 degree Celsius (72 degrees Fahrenheit) and more than 30 days at zero degree Celsius (32 degree Fahrenheit). The virus can be killed by heat, i.e., meat cooked to internal temperature of 70 degree Celsius (154 degree Fahrenheit) is not infective.

Signs and Symptoms of H5N1 Infection in Humans

The clinical manifestations of H5N1 influenza infection in humans are not well-defined as current knowledge is based on the description of a few hospitalised patients. The spectrum ranges from asymptomatic infection to fatal pneumonitis and multiple organ failure. Initial symptoms include:

- High Fever (typically >38°C/101°F);
- Respiratory symptoms, e.g., cough, sore throat, rhinitis (although upper respiratory symptoms may be absent);
- Malaise, myalgia, headache;
- More rare: gastrointestinal manifestations, e.g., frequent watery diarrhoea, abdominal pain and vomiting; and conjunctivitis.

All these symptoms are however non-specific and may also be associated with
currently circulating human influenza virus subtypes, H1N1 and H3N2. Watery diarrhoea may be present well before pulmonary symptoms develop. Another report describes a four-year-old boy with severe diarrhoea, followed by seizures, coma, and death, suggesting the clinical diagnosis of encephalitis, although H5N1 avian influenza was later detected in cerebrospinal fluid, faecal, throat, and serum specimens. Due to the non-specificity of “flu-like” symptoms potentially indicating H5N1 influenza infection, it is important to consider a wide differential diagnosis which should be guided by the patient’s history, which includes, travel, occupational exposure, contact with poultry, wild birds or sick individuals, history of symptoms, as well as the local epidemiology of disease.

Laboratory findings of patients with severe H5N1 influenza include leucopenia, lymphopenia, impaired liver function with elevated liver enzymes, prolonged clotting times, and renal impairment.

The progression of severe H5N1 infection seems to be different from that of severe diseases observed during earlier influenza pandemics. None of the patients with the severe disease reported from Hong Kong and Vietnam had evidence of secondary bacterial pneumonia, suggesting that fatal outcome was due to overwhelming primary viral pneumonia. The clinical course may include:

- Shortness of breath (dyspnea);
- Clinical pneumonia with variable x-ray findings (almost all develop this);
- Acute respiratory distress syndrome (ARDS);
- Multi-organ failure;
- Encephalitis;
- High case fatality rate.
Diagnosis of H5N1

Accurate and rapid diagnosis of suspected cases of H5N1 infection by laboratory diagnosis is of paramount importance in the initiation and continuation of appropriate treatment and infection control measures. Isolation of virus from specimens of suspected cases of avian influenza should be conducted in specialised reference laboratories with at least biosafety level 3 facilities.

Specimens for virus detection or isolation should be collected within 3 days after the onset of symptoms and rapidly transported to the laboratory. A nasopharyngeal aspirate, nasal swab, nasal wash, nasopharyngeal swab, or throat swab are all suitable for diagnosis. However, a nasopharyngeal aspirate is the specimen of choice. In cases where patients are intubated, a transtracheal aspirate and a bronchoalveolar lavage can be collected. At the same time, acute and convalescent serum samples should be collected for serological diagnosis. Swabs should be transported in virus transport medium to prevent desiccation. All specimens should arrive at the laboratory as soon as possible to avoid any degradation. Transportation in virus transport medium on ice or with refrigeration at 2-8 degree Celsius (36-47 degree Fahrenheit) is recommended if any delay in transportation is expected.

Blood (whole blood serum) specimens are collected for the purpose of antibody serology (determining the presence of antibodies to influenza). Serological diagnosis has little value in diagnosing acute influenza; however, it may have value in diagnosing recently infected patients. In order to diagnose acute infection, an at least four-fold rise in titre
needs to be demonstrated, which requires both an acute and a convalescent serum sample to be taken 14 – 21 days apart.

Different methods exist for direct detection of influenza viruses. Rapid identification of the infecting agent as an influenza A virus can be performed by ordinary influenza rapid tests that differentiate between types. The revolution in rapid diagnosis of influenza was brought about by the development of rapid antigen assays (most of which work on an enzyme immunoassay (EIA) or immunochromatography principle). These assays enable the diagnosis of influenza within 10 – 30 minutes. Some of these tests are easy to perform allowing non-laboratory personnel to conduct them. However commercial rapid chromatographic methods have a sensitivity of only 70% for avian influenza compared to culture. EIAs and direct immunofluorescence methods can either detect both influenza A and B or differentiate between types (influenza A or B), but cannot exclude H5N1 infection due to lack of sensitivity. The only direct technique that has the potential to differentiate between subtypes (i.e. on the basis of haemagglutinin and neuraminidase) is RT-PCR. Detection of influenza A/H5 by RT-PCR offers a rapid and highly sensitive method to diagnose H5N1 infection and should therefore be used.

**Management and treatment of H5N1 Influenza**

There is no known specific treatment for H5N1 influenza. Patients with suspected H5N1 influenza should promptly receive a neuraminidase inhibitor pending the results of laboratory testing. Oseltamivir (e.g., Tamiflu®) is currently regarded as the drug of choice. However, the optimal dosage and schedule for treatment of H5N1 influenza is unknown. It is recommended however that the seasonal influenza treatment regime is adjusted as indicated below. Note however, that resistance to treatment has been experienced in some H5N1 patients.

Efficacy of Oseltamivir has been proven only with early administration – within 48 hours of illness onset. However,
treatment with Oseltamivir may be beneficial even when initiated as late as eight days after the onset of symptoms, if there is evidence of ongoing viral replication.

The active metabolite of Oseltamivir (Oseltamivir phosphate) inhibits neuraminidases (NA) of influenza viruses. Furthermore, it also inhibits influenza virus growth in vitro and inhibits influenza virus replication and pathogenicity in vivo. Lastly, the active metabolite reduces shedding of influenza viruses by inhibiting the release of infectious virus from infected cells.

Ribavirin, interferon alpha and other immunomodulatory drugs have all been used, but without convincing results and should therefore not be used. Moreover, adverse reactions such as anaemia are frequent and may further compromise the patient.

In severe cases, hospitalize patients under appropriate infection control precautions. Provide supportive care. Monitor oxygen saturation and treat desaturation with supplemental oxygen as required. As nebulizers and high-airflow oxygen masks have been potentially

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<tr>
<th>Oseltamivir (e.g., Tamiflu®) Treatment Dosage for H5N1 Influenza</th>
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<td>- Longer treatment (7 to 10 days) or</td>
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<td>- Higher doses (150mg twice a day for adults)</td>
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<tr>
<th>Oseltamivir (e.g., Tamiflu®) Treatment Dosage for Seasonal Influenza</th>
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<tr>
<td>Adults (above 13 years): 75 mg twice a day for 5 days</td>
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<tr>
<td>Children &lt;1 year: not adequately studied</td>
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<tr>
<td>Children ≤ 15 kg: 30 mg twice a day for 5 days</td>
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<td>Children &gt;15 kg to ≤23 kg: 45 mg twice a day for 5 days</td>
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<tr>
<td>Children &gt;23 kg to ≤40 kg: 60 mg twice a day for 5 days</td>
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<tr>
<td>Children &gt;40 kg: 75 mg twice a day for 5 days</td>
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Form of drug:
Available in tablet and powder/suspension form

Special Precautions:
- Consider risks versus benefits
- Adjust dose for people with kidney disease
- Insufficient evidence on use by pregnant or nursing females. Is likely to be excreted in milk. Therefore should be used only when potential benefits justify the potential risks.

Effect of drug:
- Reduces influenza symptoms in 1 - 3 days
- Reduces lower respiratory tract complications, pneumonia, and hospitalization

Side effects of drug:
- Nausea
- Vomiting
- Skin rash
implicated in the nosocomial spread of severe acute respiratory syndrome, use these measures only if clinically justified and apply them under strict infection control, including airborne transmission precautions.

If a case is assessed as not requiring hospitalization, educate the patient and his or her family on personal hygiene and infection control measures (e.g. hand-washing, use of a paper or surgical mask by the ill person, and restriction of social contacts), and instruct the patient to seek prompt medical care if the condition worsens. Follow up all non-hospitalized patients.

The lymphocyte count appears to be the most valuable parameter for identification of patients who are at risk of progression to severe illness. Laboratory findings include:

- Drop in lymphocytes (white blood cell count) - (<1 x 10⁹/litre);
- Mild to moderate drop in blood platelet count;
- Mild to moderate increase in aminotransferase and aspartate transaminase (liver enzymes).

**Infection control measures**

Infection control measures include the application of standard precautions to all patients receiving care in hospitals. If the diagnosis of H5N1 influenza infection is being considered on the basis of clinical features, additional precautions should be implemented until the diagnosis can be ruled out. Although there is currently no evidence that the H5N1 virus is transmitted among humans, the World Health Organization (WHO) recommends the following precautions:

- Patients to use high-efficiency masks (European CE approved respirators or US NIOSH certified N-95) in addition to droplet and contact precautions;
- Patients should be housed in a negative pressure room;
● Patients should be isolated to a single room. If a single room is not available, cohort patients separately in designated multi-bed rooms or wards; in these rooms/wards beds should be placed more than 1 metre apart and preferably be separated by a physical barrier (e.g. partition, curtain);
● Restrict the number of visitors and provide them with appropriate personal protective equipment and instruct them on their use;
● Dispose of waste properly by placing in sealed, impermeable containers which should be clearly labelled "biohazard" and incinerated. Linen and reusable materials that have been in contact with patients should be handled separately and disinfected.

To protect healthcare workers (HCWs) and other hospital personnel, the following recommendations should be followed:
● Designated HCWs should all be properly trained in infection control precautions;
● Use of a high efficiency mask (European CE approved respirators or US NIOSH certified N-95), gown, face shield or goggles, and gloves when coming into contact with patients;
● Limit the number of HCWs who have direct contact with the patient(s); these HCWs should not look after other patients;
● The number of other hospital employees (cleaners, laboratory personnel etc.) with access to the environment of these patients should also be limited;
● HCWs with direct patient contact must monitor their own temperature twice daily and report any fever to their supervisor and facility authorities. HCWs who have a fever of >38°C (101°F), and who have had direct patient contact, should be treated immediately.
• Offer post-exposure prophylaxis (described below) to any HCW who has had potential un-protected contact with droplets from a suspected patient.

• HCWs who are unwell should not be involved in direct patient care since they are more vulnerable and may be more likely to develop severe illness when exposed to influenza A (H5N1) viruses.

Items of personal protective equipment (PPE)
Transmission Prophylaxis

As soon as a case of human H5N1 infection is suspected, precautions need to be taken to minimise nosocomial spread. If the diagnosis is confirmed, possible contacts of the index case must be identified to be put under observation during the incubation period and to facilitate early intervention with antiviral therapy, in order to reduce morbidity and mortality and limit further spread of the disease. For the purpose of prevention, Oseltamivir is also used at the dosage of once daily for 7–10 days after last exposure (initiated within 48 hours of exposure).

In general, prophylaxis is more likely to prevent serious complications from influenza than treatment. However, use of antivirals for prophylactic purposes requires a significantly larger drug supply at very high costs. Therefore, it is emphasized that antiviral use is for treatment only with the exception of priority, high-risk, essential service providers, e.g., outbreak investigation teams, personnel involved in poultry culling, and laboratory and medical personnel.

All HCWs should be vaccinated against seasonal influenza annually. An improvement in vaccination coverage levels might help to protect HCWs, their patients, and communities; improve prevention of influenza-associated disease and patient safety; and reduce disease burden.

Notification

Immediate notification of suspected cases of H5N1 influenza infection is crucial to protecting life and controlling the spread of disease. Moreover, notification to the World Health Organization (WHO) of avian influenza, as a public health emergency of international concern, is mandatory under the revised International Health Regulations (2005). Information on suspected cases should be immediately communicated through the local health officials to:

- Director of Disease Control, DGHS;
- Director of the Institute of Epidemiology, Disease Control and Research (IEDCR); and
- District Civil Surgeon.
For further information contact:

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Mohakhali, Dhaka 1212
Tel: 9898 796, 8821 237

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