A Bird's Eye View of Bird Flu

Why the Concern?

The H5N1 virus is one of 16 different known subtypes of avian influenza (bird flu) viruses. H5N1 viruses have been found in birds around the world. The virus can infect chickens, turkeys, pheasants, quail, ducks, geese, and guinea fowl, as well as a wide variety of other birds, including migratory waterfowl. As the spread of H5N1 infection among birds increases, so does the opportunity for H5N1 to be transmitted directly from birds to humans. When an influenza virus "jumps" species from an animal, such as a chicken, to infect a human, the result is usually a "dead-end" infection that cannot easily spread further in the human population. However, mutations in the virus could develop that allow efficient human-to-human transmission.

If avian and human influenza viruses were to simultaneously infect a person or animal, the two viruses might swap genes. The result could be a new virus that is readily transmissible between humans and against which humans would have no natural immunity. Such an event could trigger a worldwide influenza pandemic.

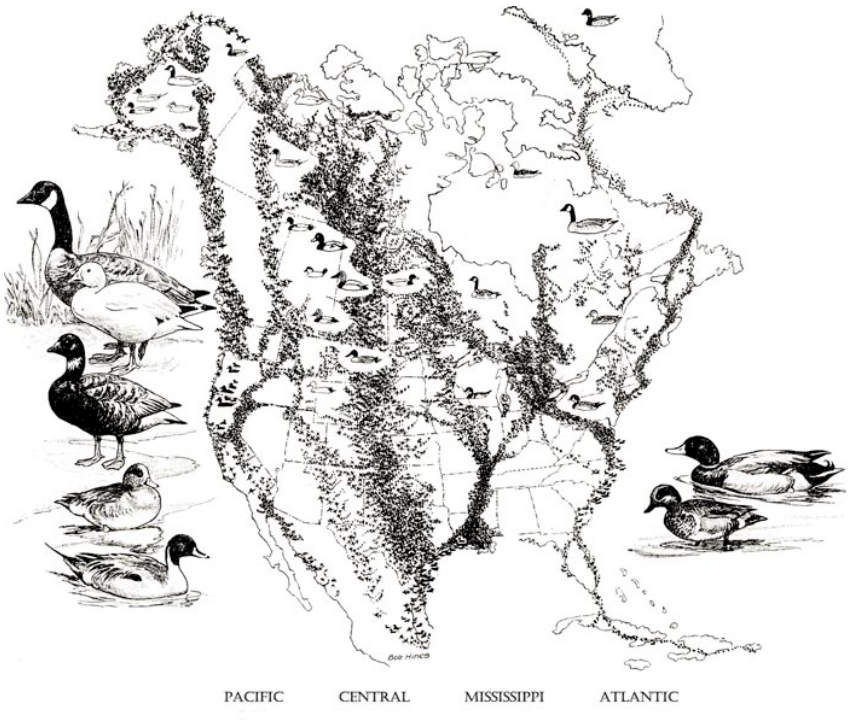
Health professionals are concerned that the continued spread of a highly pathogenic avian H5N1 virus across eastern Asia and other countries represents a significant threat to human health. The H5N1 virus has raised concerns about a potential human pandemic because:

- It is especially virulent
- It spreads via migratory birds
- It can be transmitted from birds to mammals and in some limited circumstances to humans
- Like other influenza viruses, it continues to evolve

Outbreaks of avian influenza H5N1 occurred among poultry in eight countries in Asia (Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam) during late 2003 and early 2004. At that time, more than 100 million birds in the affected countries either died from the disease or were killed in order to try to control the outbreaks. By March 2004, the outbreak was reported to be under control.

Beginning in June 2004, however, new outbreaks of influenza H5N1 among poultry and wild birds were reported in Asia. Since that time, the virus has spread geographically. Reports of H5N1 infection in wild birds in Europe began in mid-2005. In early 2006, influenza A H5N1 infection in wild birds and poultry were reported in Africa and the Near East.

Remarks Michael Leavitt, Secretary, U.S. Department of Health & Human Services (HHS) "It is only a matter of time before we discover H5N1 in birds in America. The migration patterns of the wild fowl that carry the virus make its appearance here almost inevitable." Any of the migratory birds that fly over North America can, once infected, then carry the virus hundreds — or thousands — of miles across the nation in any direction:



Waterfowl Flyways of North America

Image credit U.S. Forestry & Wildlife Service.
Image from www.pandemicflu.gov, U.S. Department of Health & Human Services, accessed 9 May 2006.

Since 2003, a growing number of human H5N1 cases have been reported in Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Thailand, Turkey, and Vietnam. More than half of the people infected with the H5N1 virus have died. Most of these cases are all believed to have been caused by exposure to infected poultry. There has been no sustained human-to-human transmission of the disease, but the concern is that H5N1 will evolve into a virus capable of human-to-human transmission.

Slow but Steady Progress in Beating H5N1 in Asia

As of May 2006, Vietnam — where almost 50 percent of the initial cases were reported — has not reported a single human case or an outbreak of flu in poultry this year. This lack of outbreak is attributed to massive-scale vaccination of the poultry whereby all of the nation's 220 million chickens were vaccinated.

Thailand — the second-hardest-hit nation — has also not seen a human case for over a year and a poultry outbreak for since late 2005. The nation culled affected birds and compensated farmers who lost their poultry stock. Thailand has also vaccinated its fighting cocks, a large source of gaming revenue and favorite sport among locals. In addition, Thailand has appointed a volunteer deputy in every village whose responsibility it is to report sick chickens to officials.

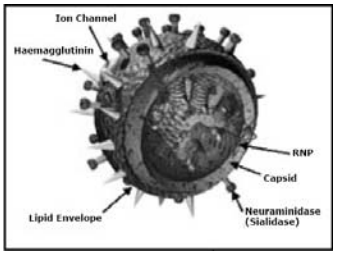
Both Vietnam and Thailand did not hold back supplies of Tamiflu, the anti-viral drug of choice for treatment of bird flu (see Chapter 4). These supplies were sent to even the smallest regional hospitals and health workers were ordered to begin treating suspected cases even if confirming diagnosis was still pending.

Another possible success case is China, where the Chinese Agriculture Ministry appears to have delivered on its promise to vaccinate all domestic poultry. The number of reported human cases in China have been low over the last two years. So far in 2006, China reported only 10 cases as compared to 8 for the same timeframe in 2005. "We are hopeful that China has turned the corner," remarked Dr. David Nabarro, chief pandemic flu coordinator for the United Nations.

"Tomorrow, the whole thing could change again," says Dr. David Nabarro. "We need to be on the alert at all times."

What is the Avian Flu?

Avian influenza — aka "bird flu" — is an infection caused by influenza viruses that occur naturally in birds. There are different subtypes of these viruses because of changes in certain proteins (hemagglutinin [HA] and neuraminidase [NA]) on the surface of the influenza A virus and the way the proteins combine. Each combination represents a different subtype denoted by the identification code H#N#.



The H5N1 virus molecule is characterized by the proteins Hemaggluttinin (HA) and Neuraminidase (NA)

Image from "Pandemic Planning Update," U.S. Department of Health & Human Services, 13 March 2006, http://www.pandemicflu.gov/plan/pdf/panflu20060313.pdf. Accessed 9 May 2006.

Prominent Bird Flu Virus Subtypes

All known subtypes of influenza A viruses can be found in birds. There are 16 known HA subtypes and 9 known NA subtypes of influenza A viruses. Avian influenza A H5 and H7 viruses can be distinguished as "low pathogenic" and "high pathogenic" forms on the basis of genetic features of the virus and the severity of the illness they cause in poultry; influenza H9 virus has been identified only in a "low pathogenicity" form. Each of these three avian influenza A viruses (named for the hemagglutinin [HA] protein, as H5, H7, or H9) theoretically can be partnered with any one of nine neuraminidase [NA] surface proteins, yielding potentially nine different forms of each subtype (e.g., H5N1, H5N2, H5N3, H5N9 etc.).

Influenza A H5
- Potentially nine different subtypes
- Can be highly pathogenic or low pathogenic
- H5 infections have been documented among humans, sometimes causing severe illness and death

Influenza A H7
- Potentially nine different subtypes
- Can be highly pathogenic or low pathogenic
- H7 infection in humans is rare, but can occur among persons who have direct contact with infected birds; symptoms may include conjunctivitis and/or upper respiratory symptoms

Influenza A H9
- Potentially nine different subtypes
- Documented only in low pathogenic form
- At least three H9 infections in humans have been confirmed to-date

Expert Insight: We are "sitting ducks" because "we do so much wrong in this country"

Dr. John B. Symes ("DogtorJ.") is a practicing veterinarian who, following his personal diagnosis of celiac disease (gluten intolerance) and subsequent recovery from numerous chronic ailments, has become an Internet medical researcher and consultant (www.dogtorj.net). The following is an excerpt from an interview conducted by Dr. Ronald Klatz with Dr. Symes; you are invited to visit www.worldhealth.net/pandemic to listen to the entire interview.

Dr. Ronald Klatz: [W]hat everyone seems to be concerned about right now, is the looming pandemic that our government tells us could possibly kill 2 million Americans and may be 150 million people worldwide and I just want to get your take on that, because after all you are veterinary researcher and this is bird flu. The disease is afflicting primarily fowl, not humans, even though, I believe the human death toll is over 200 right now. The fowl death toll is in the hundreds of millions, may be you can go into that a little bit.

Dr. John Symes: Well, fortunately it is still outside our borders, but we have been reading about it. I have not been seeing a lot in the veterinary literature. To be honest … our biggest concern is in the feline. The cat is susceptible to the H5N1 virus and they have had some actually died and had a number of them experimentally infected — even big cats, some of the leopards and tigers and some of the smaller exotic cats like civets are all susceptible to this, so the feline population is the one that we are most concerned about. There was a study done that showed that out of 600 dogs or something that were studied, a quarter of them were at least having antibodies to the Avian influenza virus, but no known clinical disease in the dog.

So, for the small animal practitioner the biggest concern will be the cat and there have been some cats reported died of the disease especially experimentally. They not only will shed the virus from the respiratory tract, but actually in their feces apparently. But, at this point, the amount of virus that they are shedding appears to be low, so they don't think that will be a major contributing factor to the spread of the disease. The main way that these cats are acquiring the virus is through the feeding or eating of raw bird carcasses because cooking fortunately does a good job of destroying this, but eating raw carcasses is the big concern. So, we see a lot of interspecies spread of these viruses. The dog, in this country, we recently had an upper respiratory virus that came from the horse and started infecting the dog. We note that these things move around, but our biggest concern is going to be the cat.

RK: Dr. Symes, what is your read on this? Do you think that the H5N1 is going to mutate into something that is going to affect people and is that concerning the veterinary community, is there any preparation going on the veterinary community?

JS: Most people have demonized viruses completely and they feel like that viruses only do bad things, but of course as you and I know viruses are essential to the operation of

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Expert Insight with Dr. Symes *(continued)*

nature and the two things that they do most that are good is they allow adaptation and they also cause variation in nature. Viruses are ubiquitous in all aspects of nature plants, animals, and humans. We are loaded up with them and that is because they help us to adapt to this ever changing environment. From the moment the world was created, it has never been the same and the viruses are in this mix to help us adapt to this ever changing environment and so when we talk about viruses mutating, if we look at it just purely that way we have a tendency, you know, to think it is just something bad. All of a sudden this [benign virus] turns out into [a malignant virusl and goes and starts killing millions of people when sometimes it happens like it did back in 1918, but the main thing is that they adapt and they are forced into adaptation because they are going to survive; that is one of the things, they are like a little robot, they are going to survive that is what their charge is and they are going to adapt and allow whatever there are living in to survive and until the adaptation process gets to the point where it has to become pathogenic to survive. So, the development of pathogenic viruses, the way I look at it my perspective is that they simply have been forced into adapting to something that our bodies no longer like because they are going to survive no matter what.

The reason why they are concerned about millions and millions of people dying in this country from this kind of thing if you were ever to do that and become the next Spanish flu is because we do so much wrong in this country with our diet and our life style and our lack of sleep and our abuses of alcohol, drugs and cigarettes and everything else and all lack of hygiene as well.

We have got to start the best preparation if we knew this thing [bird flu] is going to hit us in 10 to 15 years later on 100th-year anniversary of Spanish flu or something we would have to make a major turnaround in just how we live our lives, mainly on diet and lifestyle, that is to me the only true prevention because our immune systems and the shape that they are in right now, we are sitting ducks.

Visit www.worldhealth.net/pandemic to listen to the entire interview with Dr. Symes

Avian Influenza in Birds

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

Infected birds shed influenza virus in their saliva, nasal secretions, and feces. Domesticated birds may become infected with avian influenza virus through direct contact with infected waterfowl or other infected poultry, or through contact with surfaces (such as

dirt or cages) or materials (such as water or feed) that have been contaminated with the virus.

Infection with avian influenza viruses in domestic poultry causes two main forms of disease that are distinguished by low and high extremes of virulence. The "low pathogenic" form may go undetected and usually causes only mild symptoms (such as ruffled feathers and a drop in egg production). However, the highly pathogenic form spreads more rapidly through flocks of poultry. This form may cause disease that affects multiple internal organs and has a mortality rate that can reach 90-100% often within 48 hours.

Influenza A (H5N1) virus – also called "H5N1 virus" – is an influenza A virus subtype that occurs mainly in birds, is highly contagious among birds, and can be deadly to them. H5N1 is the strain of avian flu currently of concern for potential pandemic outbreak in humans. H5N1 virus does not usually infect people, but infections with these viruses have occurred in humans. Most of these cases have resulted from people having direct or close contact with H5N1-infected poultry or H5N1-contaminated surfaces.

Avian Flu in Birds is On the Rise

- Wild birds can carry the viruses, but usually do not get sick from them. However, some domesticated birds, including chickens, ducks, and turkeys, can become infected, often fatally if they come into contact with an infected wild bird. Domesticated birds usually die from the disease.
- The H5N1 virus is endemic in much of Asia and has now spread into Europe. Avian H5N1 infections have recently killed poultry and other birds in a number of countries.
- Strains of avian H5N1 influenza may infect various types of animals, including wild birds, pigs, and tigers.
- Symptoms in birds and other animals vary, but virulent strains can cause death within a few days.

Human Infection with Avian Influenza Viruses

"Human influenza virus" usually refers to those subtypes that spread widely among humans. As of this writing, there are only three known A subtypes of influenza viruses (H1N1, H1N2, and H3N2) currently circulating among humans. All known subtypes of influenza A viruses can be found in birds. It is likely that some genetic parts of current human influenza A viruses originally came from birds. Influenza A viruses are constantly changing, and other strains might adapt over time to infect and spread among humans.

The risk from avian influenza is generally low to most people, because the viruses do not usually infect humans. H5N1 is one of the few avian influenza viruses to have crossed the species barrier to infect humans, and it is the most deadly of those that have crossed the barrier.

Usually, "avian influenza virus" refers to influenza A viruses found chiefly in birds, but infections with these viruses can occur in humans. Although avian influenza A viruses usually do not infect humans, more than 200 confirmed cases of human infection with avian

influenza viruses have been reported since 1997. Most cases of H5N1 influenza infection in humans have resulted from contact with infected poultry (such as, domesticated chicken, ducks, and turkeys) or surfaces contaminated with secretion/excretions from infected birds.

Because of concerns about the potential for more widespread infection in the human population, public health authorities closely monitor outbreaks of human illness associated with avian influenza. To date, human infections with avian influenza A viruses detected since 1997 have not resulted in sustained human-to-human transmission. So far, the spread of H5N1 virus from person to person has been limited and has not continued beyond one person. Researchers from the University of Wisconsin's School of Veterinary Medicine (USA) found that the receptors favored by the H5N1 virus are located deep within the lower respiratory tract — primarily on cells of the alveoli and some in the bronchi — suggesting that the unimpeded transmission of H5N1 may require the ability of the virus to recognize yet-unrecognized human flu receptors. Nevertheless, because all influenza viruses have the ability to change, scientists are concerned that H5N1 virus one day could be able to infect humans (perhaps by recognizing the receptors deep in the lungs) and then spread easily from one person to another.

In the current outbreaks in Asia, Europe, and Africa, more than half of those infected with the H5N1 virus have died. Most cases have occurred in previously healthy children and young adults. However, it is possible that the only cases currently being reported are those in the most severely ill people, and that the full range of illness caused by the H5N1 virus has not yet been defined.

Why So Deadly?

The H5N1 virus is highly effective at replication. After invading its first host cell, the virus takes over so much of the cell's machinery that the cell dies. The virus then ejects itself to new, live host cells, one by one, to repeat the process again and again. An accumulation of dead cells in the airways results in a runny nose and scratchy throat. Too many dead cells in the lungs result in death.

Contrary to the commonly held belief that the bird flu virus has little affinity for human respiratory tissues, a researcher team from Erasmus Medical Center (Netherlands) has found that the H5N1 virus readily attaches to, and proliferates, within the bronchioles and alveoli of the human lungs. The team notes that this preference by the virus for cells in the deepest passageways of lung tissue "may contribute to the severity of the pulmonary lesion [caused by bird flu infection]."

Because these viruses do not commonly infect humans, there is little or no immune protection against them in the human population. If H5N1 virus were to gain the capacity to spread easily from person to person, a pandemic (worldwide outbreak of disease) could begin. No one can predict when a pandemic might occur. However, experts from around the world are watching the H5N1 situation very closely and are preparing for the possibility that the virus may begin to spread more easily and widely from person to person.

Symptoms of Bird Flu in Humans

Symptoms of bird flu in humans range in severity and may include:

- Typical human influenza-like symptoms, including:
  - Fever: temperature over 100.4°F (38°C)
  - Cough
  - Sore throat
  - Muscle aches
- Early symptoms may include diarrhea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums (watery diarrhea without blood appears to be more common in H5N1 avian influenza than in normal seasonal influenza)
- Eye infections (conjunctivitis)
- Pneumonia
- Severe respiratory diseases (such as acute respiratory distress)
- Viral pneumonia
- Other severe and life-threatening complications

Infection and Transmission

The U.S. federal government has made these assumptions about pandemic flu:

- Persons who become ill may shed virus and can transmit infection for up to one day before the onset of illness. Viral shedding and the risk of transmission will be greatest during the first 2 days of illness. Children usually shed the greatest amount of virus and therefore are likely to pose the greatest risk for transmission.
- On average, infected persons will transmit infection to approximately two other people.

Progression of the Disease

The World Health Organization (WHO) has made these observations regarding the progression of the disease in affected individuals:

- Time between onset of illness to the development of acute respiratory distress can range between 4 to 13 days – 6 days is typical. Some severe cases have been observed to arrive at respiratory failure 3 to 5 days after symptom onset.
- Difficulty in breathing develops around five days following the first symptoms. Respiratory distress, a hoarse voice, and a crackling sound when inhaling are commonly seen. Sputum production is variable and sometimes bloody.
- Abnormal lab tests commonly include: leukopenia (mainly lymphopenia), mild-to-moderate thrombocytopenia, elevated aminotransferases, and, in some instances – disseminated intravascular coagulation.
- Almost all patients develop pneumonia. Multiorgan dysfunction is common. Pneumonia and/or multiorgan dysfunction cause death.

Differentiating Bird Flu from Seasonal Influenza

Unlike seasonal influenza, in which infection usually causes only mild respiratory symptoms in most people, H5N1 infection may follow an unusually aggressive clinical course, with rapid deterioration and high fatality. Primary viral pneumonia and multi-organ failure have been common among people who have become ill with H5N1 influenza.

Seasonal (or common) flu is a respiratory illness that can be transmitted person to person. Most people have some immunity, and a vaccine is available. More information about seasonal influenza is available from the US Centers for Disease Control & Prevention, at http://www.cdc.gov/flu/.

Avian (or bird) flu is caused by influenza viruses that occur naturally among wild birds. The H5N1 variant is deadly to domestic fowl and can be transmitted from birds to humans. There is no human immunity and no vaccine is available.

IMPORTANT: The influenza vaccine administered for the 2005-06 season does not provide protection against avian influenza. The seasonal flu vaccine contains two strains of the most recent form of influenza A as well as one strain of influenza B. These strains have widely circulated in humans for a number of years. The vaccine for bird flu being tested is made with an inactivated H5N1 virus that approximates the strain of avian flu anticipated to affect humans (see Chapter 4 for the discussion on Bird FluVaccine).

Expert Insight: "Brain washed with the idea of immunity"

Mr. Fintan Dunne is a technical and medical journalist and editor of MyLongLife.com (www.mylonglife.com). He has written on medical issues as diverse as HIV/AIDS, SARS, and the social psychology of medicine. The following is an excerpt from an interview conducted by Dr. Ronald Klatz with Mr. Dunne; you are invited to visit www.worldhealth.net/pandemic to listen to the entire interview.

Dr. Ronald Klatz: Tell us about the scientific process involved in identifying the bird flu virus organism.

Mr. Fintan Dunne: If you want to prove the existence of a new pathogenic strain, you should ideally isolate it in sufficient titre (in other words in sufficient quantity) from an animal or person suspected to have it. From that you should be able to grow it in-culture, you should be able to centrifuge it, and you should be able to find significant numbers of similar multigenic (similar size, similar shape) — to indicate you have isolated something. Then you can take that something — still unproven as to effect — inject it into another animal or person, and it should achieve the same symptoms as in the first person or animal. It's a long time since we've done that, and we don't — believe it or not — do it with HIV AIDS. Of course it is difficult: you cannot potentially inject somebody with something which is going to cause AIDS, but surprising we are not doing that kind of stuff in things like SARS and bird flu, but we are making inferences based on antibody responses and we are relying on technology such as for example PCR which is a DNA or RNA amplification techniques.

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Expert Insight with Mr. Fintan Dunne *(continued)*

Now you can amplify for that does improve sufficient titre, but that they might been something there which is disease causing and seeing sufficient titre or not could be indicative of a problem.

RK: Fintan, you are saying that we have not isolated this specific organism that causes bird flu that all these things of dead chickens and other fowl or no body has gone so far to take tissue samples from them and isolate out an organism?
FD: Isolation can done in individual instances where you're attempting to prove that such and such causes a disease. The problem is that when it goes on to doing the kind of testing which we rely on to determine whether it is an epidemic or not. We are not using that. We are using indirect markers, which are basically the culpability of hemagglutinin — so we're inferring that hemagglutinin in influenza virus — we're inferring. The H5N1 stands for hemagglutinin N5 and neuraminidase N1. And this is in theoretical construct, I'm afraid. If you look at possible causes for what we see, the pattern is that we're not seeing the spread in wild birds as was projected, we're not seeing this H5N1 to any degree as the so-called outbreak in mass production poultry facilities (if you look there, the key issue there may be the levels of selenium which the birds have, selenium is very important in its antiviral effect within the animal and human body, and selenium is becoming deficient in these birds). We're also looking at so-called human cases associated with these. After these case are taking place against a backdrop of 3.5 million upper respiratory tract infections, which are taking place around the globe annually. So to isolate out small set of the 5, 6, 7, or 10 here there. Unfortunately, that the cases we are dealing with within realms of the normal error risk of any procedure. So you can't inference from these isolated cases. We saw this in SARS where Dr. Frank Plummer in Canada, with Toronto being one of the epicenters of SARS, was finding that these so called coronavirus, which was the alleged cause of this syndrome was in at first 40% of the patients that were suspected, then 30%, then 20%. In other words, 80% of the people that were hospitalized and suspected of SARS were suffering just from influenza and there we have no proof that coronavirus was actually the cause. I think it is a growing symptom that it's the terrain — underlying substrate — in the susceptibility of an individual towards these tendencies.

RK: So you are saying, if, my understanding is correct, you are saying that we have not or the established medical authorities have not proven an isolatable specific organism for either SARS nor for avian flu.
FD: The problem arises because we have been brain washed with this idea of immunity. It is very controversial issue in relation to vaccination, but the idea is that antibody immunity confers protection. We know from there have been various campaigns which have been conducted to vaccinate, but we have had epidemics among the vaccinated (which don't seem

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Expert Insight with Mr. Fintan Dunne *(continued)*

to differentiate whether they've been vaccinated or not), and so antibody immunity is a bit of a misnomer. And so indeed, there is this whole idea of a small set of external viruses which come after us and get us. For example, in the case of HIV there is clear evidence that 95% actually have the genetic sequence of HIV endogenously within the cells and that this only emerges and becomes active in particular when the selenium levels are low or in response to toxic assaults or the overall nutritional condition of metabolic condition of the body. So, we are very focused on this idea of external agents, but we have a multiple mess of animal and human viral bits of pieces in there in what they call the junk DNA section of our DNA. In many cases we have taken a superfluous route that everything in the body is perfect and everything that comes from outside is a threat and so we developed this whole rationale and we see all these epidemics in that light. But if we look at them and we know that in fact it is those who have compromised health — on the one hand we think that there are germs out there which will come and get you, it doesn't matter if you're a quarterback in perfect physical health, it will take you down — but at the same time we do accept that the aged and the younger are the ones most at-risk when there's any kind of an epidemic. I suggest that it's the health of an individual that is the key in all of this.

RK: Okay. Well, I certainly can accept that but I have a hard time getting that we are dealing with a phantom when it comes with when it comes like avian flu, certainly with all the government prepared. The TV specials, the World Health Organization leafleting everybody at the airports; in US alone $7 Billion has been earmarked for preparedness for the avian flu epidemic that is supposed to come any day. There is even talk of special quarantine areas they want to initiate... What is behind all this stuff?
FD: Well, there is an agenda. The agenda is to a degree, a conscious agenda to say, the conscious agenda is to continue with this that there is external agents which can take you down with regard to health status, which is incredibly simplistic, but it does serve to bolster the weak position — growing weaker by the day — of the entire pharmaceutical/corporate complex based around this notion of disease. So it suits that agenda. There are suspicions behind this agenda as well, to demonize the small owner, who has small stocks of animals, at the expense of large production units, and then following hysteria about the bird flu epidemic to begin to make the claim that only large production units could possibly have the safety standards to make sure that never happens again. But that's the world of politics, so leave that to them … there's a lot of politics in health.

Visit www.worldhealth.net/pandemic to listen to the entire interview with Mr. Dunne