

Don't miss out on.....
**THE CONSISTENT
BLOCKBUSTER
SPECTACULAR**
Of All Lifeforms

By Tri Luong

The Avian Influenza

featuring

~ THE VIRUS ~

~ THE DETECTION ~

~ THE PANDEMIC ~

~ THE RESPONSE ~

What is avian influenza (bird flu)?

- Bird flu is an infection caused by avian (bird) influenza (flu) viruses. These flu viruses occur naturally among birds. Wild birds worldwide carry the viruses in their intestines, but usually do not get sick from them. However, bird flu is very contagious among birds and can make some domesticated birds, including chickens, ducks, and turkeys, very sick and kill them.

What is the bird flu virus?



(Don't let this silly dancing bird fool you!)

Let's examine general influenza viruses.

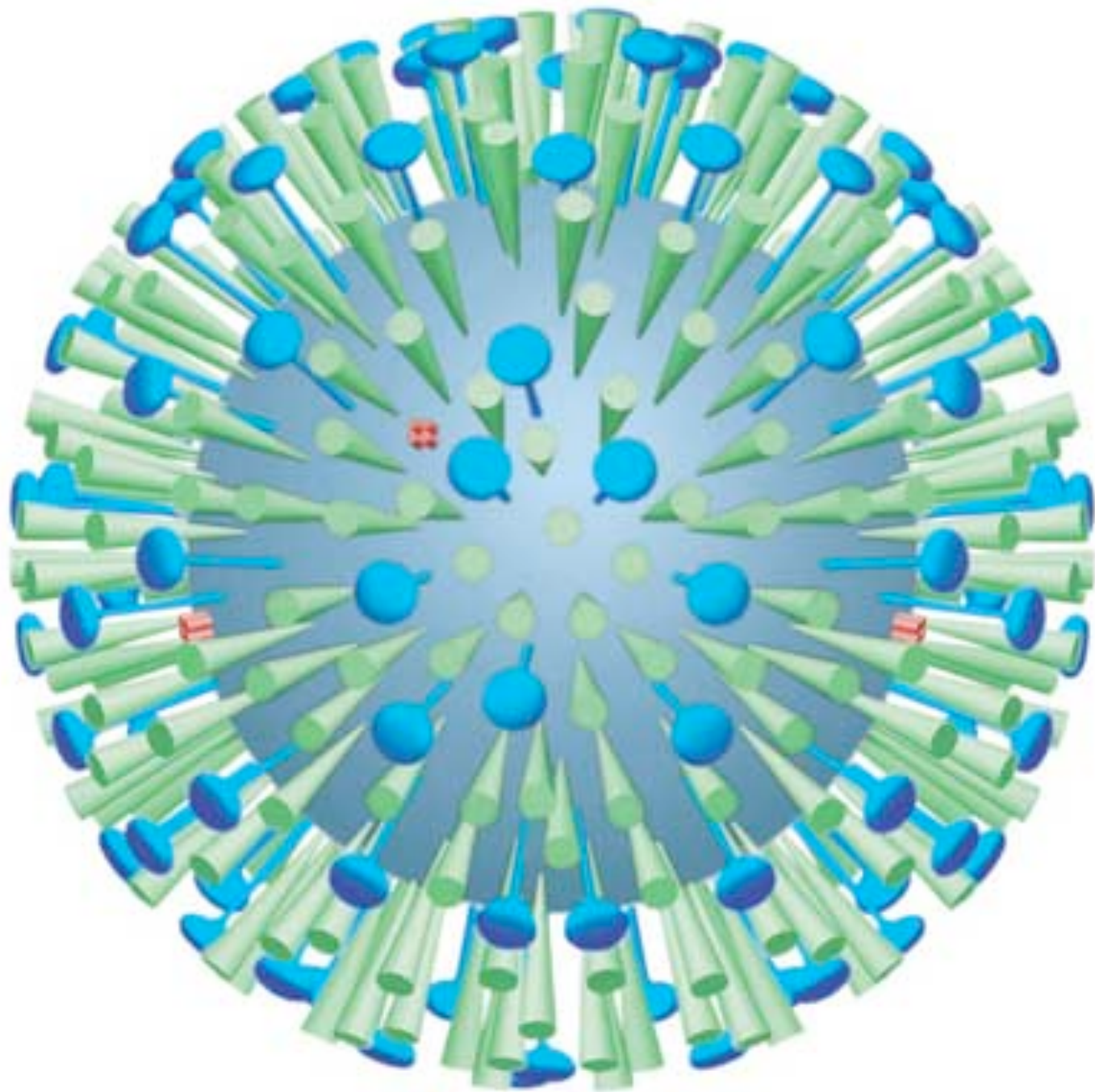
The Influenza Virus

Types, Subtypes, and Strains

- Influenza Type A
Can infect people, birds, pigs, horses, seals, whales, and other animals, but wild birds are the natural hosts for these viruses.
- Influenza Type B
Influenza B viruses are normally found only in humans. Although influenza type B viruses can cause human epidemics, they have not caused pandemics.
- Influenza Type C
Influenza type C viruses cause mild illness in humans and do not cause epidemics or pandemics.

Identification of Influenza viruses

- Influenza type A viruses are divided into subtypes based on two proteins on the surface of the virus. These proteins are called **hemagglutinin** (HA) and **neuraminidase** (NA). There are **15** different HA subtypes and **9** different NA subtypes.
- Only some influenza A subtypes (i.e., H1N1, H1N2, and H3N2) are currently in general circulation among people. Other subtypes are found most commonly in other animal species. For example, H7N7 and H3N8 viruses cause illness in horses
- “H7N2 virus” designates an influenza A subtype that has an HA 7 protein and an NA 2 protein. Similarly an “H5N1” virus has an HA 5 protein and an NA 1 protein



How are Avian Influenza Viruses different from Human Influenza Viruses?

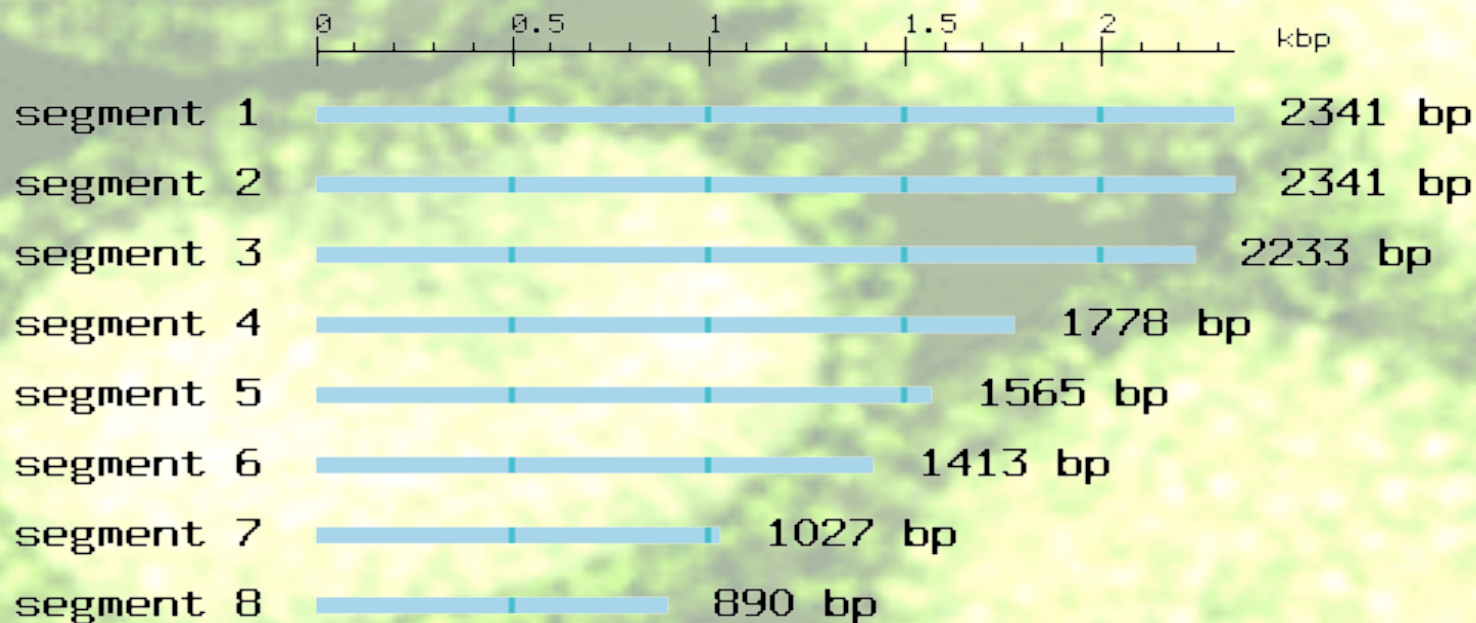
- Humans can be infected with influenza types A, B, and C. However, the only subtypes of influenza A virus that normally infect people are influenza A subtypes H1N1, H1N2, and H3N2. Between 1957 and 1968, H2N2 viruses also circulated among people, but currently do not.
- Only influenza A viruses infect birds. Wild birds are the natural host for all subtypes of influenza A virus. Typically wild birds do not get sick when they are infected with influenza virus. However, domestic poultry, such as turkeys and chickens, can get very sick and die from avian influenza, and some avian viruses also can cause serious disease and death in wild birds.

Genetics of the Flu

- The [Influenza Genome Sequencing Project](#), funded by The National Institute of Allergy and Infectious Diseases (NIAID), aims to rapidly sequence flu viruses from samples collected from all over the world, from birds, pigs, and other animals, as well as humans. The viral sequences generated from this NIAID project by TIGR are deposited in GenBank, and these data have been used to create the ***Influenza Virus Resource***.
- This resource enables scientists to compare influenza virus strains so that emergent variants can be more rapidly identified, and vaccines developed accordingly. As the library of viral sequences grows, it will act as a reference to help further our understanding of how avian viruses spread to humans, and how influenza activity spreads all over the world

The Genes

- The [Influenza A viral genome](#) consists of eight, single negative-strand RNAs that can range between 890 and 2340 nucleotides long. Each RNA segment encodes one to two proteins.

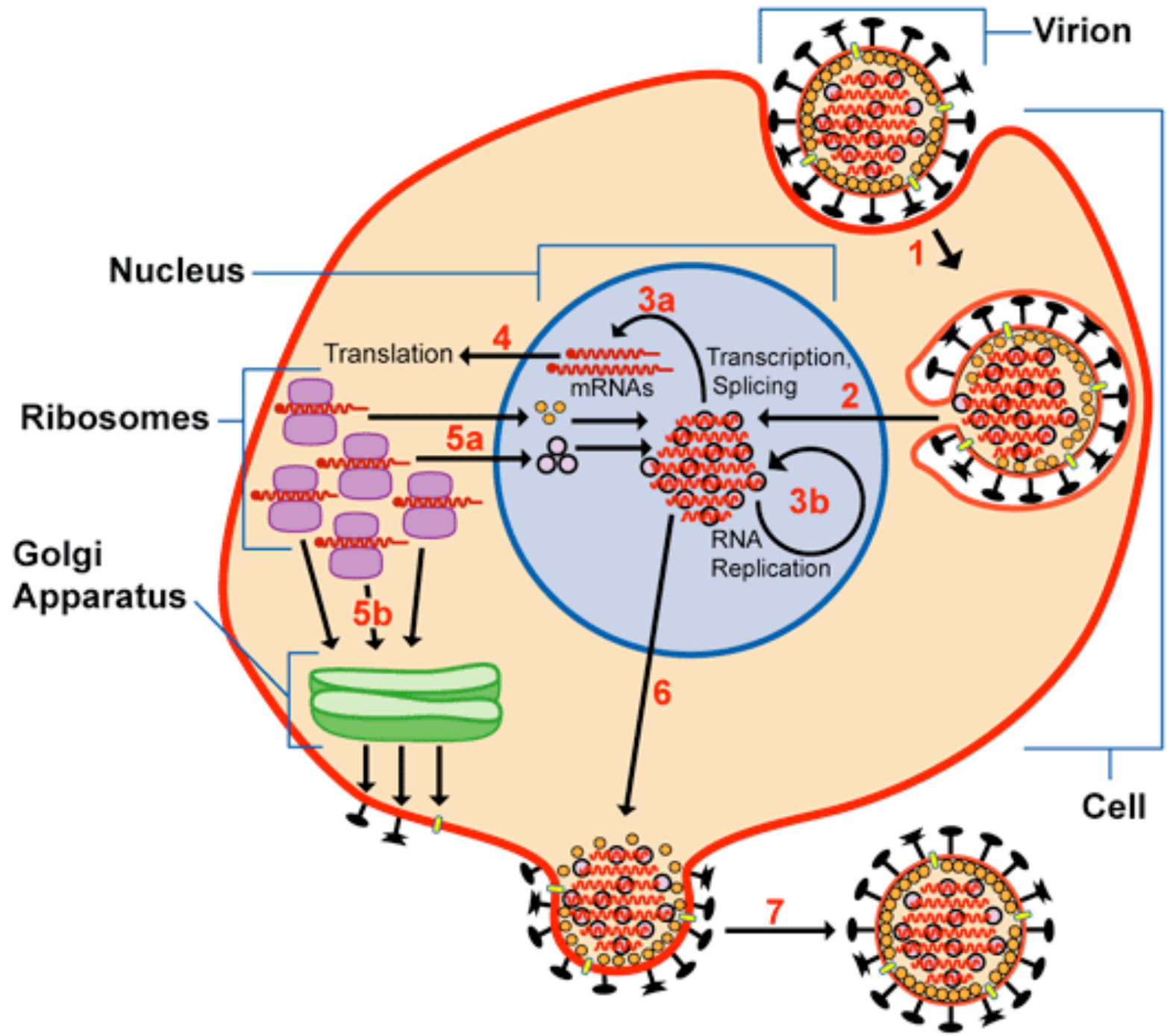


A microscopic image of a cell, likely a plant cell, showing a cell wall and internal organelles. The image is overlaid with a semi-transparent grey rectangle containing text. The text is arranged in three lines: 'INFLUENZA A' in black serif font, 'starring in' in black sans-serif font, and 'Attack of the Cell' in large red sans-serif font.

INFLUENZA A

starring in

Attack of
the Cell



- A virion attaches to the host cell membrane via HA and enters the cytoplasm by receptor-mediated endocytosis (STEP 1), thereby forming an endosome.
- A cellular trypsin-like enzyme cleaves HA into products HA1 and HA2 (not shown). HA2 promotes fusion of the virus envelope and the endosome membranes. A minor virus envelope protein M2 acts as an ion channel thereby making the inside of the virion more acidic. As a result, the major envelope protein M1 dissociates from the nucleocapsid and vRNPs are translocated into the nucleus (STEP 2) via interaction between NP and cellular transport machinery.
- In the nucleus, the viral polymerase complexes transcribe (STEP 3a) and replicate (STEP 3b) the vRNAs.
- Newly synthesized mRNAs migrate to cytoplasm (STEP 4) where they are translated.
- Posttranslational processing of HA, NA, and M2 includes transportation via Golgi apparatus to the cell membrane (STEP 5b). NP, M1, NS1 (nonstructural regulatory protein - not shown) and NEP (nuclear export protein, a minor virion component - not shown) move to the nucleus (STEP 5a) where they bind freshly synthesized copies of vRNAs.
- The newly formed nucleocapsids migrate into the cytoplasm in a NEP-dependent process and eventually interact via M1 with a region of the cell membrane where HA, NA and M2 have been inserted (STEP 6).
- Then the newly synthesized virions bud from infected cell (STEP 7). NA destroys the sialic acid moiety of cellular receptors, thereby releasing the progeny virions.

Spread of Avian Influenza Viruses among Birds

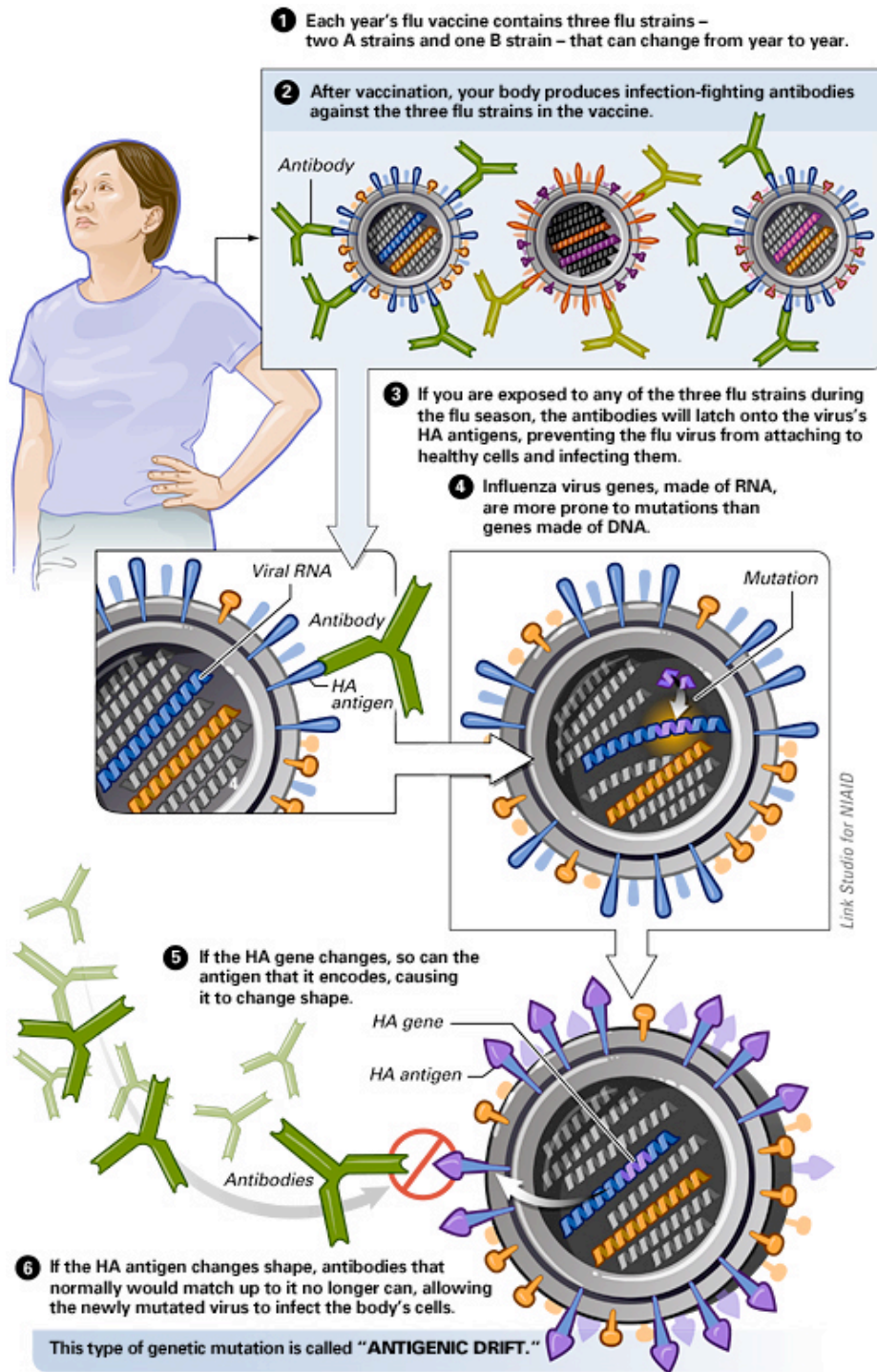
- Certain birds, particularly water birds, act as hosts for influenza viruses by carrying the virus in their intestines and shedding it.
- Infected birds shed virus in saliva, nasal secretions, and feces.
- Susceptible birds can become infected with avian influenza virus when they have contact with contaminated nasal, respiratory, or fecal material from infected birds.
- Fecal-to-oral transmission is the most common mode of spread between birds.

Low Pathogenic vs. Highly Pathogenic Avian Influenza Viruses

- H5 and H7 subtypes of avian influenza A viruses can be further classified as either highly pathogenic avian influenza (HPAI) or low pathogenic avian influenza (LPAI)
- HPAI is usually associated with high mortality in poultry
- This distinction is made on the basis of genetic features of the virus
- HPAI viruses can kill 90 to 100% of infected chickens, whereas LPAI viruses cause less severe or no illness if they infect chickens
- It is not certain how the distinction between “low pathogenic” and “highly pathogenic” is related to the risk of disease in people

Influenza Viruses Change

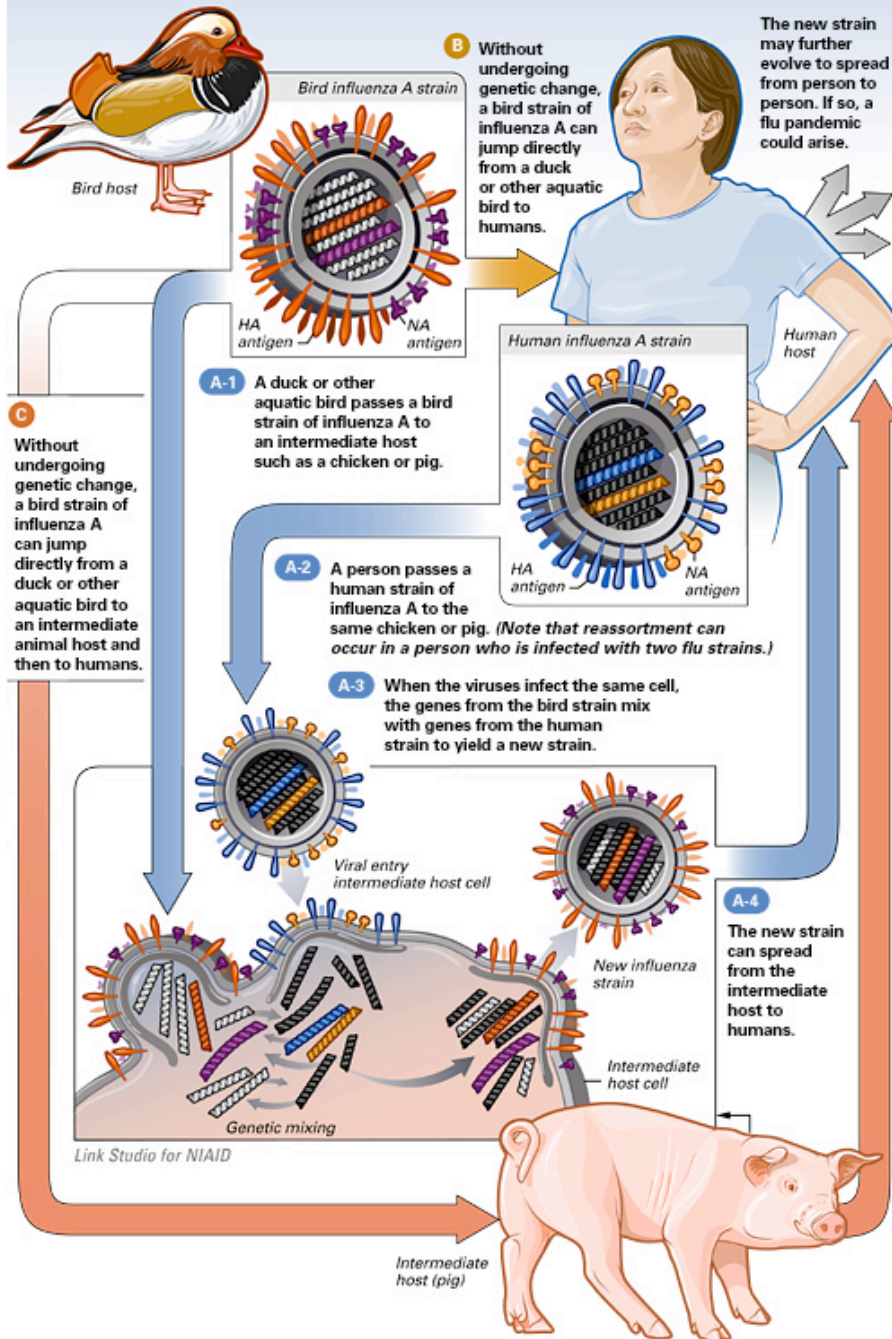
- **Antigenic Drift** - small changes in the virus that happen continually over time that produce new virus strains that may not be recognized by antibodies to earlier influenza strains
- **Antigenic Shift** - abrupt, major change in the influenza A viruses, resulting in a new influenza virus that can infect humans and has a hemagglutinin protein or hemagglutinin and neuraminidase protein combination that has not been seen. This results in a new influenza A subtype.
- Influenza viruses are changing by antigenic drift all the time, but antigenic shift happens only occasionally



Antigenic Drift

- Accumulation of normal mutations in RNA
- Minor changes that can make antigens ineffectual

The genetic change that enables a flu strain to jump from one animal species to another, including humans, is called "ANTIGENIC SHIFT."
Antigenic shift can happen in three ways:



Antigenic Shift

- Mixing of different strains of influenza viruses in the same intermediate host gives rise to new virus
- The new subtype can be more harmful than the first two strands due to the lack of prior familiarity/immunity.

Problem:

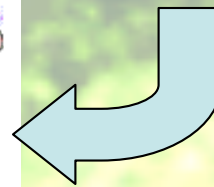
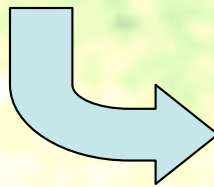
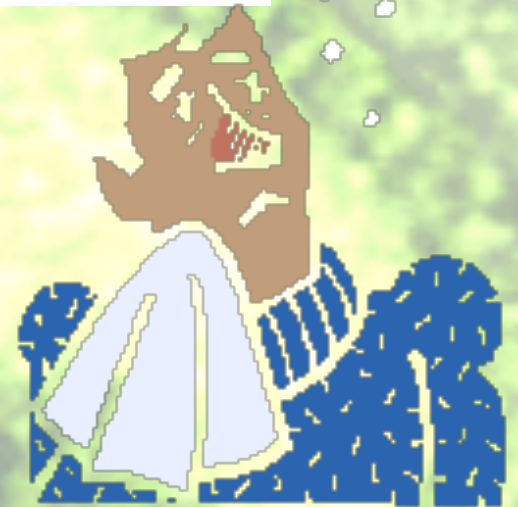
If a new subtype of influenza A virus is introduced into the human population, **most people have little or no protection against the new virus**, and if **the virus can spread easily from person to person**, a PANDEMIC (worldwide spread) may occur.



Birds
with
avian
flu



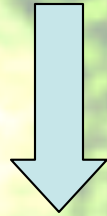
People
with
the flu



Unsuspecting Happy Mr. Pig is going to get a little surprise.



Sick Pig with both Strands of Influenza



PANDEMIC

Difference between Pandemics and Epidemics

- Pandemics are different from seasonal outbreaks or “epidemics” of influenza.
- Seasonal outbreaks are caused by subtypes of influenza viruses that are **already in existence among people**.
- Pandemic outbreaks are caused by **new subtypes** or by subtypes that have **never circulated among people** or that have **not circulated among people for a long time**.

Historical Pandemics and Mortalities

- **1918-19: "Spanish flu"** [A (H1N1)], caused the highest number of known influenza deaths: more than 500,000 people died in the United States, and up to 50 million people may have died worldwide. Many people died within the first few days after infection, and others died of complications later. Nearly half of those who died were young, healthy adults. Influenza A (H1N1) viruses still circulate today after being introduced again into the human population in the 1970s.
- **1957-58: "Asian flu"** [A (H2N2)], caused about 70,000 deaths in the United States. First identified in China in late February 1957, the Asian flu spread to the United States by June 1957.
- **1968-69: "Hong Kong flu"** [A (H3N2)], caused about 34,000 deaths in the United States. This virus was first detected in Hong Kong in early 1968 and spread to the United States later that year. Influenza A (H3N2) viruses still circulate today.

Stages of Pandemic

- The **World Health Organization (WHO)** has developed a [global influenza preparedness plan](#), which defines the stages of a pandemic, outlines WHO's role and makes recommendations for national measures before and during a pandemic.
- **Interpandemic period**
 - **Phase 1:** No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low.
 - **Phase 2:** No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.
- **Pandemic alert period**
 - **Phase 3:** Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact.
 - **Phase 4:** Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.
 - **Phase 5:** Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).
- **Pandemic period**
 - **Phase 6:** Pandemic: increased and sustained transmission in general population.

Cases of Human Avian Flu

- **H5N1, Hong Kong, 1997** : Avian influenza A (H5N1) infections occurred in both poultry and humans. This was the first time an avian influenza virus had ever been found to transmit directly from birds to humans. During this outbreak, 18 people were hospitalized and six of them died. To control the outbreak, authorities killed about 1.5 million chickens to remove the source of the virus. Scientists determined that the virus spread primarily from birds to humans, though rare person-to-person infection was noted.
- **H9N2, China and Hong Kong, 1999** : Avian influenza A H9N2 illness was confirmed in two children. Both patients recovered, and no additional cases were confirmed. The evidence suggested that poultry was the source of infection and the main mode of transmission was from bird to human. However, the possibility of person-to-person transmission could not be ruled out. Several additional human H9N2 infections were reported from mainland China in 1998-99.
- **H7N2, Virginia, 2002**: Following an outbreak of H7N2 among poultry in the Shenandoah Valley poultry production area, one person was found to have serologic evidence of infection with H7N2.
- **H5N1, China and Hong Kong, 2003** : Two cases of avian influenza A (H5N1) infection occurred among members of a Hong Kong family that had traveled to China. One person recovered, the other died. How or where these two family members were infected was not determined. Another family member died of a respiratory illness in China, but no testing was done.
- **H7N7, Netherlands, 2003** : The Netherlands reported outbreaks of influenza A (H7N7) in poultry on several farms. Later, infections were reported among pigs and humans. In total, 89 people were confirmed to have H7N7 influenza virus infection associated with this poultry outbreak. These cases occurred mostly among poultry workers. There was one death among the 89 total cases. The death occurred in a veterinarian who visited one of the affected farms. Dutch authorities reported three possible instances of transmission from poultry workers to family members. Since that time, no other instances of H7N7 infection among humans have been reported.

- **H9N2, Hong Kong, 2003** : H9N2 infection was confirmed in a child in Hong Kong. The child was hospitalized but recovered.
- **H7N2, New York, 2003**: In November 2003, a patient with serious underlying medical conditions was admitted to a hospital in New York with respiratory symptoms. One of the initial laboratory tests identified an influenza A virus that was thought to be H1N1. The patient recovered and went home after a few weeks. Subsequent confirmatory tests conducted in March 2004 showed that the patient had been infected with an H7N2 avian influenza virus. An investigation to determine the source of infection is ongoing.
- **H5N1, Thailand and Vietnam, 2004**: In January 2003, outbreaks of highly pathogenic influenza A (H5N1) in Asia were first reported by the World Health Organization. From December 30, 2003, to March 17, 2004, 12 confirmed human cases of avian influenza A (H5N1) were reported in Thailand and 23 in Vietnam, resulting in a total of 23 deaths.
- **H7N3 in Canada , 2004**: In February 2004, human infections of H7N3 among poultry workers were associated with an H7N3 outbreak among poultry. The H7N3-associated illnesses consisted of eye infections.
- **H5N1, Thailand and Vietnam, 2004**: Beginning in late June 2004, new lethal outbreaks of H5N1 among poultry were reported by several countries in Asia. The new outbreaks of H5N1 in poultry in Asia were followed by renewed sporadic reporting of human cases of H5N1 infection in Vietnam and Thailand beginning in August and continuing into 2005. Of particular note is one isolated instance of probable limited human-to-human transmission occurring in Thailand in September.

Most Recent Update from WHO

Thailand

Avian Influenza in human, 2005 (09 May Update)

From 1 January 2005 to 9 May 2005, the Ministry of Public Health, Bureau of Epidemiology's daily surveillance reported a total of 549 influenza like illness and/or pneumonia patients, of which 549 have been excluded.

The situation can conclusively be described as follows:

- No new confirmed case

- One new case reported for investigation

- 549 cases have been excluded.

Avian Influenza in human, 2004

- Confirmed cases by laboratory detection of Influenza A (H5N1).

 - Total = 17; recovered = 5 and deaths = 12

- Suspected cases, which the signs complied with the definitions.

 - Total = 22; recovered = 13 and deaths = 9

Viet Nam

Avian Influenza in human, 2005

Since mid-December 2004, Viet Nam has reported 44 cases of H5N1 avian influenza. Of these cases, 16 have been fatal. WHO has offered support to review the situation, assess the public health risk and advise on appropriate responses. WHO continues to work closely with the Vietnamese Ministry of Health to further investigate additional cases that may have occurred, and will update its cumulative list of confirmed cases accordingly.

Cambodia

Avian Influenza in human, 2005

As of 09 May, 2005 there have been 4 deaths out of 4 laboratory confirmed cases have been officially reported. The latest case was a 20-year-old woman from Kampot province Cambodia, who died on 19 April in a hospital in Viet Nam. The woman, a secondary school student, was from Kompong Trach district in Kampot province, the same district as the first case reported from Cambodia in February. Samples taken from the woman tested positive for avian influenza A/H5 virus by the Pasteur Institute in Ho Chi Minh City, Viet Nam.

When all seems bleak.....

.....The **COME-BACK**.

The Modern World's

RESPONSE TO PANDEMICS

Antiviral Medications to Prevent and Treat Pandemic Influenza

- Four different influenza antiviral medications (**amantadine**, **rimantadine**, **oseltamivir**, and **zanamivir**) are approved by the U.S. FDA for the treatment and/or prevention of influenza.
- All four work against influenza A viruses. However, sometimes influenza virus strains can become resistant to one or more of these drugs.
- For example, the influenza A (H5N1) viruses identified in human patients in Asia in 2004 and 2005 have been resistant to **amantadine** and **rimantadine**
- Two other antiviral medications, **oseltamavir** and **zanamavir**, would probably work to treat flu caused by the H5N1 virus, though studies still need to be done to prove that they work.

TABLE 52-3 Mechanism of Action of and Main Targets for Major Antiviral Compounds

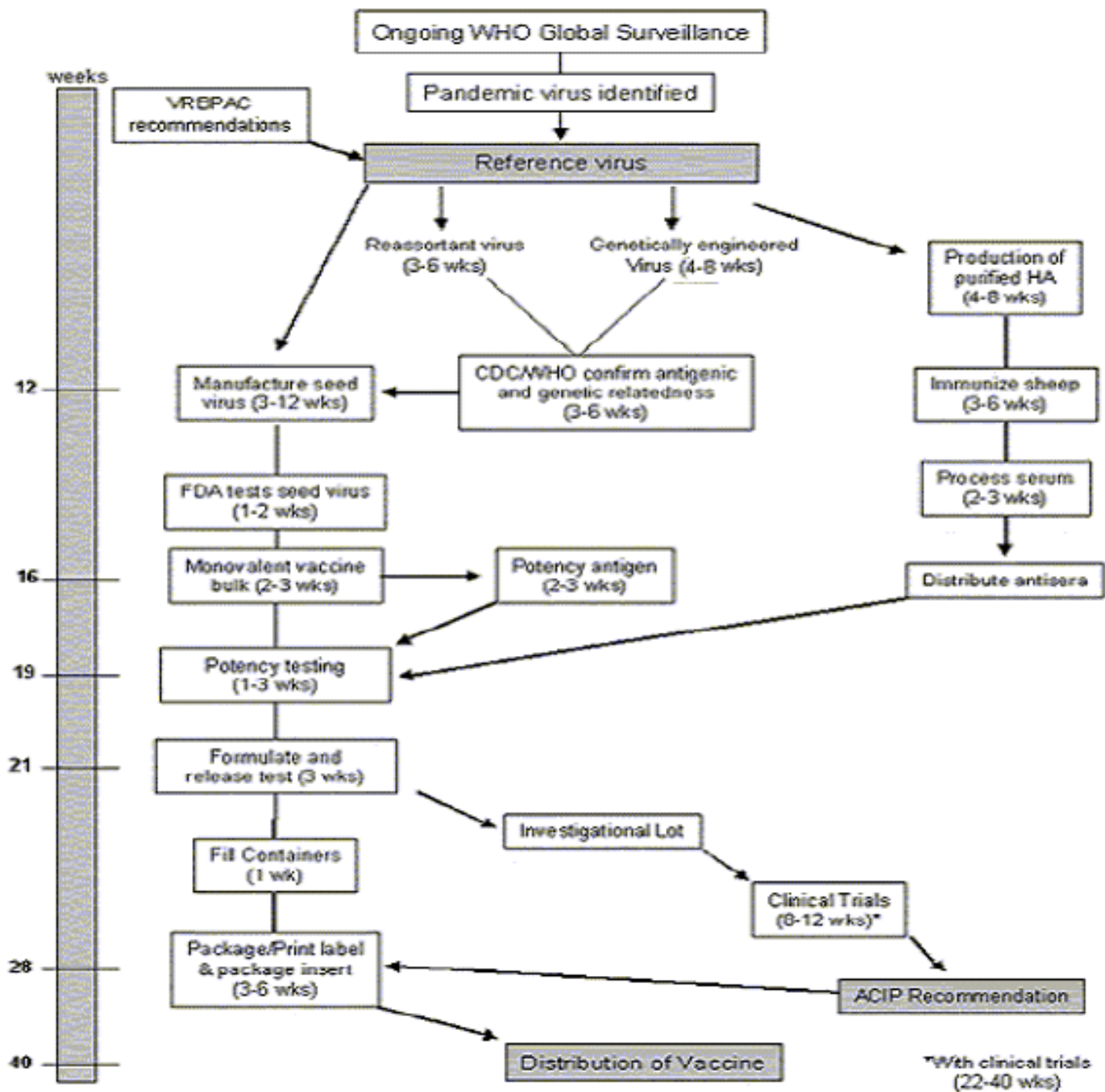
Compound	Intracellular Activation Steps	Main Target for Antiviral Action
Amantadine, rimantadine	None	Penetration, uncoating and assembly
Ribavirin	Phosphorylation to 5'-mono and tri-phosphate by cellular enzymes	Inhibition of 5'-capping of viral mRNA; inhibition of IMP dehydrogenase
Idoxuridine	Phosphorylation to 5'-triphosphate by cellular enzymes	Incorporation into DNA
Trifluridine	Phosphorylation to 5'-monophosphate by cellular thymidine kinase	Inhibition of thymidylate synthase
Vidarabine	Phosphorylation to 5'-triphosphate by cellular enzymes	Incorporation into DNA and inhibition of HSV DNA polymerase
Acyclovir ^a , Penciclovir ^b	Phosphorylation to monophosphate by HSV-specified thymidine kinase, and then to di- and triphosphate by cellular enzymes	DNA chain termination
Ganciclovir	Phosphorylation to monophosphate by CMV-specified protein kinase and to triphosphate by cellular enzymes	Inhibition of viral DNA polymerase
Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine and other dideoxy-nucleosides	Phosphorylation to 5'-triphosphate by cellular enzymes	Inhibition of reverse transcriptase; DNA chain termination
Foscarnet	None	Inhibition of viral DNA polymerase and of reverse transcriptase
Bromovinyldeoxyuridine	Phosphorylation to 5'-diphosphate by HSV-1-specified thymidine kinase and then to 5'-triphosphate by cellular enzyme(s)	Inhibition of viral DNA polymerase and incorporation into viral DNA
Acyclic nucleoside phosphonates (HPMPC, PMEA)	Phosphorylation to diphosphoryl derivatives by cellular enzymes	Inhibition of viral DNA polymerase; DNA chain termination
NNRTIs	None	HIV-1 reverse transcriptase
Polyanions	None	Viral adsorption
Viral protease inhibitors	None	HIV protease
Oxazoliny isoxazole and piperaziny pyridazine derivatives	None	Viral uncoating

^aValaciclovir acts as prodrug of acyclovir.

^bFamciclovir acts as prodrug of penciclovir.

Vaccine Development

- There currently is no vaccine to protect humans against the H5N1 virus that is being seen in Asia. However, vaccine development efforts are under way. Research studies to test a vaccine to protect humans against H5N1 virus began in April 2005. (Researchers are also working on a vaccine against H9N2, another bird flu virus subtype.)
- **NIAID Announces Contracts to Develop Vaccine Against H5N1 Avian Influenza** (Thursday, May 27, 2004)
- two contracts to support the production and clinical testing of an investigational vaccine based on a strain of avian influenza, H5N1, which might have the potential to cause pandemic influenza
- The new contracts were awarded to Aventis Pasteur Inc. of Swiftwater, PA, and to Chiron Corporation of Emeryville, CA. Both companies already manufacture inactivated influenza virus vaccines that are licensed for use during annual influenza seasons
- To develop their inactivated vaccines, the two companies will use a strain of H5N1 avian influenza taken from a Vietnamese patient in February 2004. With approval from the U.S. Food and Drug Administration, the investigational vaccines will then be tested for safety and immunogenicity in Phase I and Phase II clinical trials. These trials, to be conducted by NIAID's Vaccine and Treatment Evaluation Units (VTEUs), will study the vaccine in healthy adults first with subsequent studies planned in children and the elderly
- Aventis Pasteur and Chiron will each produce between 8,000 and 10,000 doses of the investigational vaccine made through established techniques in which the virus is grown in eggs and then inactivated and further purified before being formulated into vaccines. The use of established techniques to develop the investigational vaccines will help to promote rapid licensing of commercial pandemic vaccines in the event of a pandemic outbreak



Influenza Vaccine Manufacturing Process

Eggs are held in incubators until the proper age (9-11 day embryos). Eggs are candled to permit nonviable eggs to be discarded.



After inoculation of the specific influenza virus, incubation for optimal time (usually 48-96 hours) at optimal temperature (33-36 C) is carried out before the eggs are candled again to discard additional nonviable eggs.



Eggs are pre-chilled in refrigerators to increase yield at harvest of the infected allantoic fluids. The allantoic or tissue culture fluids are further processed to remove egg or cell proteins and cell debris, chemically inactivated, and stored as bulk vaccines until formulation can proceed.



Potency assignment is done on each monovalent vaccine pool using SRID, which requires a standard antigen of known HA quantity, and a HA specific antiserum

Answers from Current Researcher

How far along are the clinical testings right now for the vaccine against H9 - which clinical phase?

The phase I H9 clinical trial in healthy adults has been completed. We are waiting for the laboratory testing of the sera to be completed. Larger studies will be done if H9 re-emerges as a threat.

What is the reason why a vaccine was developed against the H9 strand instead of the H5N1 strand that has actually killed humans? What is the basis for this decision?

H9 viruses have also demonstrated the ability to infect humans, so they are on the WHO list of high-priority targets for vaccine development. H5 vaccines have also been developed and are in phase I testing.

Is Rochester's research on the flu vaccine completely independent of the research done at Aventis Pasteur Inc. of Swiftwater, PA, and Chiron Corporation of Emeryville, CA? or are there any connections of research between your institution and these companies?

Chiron and Aventis have produced candidate H5 vaccines for NIH under a contract. Our center tests vaccines for NIH under a different contract. Chiron and Aventis are not directly involved with our center in the testing.

John Treanor, M.D.
Professor of Medicine
Infectious Diseases Unit, Room 3-6308
University of Rochester Medical Center

The Next Pandemic

- Many scientists believe it is only a matter of time until the next influenza pandemic occurs. The severity of the next pandemic cannot be predicted, but modeling studies suggest that its effect in the United States could be severe.
- In the absence of any control measures (vaccination or drugs), it has been estimated that in the United States a “medium–level” pandemic could cause
 - 89,000 to 207,000 deaths,
 - between 314,000 and 734,000 hospitalizations,
 - 18 to 42 million outpatient visits,
 - 20 to 47 million people being sick.
 - between 15% and 35% of the U.S. population could be affected by an influenza pandemic,
 - economic impact could range between \$71.3 and \$166.5 billion.

Plan to Limit Transmission in case of Pandemic (by HHS)

	Healthcare setting	Community
Decrease potential for contact	<ul style="list-style-type: none"> • Private room or cohorting with other influenza patients • Negative pressure room, if feasible • Designate specific wards or hospitals for admission of case patients • Minimize transportation of patient outside of room • Limit the number of healthcare workers caring for influenza patients • Limit number of visitors to influenza patients 	<ul style="list-style-type: none"> • Provide advisories or limit travel to areas where a novel influenza strain is causing disease • Screen travelers for febrile and respiratory illness on exit from an area where a novel influenza strain is causing disease or on entrance to the U.S. • Cancel large group gatherings • Close schools • Encourage telecommuting • Limit availability of public transportation
	<ul style="list-style-type: none"> • Environmental decontamination for influenza following existing guidelines 	<ul style="list-style-type: none"> • Avoid unnecessary visits to hospitals • Discourage hand shaking • Identify cases early through public education and self-assessment for symptoms, including fever, leading to early isolation at home or in healthcare settings • Early quarantine of contacts of suspected cases

Review

- Influenza Viruses
- How does Avian Flu spread to humans
- Detection of novel flu strands in humans
- Pandemic possibilities
- Response to Pandemics
 - Vaccines
 - Antiviral drugs
 - Preparation guidelines

Sources

- <http://www.cdc.gov/flu/avian>



Department of Health and Human Services

Centers for Disease Control and Prevention

- <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>



- <http://www.niaid.nih.gov/default.htm>



NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
NATIONAL INSTITUTES OF HEALTH

- <http://www.dhhs.gov/nvpo/pandemics/>



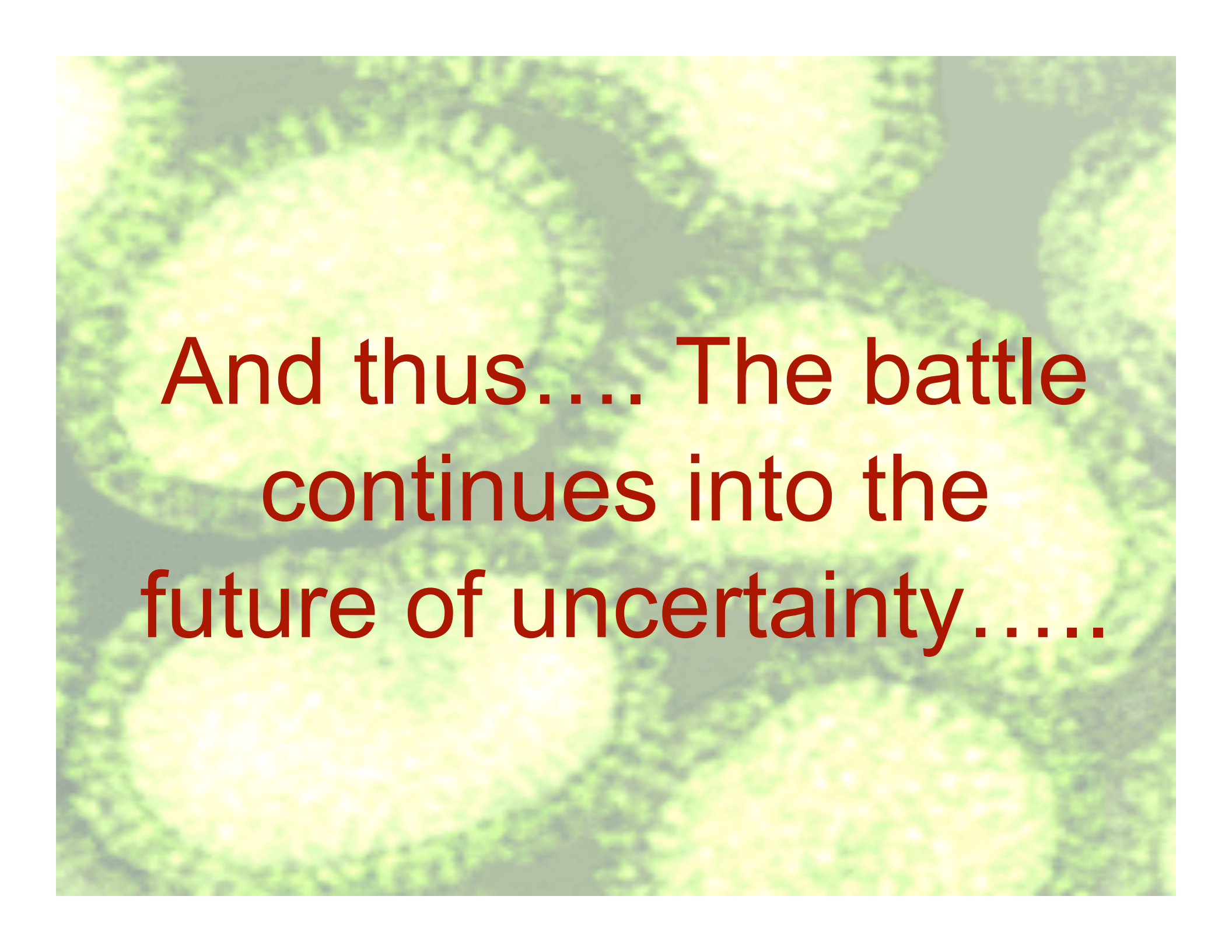
United States Department of
Health & Human Services

- <http://w3.whosea.org/en/Section10/Section1027.htm>



World Health Organization

Regional Office for South-East Asia



And thus.... The battle
continues into the
future of uncertainty.....



FINN

BAWK!