UNIT NO. 3

AVIAN INFLUENZA – ARE WE PREPARED?

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ABSTRACT

The widespread occurrence and continued spread of avian influenza A (H5N1) virus in poultry have aroused global concerns about their potential to spark a catastrophic human pandemic[1]. While the H5N1 virus transmits zoonotically from infected poultry to humans, often with fatal consequences, such transmission remains inefficient.

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WHY IS AVIAN INFLUENZA A CONCERN?

H5N1 virus was first detected in diseased geese in Guangdong Province, Peoples Republic of China in 1996 and designated A/Goose/Guangdong/1/96[2].

In 1997, the first epidemic of H5N1 bird flu in human was reported in Hong Kong with 18 confirmed cases and six deaths[4]. A second outbreak among live bird markets was reported in Hong Kong in 2001, but no human cases occurred due to the culling of infected poultry.

In 2003, highly pathogenic A (H5N1) appeared again in China and Hong Kong. Two cases occurred among members of a Hong Kong family that had travelled to China[5].

From December 2003, Japan, South Korea, Vietnam, Thailand, Indonesia, Mainland China, Cambodia, Laos and Malaysia reported outbreaks of HPA 1H5N1 virus disease in poultry[6].

In December 2003, the first human cases associated with the Southeast Asia outbreak occurred in Vietnam. Further human cases were reported from Thailand, Cambodia and Indonesia. By 2005, the virus had spread to other parts of Asia, Europe, Africa and the Middle East[7] after infecting wild birds in Qinghai Lake, China.

As of 25 July 2007, 319 reported cases of H5N1 infection in people had occurred in 12 countries; 192 of these have been fatal. Updated are available from the WHO website: www.who.int/csr/avian_influenza/country.

H5N1 viruses can be divided into clade I and clade 2, the latter can be further subdivided into three subclades. The majority of H5N1 clade 1 viruses (e.g. A/Vietnam/1203/2004) are resistant to adamantanes (amantadine and rimantadine) but the majority of clade 2 viruses (eg A/Indonesia/5/2005) are sensitive.

International health experts indicate that two of the three conditions for an influenza pandemic have already been met.

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First, following the latest outbreaks of A(H5N1), the virus has reemerged to which humans have little or no immunity. It has caused the greatest number of human cases of very severe disease and the greatest number of deaths.

Second, this strain can jump between species. The third is that this strain of avian influenza has not yet mutated to a form that is easily transmitted from human to human[8].

Cases of probable person-to-person transmission of avian influenza were reported in mother and aunt caring for an extremely ill child in Thailand[9].

Some scientists believe that reassortment between an avian and a human strain could occur in the human population without an intermediary host. If this proves true, as more humans become exposed and infected, the potential for reassortment with a human strain may also increase. It is also possible that a pandemic strain could emerge following a more gradual process of adaptive mutation in humans.

PREVENTION AND CONTROL OF AVIAN INFLUENZA

Antiviral Treatment

Two groups of antiviral agents are available for treatment and prophylaxis of influenza: M2 ion-channel inhibitors (the adamantanes [amantadines and rimantadines]) and the neuraminidase inhibitors (oseltamivir and zanamivir).

The genotype Z clade I virus infecting humans in Vietnam, Cambodia and Thailand since 2003 contained Ser31Asn and Leu26Ile amino acid replacements in M2 which confer high-level resistance against amantadines[10].

H5N1 viruses isolated from untreated patients have been shown to be susceptible to oseltamivir and zanamivir in vitro[11].

Both NI inhibitors have been shown in laboratory studies to reduce the severity and duration of illness caused by seasonal influenza[12]. For cases of human infection with H5N1, the drugs may reduce the severity of disease. Early oseltamivir treatment appears to be useful in reducing H5N1 associated mortality[13]. Given the evidence of prolonged viral replication in this disease, administration of the drug should be considered in patients with late presentation. Modified regimens of oseltamivir, including two-fold higher dosage, longer duration and possibly combination with amantadine (in countries where H5N1 is susceptible to amantadine) may be considered in patients with pneumonia or progressive disease[14].

Finally, the emergence of drug-resistant viruses in patients on therapy may adversely affect the clinical efficacy of oseltamivir in H5N1 influenza virus[15].

Nevertheless, mathematical modelling has suggested that antiviral agents may play an important role for limiting the extent of pandemic influenza and some experts have called for

stockpiling of these agents[16]. Mass administration of prophylactic antiviral drugs to large numbers of healthy people for extended periods is not recommended because it could accelerate the development of drug resistance.

The development of novel drugs directed at alternative viral targets may need consideration such as the viral polymerase complex. Small peptides that have broad spectrum activity in blocking virus entry have been described[17]. Passive immunotherapy using convalescent-phase serum is believed to have conferred clinical benefit in the 1918 pandemic and remains a possible consideration for the management of human H5N1 disease[18].

Vaccines

There is currently no commercially available human vaccine against avian influenza. Experience with H1N1 vaccines in 1976 demonstrated that in the absence of prior immune priming, immunogenicity of a vaccine will be lower than of seasonal vaccines, and two doses were more likely needed. Whole-virus vaccines were more immunogenic and reactogenic than subunit or split-product vaccines[19].

Natural infection with avian influenza virus induces poor HA inhibition titres and better neutralisation titres. Avian influenza HA is generally less immunogenic than mammalian influenza virus HAs[20].

The clades and subclades of H5N1 viruses probably differ in their antigenic structure to warrant the preparation of different vaccines. Studies in ferrets suggest that vaccine against one clade will not protect against another clade, although it will protect against influenza-associated death[21].

WHO offers prototype of clade 1 (A/Vietnam/1203/04-like), clade 2.1 (A/Indonesia/5/05), clade 2.2 (A/Bar-Headed Goose/Qinghai/A/05-like) and clade 2.3 (A/Anhui/1/05) (Fujian-like sublineage) for vaccine development[22].

Phase 1 clinical trials involving a Sanofi Pasteur H5N1 vaccine (nonadjuranted) found that 54% of 99 subjects who received two doses of vaccine (90ug of HA per dose) had neutralisation antibody titres that reached 1:40 or greater[23]. H5N1 subunit vaccines adjuvanted with aluminium phosphate moderately increased immunogenicity[24]. An alum-adjuvanted inactivated whole-virus H5N1 vaccine has provided more promising results, with 78% of volunteers developing an antibody response after two doses of 10ug HA per dose[25]. The role of alternative adjuvants (eg MF59) and priming doses or alternative routes of immunisation are being considered[26].

A vero-cell-based vaccine produced by Baxter found that the vaccine was relatively immunogenic at low doses (3.75 and 7.5mcg) and also showed evidence of cross-protection against other H5N1 strains (Hartmut Ehrlich, personal communication).

A universal vaccine that would be effective against all types of influenza, including emerging pandemic strains, is being developed by various researchers. Such vaccine focus on the M2 viral protein which does not change and is made through bacterial fermentation technology.

Even though program is being made, several barriers exist to actually having effective vaccines against H5N1 influenza available for practical use:

1. Research and development of vaccines that are "market ready" will likely take several more years despite current candidate vaccines under study.
2. Limited global vaccine production capacity exists (500 million doses of seasonal trivalent vaccine can be produced annually).
3. Developing an effective vaccine may require having the pandemic strain on hand, which will mean that a vaccine cannot be produced until the onset of the pandemic.

Infection Control

Enhanced precautions have been recommended by the CDC and WHO to protect health care workers who care for patients with known or suspected avian influenza[26,27]. Patients with a known history of travel within ten days to a country with avian influenza activity and are hospitalised with a severe febrile respiratory illness or suspected avian influenza should be managed using isolation precautions identical to those recommended for patients with known SARS.

The patient should be placed in an airborne isolation room with negative air pressure (6 to 12 air changes per hour and exhaust air directly outside or have recirculated air filtered by a high-efficiency particulate air (HEPA) filter. If such a room is unavailable, a portable HEPA filter should be used in the patient's room.

A fit-tested respirator (N-95 disposable respirator or EU FFP2 or equivalent) should be worried when entering the room. Contact precautions (hand-hygiene, gloves, gowns, dedicated equipment and eye protection within three feet of the patient) should be instituted for all patient contact.

Inpatient precautions should be continued for 14 days after onset of symptoms or until diagnostic tests indicate that the patient is not infected with influenza A virus.

The primary strategies for preventing pandemic influenza are the same as those for seasonal influenza: vaccination, early detection and treatment with antiviral medications and the use of infection control measures to prevent transmission during patient care.

Controlling Transmission in Poultry

Controlling H5N1 influenza by eradicating it at the source in domestic poultry has worked for Japan and South Korea in 2003 through a strategy of quarantine and culling of poultry.

An alternative strategy adopted by China, Indonesia and Vietnam has been to vaccinate uninfected poultry in conjunction with quarantine and culling of infected poultry.

Preparation for a possible influenza pandemic is essential and timely. Although the timing and severity of the next influenza pandemic remains unknown, planning for an influenza pandemic will improve the ability of health care facilities to respond to other risks as well as future seasonal epidemics of human influenza.

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LEARNING POINTS

- **Mathematical modelling has suggested that antiviral agents may play an important role for limiting the extent of pandemic influenza.**
- **A universal vaccine that would be effective against all types of influenza, including emerging pandemic strains, focus on the M2 viral protein which does not change and is made through bacterial fermentation technology.**
- **Patients with a known history of travel within ten days to a country with avian influenza activity and are hospitalised with a severe febrile respiratory illness or suspected avian influenza should be managed using isolation precautions identical to those recommended for patients with known SARS.**
- **The primary strategies for preventing pandemic influenza are the same as those for seasonal influenza: vaccination, early detection and treatment with antiviral medications and the use of infection control measures to prevent transmission during patient care.**