Avian influenza

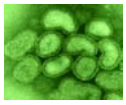
Sophie Molia

Information sources:
FAO Animal Production & Health Division, Foreign Animal Diseases (the "Gray book"), Marie Michaud (IM resident PGY2)

Influenza

- Influenza viruses = members of the family Orthomyxoviridae
- Classified into 3 types : A, B, and C, based on differences between their nucleoprotein and matrix protein antigens
- Certain subtypes of influenza A as well as influenza B circulate among humans and cause yearly epidemics.
- Wild birds are the natural hosts of all subtypes of influenza A but it can also infect humans, pigs, cats, horse seals, whales, mink, and ferrets
- Influenza B and C do not infect domestic animals. Influenza C is mild and does not cause epidemics

Avian influenza



- Avian influenza is caused by a subtype of the type A influenza virus
- In birds, type A influenza has two forms:
  - The first form causes mild illness only (respiratory symptoms)
  - The second form is known as highly pathogenic avian influenza
- The virus is divided into subtypes based on 2 proteins on the surface of the virus:
  - Haemagglutinin (HA): 16 subtypes
  - Neuraminidase (NA): 9 subtypes
- To date all highly pathogenic AI viruses that cause generalised rather than respiratory disease belong to either the H5 or H7 subtypes (all H5 and H7 strains are regarded by OIE as Notifiable AI strains, even if their pathogenicity is found not to be high)

Antigenic drift

- Type A influenza viruses, whether they appear in animals or humans, are genetically labile
- Segments break apart during replication to mix and reassort
- This allows the genetic composition of the virus to change as it replicates in humans and animals
- Gene mutations coding for surface proteins result in minor changes. New strain very close to previous but accumulation of modifications ➔ antigenic drift
- Hence need to change vaccine strains regularly in humans

Antigenic shift

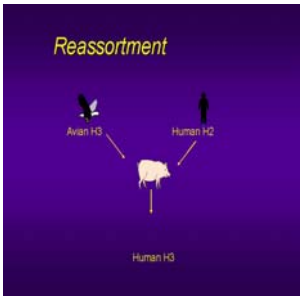
- Influenza A viruses can also swap genetic materials with other subtypes of influenza A including those of different species. This reassortment occurs when one individual is infected with two different subtypes of influenza A at the same time and is called antigenic shift
- The individual or "mixing vessel" that enables the scrambling of influenza genetic material from two different species can be either humans or pigs because both species can be infected with human influenza and avian influenza simultaneously
- Therefore, antigenic shift, results in a new subtype of influenza virus that is different to that of both parents

Antigenic shift (cont)

- Antigenic shift has occurred at least 3 times in the past, resulting in highly lethal pandemics
- All three pandemics in the 20th century spread world wide within one year of detection
  - 1918 Spanish flu (H1N1): 20-40 million deaths
  - 1957 Asian flu (H2N2): more than one million deaths
  - 1968 Hong Kong flu (H3N2). 2 million deaths. This subtype still circulates today
  - 1997-2005 bird flu (H5N1): pandemic potential?

Antigenic shift (cont)

- Favorable conditions for antigenic shift are common in Asia where humans live in close proximity to domestic poultry and pigs



H5N1

- First identified in South African wild terns in 1961
  - Spread naturally among global bird populations over 4 decades
- Appeared in poultry populations in 2003
  - Outbreak in 8 countries in Asia: Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam
  - Rapid spread in this many countries historically unprecedented
  - Loss of more than 100 million domestic birds
- Outbreak appeared under control until June of 2004 when it reappeared in 4 of the same countries and Malaysia. Situation worsened after December 2004
- Control difficult as up to 80% of the poultry in some affected countries is in small backyard farms in remote rural areas

H5N1 and humans

- H5N1 first infected a human population in Hong Kong in 1997
  - 18 documented cases, 6 deaths. Human to human transmission
  - Reappeared in 2 cases, causing 1 death in 2003
  - Soon broke out in Vietnam, Thailand and Cambodia
- As of Sept 2005: 121 documented human cases
  - 51% mortality rate (Vietnam, Thailand, Cambodia, Indonesia)
  - Transmission is result of direct contact with infected poultry, human to human transmission confirmed once in Thailand in 2004 (also suspected in Cambodia, Vietnam)
- Could become a pandemic
  - Highly virulent organism
  - Lack of human immunity to the organism
  - Does **not yet** have ability to easily transmit from human to human

H5N1 and humans (cont)

Concerns

- Host range of H5N1 is expanding
  - Includes pigs, horses, cats, tigers, leopards, whales and seals
- Expansion of the domestic bird population in Asia
- More domestic pigs, which are catalytic mixers of genetic brews
- Every human infection with AI allows opportunity for co-infection with both avian and human influenza and thus gene swapping

  ⇨ The longer the epidemic among poultry, the more likely the virus will mutate to a form that facilitates human to human transmission

H5N1 and humans (cont)

Concerns

- There are 2 classes of drugs available that are effective against the influenza virus:
  - The M2 inhibitors: amantadine and rimantadine
  - The neuraminidase inhibitors: oseltamivir and zanamivir

- In preliminary studies, H5N1 has been shown to be resistant to the M2 inhibitors

H5N1 and humans (cont)

Presentation

- Unlike influenza viruses in which respiratory symptoms dominate, H5N1 replicates in a wide range of cell types, resulting in severe disseminated disease affecting multiple organs and causing high mortality
- Patients with documented H5N1 typically present to the hospital 2-6 days after the onset of fever and cough. Other early symptoms include sore throat, runny nose and myalgias
- All patients have clinically apparent pneumonia with either patchy or interstitial infiltrates, and go on to develop disseminated disease

Other subtypes and humans

- 2 other AI subtypes transmitted to humans recently
  - Hong Kong 1999:
    - H9N2 (which is not highly pathogenic in birds) caused 4 infections but no deaths. All transmissions were poultry to human
  - Netherlands 2003:
    - H7N7 (which is highly pathogenic) caused 83 infections in poultry workers and their families with 1 death. Most infections were conjunctivitis with some respiratory complaints. Documented human to human transmission
    - 30 million poultry culled in one week, 500 million € losses
  - Hong Kong 2003:
    - H9N2 caused mild illness in one child

AI natural hosts

- **Chicken**, **turkeys**, ducks, geese, guinea fowl, quail, pheasant, partridge, emus & ostriches are susceptible
- Disease outbreaks occur most frequently in domestic fowl and turkeys
- A particular isolate may produce severe disease in turkeys but not in chickens or any other avian species
- Many species of wild birds, particularly waterbirds and seabirds, are also susceptible, but infections in these birds are generally subclinical

AI distribution

- AI viruses probably ubiquitous in wild waterbirds
- Pathogenic strains could emerge and cause disease in domestic poultry in any country at any time without warning
- In fact, outbreaks have occurred at irregular intervals on all continents
- The most serious epidemic in recent times were:
  - Hong Kong 1997-1998 and 2003
  - The Netherlands 2003
  - South-Korea 2003

AI epidemiology

- Source of infection for domestic poultry: direct or indirect contact with infected wild aquatic birds, including migratory birds who fly long distances
- Once established in domestic poultry, AI is highly contagious and wild birds are no longer essential for spread
- Infected birds excrete virus in high concentration in their **faeces** and also in **saliva, nasal and ocular discharges**
  - A single gram of contaminated feces contains enough virus to infect 1 million birds
  - The virus can survive in contaminated manure for up to three months and in contaminated water up to 30 days

AI epidemiology (cont)

- Birds that survive infection excrete virus for at least 10 days, orally and in feces, thus facilitating further spread
- Dissemination between flocks:
  - movement of infected birds, contaminated equipment, egg flats, feed trucks, etc
  - Airborne transmission possible if close proximity
  - Vertical transmission unresolved

AI clinical signs

- Incubation period is usually 1 to 7 days, depending upon dose, isolate, species…
- Clinical signs very variable. Influenced by virulence, species affected, age, sex, concurrent diseases, etc

- **HPAI:** marked depression, ruffled feathers, inappetence, excessive thirst, cessation of egg production (may at first lay soft-shelled eggs), and watery diarrhea
- Death may occur within 24 hours of first signs of disease, frequently within 48 hours, or be delayed for as long as a week

- Mortality from 50 to 100%
  - Some severely affected hens may occasionally recover

AI clinical signs (cont)

- Sick birds often sit or stand in a semi-comatose state with their heads touching the ground
- Mature chicken frequently have cyanotic and oedematous combs and wattles (possible petechial or ecchymotic haemorrhages at their tips) and oedema surrounding eyes
- Diarrhoea begins as watery bright green and progresses to almost totally white
- Edema of the head, if present, is often accompanied by edema of the neck. The conjunctivae are congested and swollen with occasional hemorrhage.



AI clinical signs (cont)

- Legs, between hocks and feet, may have areas of diffuse hemorrhage. Haemorrhages may occur on unfeathered areas of skin

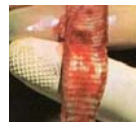
- Respiratory signs can be a significant feature of the disease, depending on the extent of tracheal involvement. Mucus accumulation can vary
- It is not unusual in caged layers for the disease to begin in a localized area of the house and severely affect birds in only a few cages before it spreads to neighboring cages

AI clinical signs (cont)

- Broilers
  - Signs frequently less obvious with severe depression, inappetence, marked increase in mortality being the first abnormalities observed
  - Oedema of the face and neck, neurological signs (torticollis, ataxia) may also be seen
- Turkeys
  - Similar to signs in layers but lasts 2 or 3 days longer and is occasionally accompanied by swollen sinuses
- Domestic ducks and geese
  - Signs of depression, inappetence, and diarrhea similar to those in layers, though frequently with swollen sinuses. Younger birds may exhibit neurological signs

AI pathology

- Peracute disease & yound birds
  - Minimal gross lesions (dehydration, congestion of viscera and muscles)



- Prolonged clinical course
  - Petechial and ecchymotic haemorrhages throughout the body, particularly in the larynx, trachea, proventriculus and epicardial fat, and on serosal surfaces adjacent to the sternum
  - Extensive subcutaneous oedema, particularly around the head and hocks. The carcass may be dehydrated
  - Yellow or grey necrotic foci may be present in the spleen, liver, kidneys and lungs. The air sacs may contain an exudate. The spleen may be enlarged and haemorrhagic

AI differential diagnostic

- Other diseases causing sudden high mortality:
  - Newcastle disease
  - Infectious laryngotracheitis
  - Duck plague
  - Acute poisonings
- Other diseases causing swelling of the combs and wattles:
  - Acute fowl cholera and other septicaemic diseases
  - Bacterial cellulitis of the comb and wattles
- Less severe forms of the disease may be confused with, or complicated by, many other diseases with respiratory or enteric signs

AI diagnostic

Samples required

- Collected from at least six birds (3 acute disease and 3 recently dead)
- Bacteriological swabs of tracheal and cloacal contents, brain and heart blood (aseptical collection and mix to transport medium)

- At necropsy, unpreserved specimens of brain, trachea, spleen and intestinal contents (for isolation of the virus)
- Impression smears of internal organs, including kidney and pancreas (for detection of viral antigen)
- Serum samples

AI diagnostic (cont)

Techniques

- Inoculation of swab material or tissue homogenates into 9-11-day-old embryonated chicken eggs followed by haemagglutinin tests on harvested allantoic fluid
- Immunofluorescence or ELISA on tissue impression smears or homogenates
- RT-PCR
- ELISA and haemagglutination inhibition tests for antibody detection

AI vaccine

- Inactivated quality assured oil-emulsion vaccines demonstrated to be effective in reducing mortality, preventing disease, or both, in chickens and turkeys
- However, they may not prevent infection in some individual birds and infected birds could shed virulent virus
- Nevertheless, the amount of virus shed is considerable less than that of non-vaccinated and infected birds
- Need to know antigenic strain of AI virus since no crossprotection among the 16 known H subtypes

AI surveillance

Minimum requirements

- HPAI must be notifiable
- Veterinary services must have a system for detecting and investigating outbreaks and for reporting confirmed cases internationally, in accordance with OIE guidelines
- Technical capability to diagnose HPAI
- Have a system for recording, managing and analysing diagnostic and surveillance data
- Participate in regional surveillance and diagnostic network, including the public health sector
  - Sharing of information to characterize risk, prevent disease spread, and enhance control efforts

AI surveillance (cont)

Animal health information system

- Computerized information system including database and geographic information system for entry, management, analysis and presentation of non-spatial and spatially referenced data, respectively
- Census of poultry (and pigs)
- Usual birth and mortality rates
- Movement data (e.g. market's catchment area)

AI surveillance (cont)

Specific recommendations for HPAI free countries

Implement specific surveillance activities in the following higher risk sites or situations to provide early warning of infection (i.e. before disease occurs in terrestrial poultry farms):

- Borders and international entry points
- Domestic waterfowl
- Unusual mortality in wild birds
- Live bird markets

AI surveillance (cont)

Border areas

- Inspection of transport vehicles carrying poultry for dead or sick poultry (if dead birds are detected, collect cloacal swab for virus isolation)
- Surveillance of live bird markets
- Surveillance of slaughterhouses
- Targeted surveillance on selected farms, especially those near roads or wetlands

AI surveillance (cont)

Domestic waterfowl

- For unvaccinated domestic waterfowl with no evidence of infection, serological testing should be undertaken to assess whether birds may have been exposed to H5 virus (using a screening test)
- In a sample of farms in the area, test individual farms at a level to give a 95% probability of detecting at least one seropositive bird if infection is present above 20% Statistical tables should be consulted to derive the appropriate number of samples for flocks of different sizes (e.g. 14 samples for flocks of 500 birds)
- If seropositive, then perform virus isolation on cloacal swabs (pools of 5 swabs per sample bottle) at a level to give a 95% probability of detecting at least one virus positive bird if 2% of ducks are excreting virus (e.g. 100 swabs for flocks of 500 birds). As a supplement, seronegative sentinel ducks could be introduced to the farm and cloacal swabs collected twice weekly for three weeks

AI surveillance (cont)

Unusual mortality in wild birds

- Cloacal swabs

Live bird markets

- Select several live bird markets for sampling based on perceived risk (large throughput, mixed species, markets near borders)
- Collect samples from dead birds, according to a protocol such as:
  - Weekly collection
  - Monthly collection
  - All dead birds in one week
  - Dead birds if increase in mortality 50% above normal

AI surveillance (cont)

Networking!!

- Field persons
  - Farmers, veterinarians, slaughterhouses staff
- Veterinary services
- Public health sector
- Animal production private sector
- Regional coordination, communication & transparency
- OIE, FAO and other international organisations
- Experts (infected countries…)

Thank you for your attention!