AVIAN INFLUENZA: ANOTHER INFLUENZA PANDEMIC?

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INTRODUCTION

The world is now closer to another influenza pandemic than at any time since 1968, when the last of previous century's three pandemics began. While influenza pandemics are infrequent events, they are rightly feared as they spread very rapidly to affect all countries and cause abrupt and significant increases in morbidity. Neither the timing nor the severity of the next pandemic can be predicted, but severe pandemics in the past have resulted in tens of millions of deaths. As the SARS experience clearly demonstrated, the first influenza pandemic of the 21st century could have significant economic and social consequences that go well beyond the absolute impact on health[1].

Avian Influenza (Bird flu) is an infectious disease of birds caused by avian (bird) influenza (flu) viruses. In other words Influenza viruses that infect birds are called "avian influenza viruses". These viruses are genetically distinguishable from influenza that normally infects humans and 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[2, 3].

The disease, capable of causing extremely high mortality amongst infected fowl, was first discovered in Italy in 1878 and became known as fowl plague now occurs worldwide [3,4]. Bird flu viruses do not normally infect species other than birds and pigs.

The first documented infection of humans with bird flu virus occurred in Hong Kong in 1997 [5], when the H5N1 strain caused severe respiratory disease in 18 humans, out of

whom 6 died. This infection of humans coincided with an epidemic of highly pathogenic avian influenza (HPAI), caused by the same strain, in Hong Kong poultry population [6].

With the exception of the Hong Kong outbreak, all human pandemic strains have been reassortants between avian and human influenza viruses [6]. Evidence supports the model that pigs serve as 'mixing vessel' for reassortants as their cells contain receptors recognised by both human and bird flu viruses[7]. Most experts agree that pigs played a role in the emergence of pandemic viruses in 1957 and 1968, and that humans could also serve as "mixing vessels" if concurrently infected with human and bird flu virus strains [8].

CAUSATIVE AGENT OF AVIAN INFLUENZA

The causative organism of this disease was shown to be a virus as early as 1901 but it was not until 1955 that the relationship to mammalian influenza A viruses was demonstrated [3, 9].

Influenza A (H5N1) virus was first isolated from birds (terns) in South Africa in 1961 [2]. Influenza A belongs to the family *Orthomyxoviridae*, which comprises the genus *Influenza virus*, which contains two species, A and B; and an unnamed genus which contains influenza C virus[10].

Influenza type A viruses can infect humans, birds, pigs, horses, seals, whales and other animals but wild birds are the natural hosts for these viruses.

The virus is typically an enveloped virion. It is spherical and about 100nm in diameter, but larger and more pleomorphic forms are commonly seen [11]. The envelope consists of host lipid from which project oval-shaped haemagglutinin (HA) and mushroom-shaped neuraminidase (NA) peplomers, both of which are glycoproteins.

Influenza type A viruses are divided into subtypes based on these two proteins, all of which share a common nucleoprotein and matrix protein but differ in their HA and/or NA[6]. Many different combinations of HA and NA proteins are possible. There are 15 known HA subtypes (HA 1 to HA 15) and 9 of NA (NA 1 to NA 9). While all subtypes can be found in birds and are thereore referred to as ''bird flu viruses'', only 6 subtypes of HA (H1, H2, H3, H5, H7 and H9) and 3 subtypes of NA (N1 N2 and N7), (i.e. H1N1, H2N2, H3N2, H5N1, H7N7 and H9N2) are currently in general circulation among humans and are referred to as ''human flu viruses'' [12-17].

Between 1957 and 1968, H2N2 viruses also circulated among humans but currently do not. It is likely that some genetic parts of current human influenza A viruses came from birds originally. Other subtypes are found most commonly in other animal species. For example, H7N7 and H3N8 viruses cause illness in horses.[16]

Subtypes of influenza A virus are named according to their HA and NA surface proteins. For example, an ''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 [12, 18].

Beneath the envelope there is a matrix (M) protein, and within the envelope-matrix protein coat there is a ribo-nucleoprotein which determine species specificity, but being internal they have no role in attachment and antibodies to them are not protective. Subtype-specific antigenic determinants are carried by HA and NA peplomers. The negative sense ssRNA genome occurs as eight separate molecules most of which code for a single protein.

Because of the segmented genome, genetic reassortment can occur in cells infected with two different strains of influenza A virus. Reassortment of the genes for HA or NA produces antigenic shift. Mutations in these genes cause antigenic drift. It is believed that this constant change in Influenza viruses is very critical as they might adapt over time to infect and spread among humans.

Influenza viruses are sensitive to heat (56^{o}C for 30 mins), acid treatment (PH 3), and treatment with lipid solvents and are thus very labile under ordinary environmental conditions [9].

EPIDEMIOLOGY OF AVIAN INFLUENZA

Prevalence/Incidence

The epidemiology of bird flu is poorly understood because of the role of wild birds, the great variety of different strains and the variable effects in different host species[19].

At least 10 global influenza pandemics have occurred during the past 200 years [20]. Influenza pandemic is a global outbreak of influenza and occurs when a new influenza virus emerges, spreads, and cause disease worldwide. Past pandemics have led to high levels of illness, death, as well as social disruption and economic loss.

There were 3 most prominent pandemics in the 20th century. All of them spread worldwide within one year of being detected. They are: -

"Spanish flu" [ACH1N1] (1918-1919), caused the highest number of flu deaths: more than 500,000 people died in the USA and probably 20 to 50 million people worldwide. Many people died within the first few days after infection and others died of complications soon after. Nearly half of those who died were young, healthy adults.

"Asian flu" [ACH2N2] (1957-1958), caused about 70,000 deaths in the USA. First identified in China in late February 1957, the Asian flu spread to the USA by June 1958.

"Hong Kong flu" [ACH3N2] (1968-1969), caused approximately 34,000 deaths in USA. This virus was first detected in Hong Kong in early 1968 and spread to the USA later

that year. Type A (H3N2) viruses still circulate today.

Although there is no regular periodicity in the occurrence of the pandemic, every 10-40 years when a new subtype of influenza A appears, a pandemic results [21].

In February 2003, the outbreak of H5N1 bird flu in Hong Kong caused 2 cases and 1 death in members of a family who had recently travelled to southern China. This marked the beginning of another epidemic [17]. Two other bird flu viruses have recently caused illness in humans. An outbreak of highly pathogenic H7N7 bird flu, which began with Netherlands in February 2003, caused the death of one veterinarian two months later, and mild illness in 83 other humans[14]). Mild cases of bird flu H9N2 in children occurred in Hong Kong in 1999 (2 cases) and in mid – December 2003 (one case) [15]. Another cause for alarm occurred in January 2004, when laboratory tests confirmed the presence of H5N1 bird flu virus in human cases of severe respiratory disease in Northern part of Viet Nam[16].

Beginning in late June 2004, however, new deadly outbreak of influenza H5N1 among poultry were reported in 12 Asian countries. As of 22-10-2005, 12 Asian countries had been affected {South Korea, Vietnam, Japan, Taiwan, Thailand, Combodia, Hong Kong SAR, Lao, PDR, Pakistan, Indonesia, China, and Malaysia). By October 2005, 8 other countries including Africa were affected (USA, Canada, Netherlands, Turkey, Romania, Russia, South Africa and Egypt). In February 2006 Iraq, Nigeria, Azerbaijan, Bulgaria, Greece, Italy, Slovenia, Iran, Austria, Germany, India, France, Hungary and Niger had had their share of the epidemic[22]. The implication of the spread to Africa and the Middle East is that poor poultry farmers will be unable to report, manage or contain it effectively. There is also a higher chance of lethal mutation into a human form of the virus because of the closer contact between humans and animals.

Globally the cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO as at 29th march 2006 shows that 186 laboratory-confirmed human cases were recorded with a total of 105 deaths since 2003. These are recorded in Cambodia, china, Indonesia, Iraq, Thailand, Turkey and Vietnam. The highest cases and deaths were recorded in Vietnam followed by Indonesia and Thailand in that order[22].

Well over 100 million birds in the affected countries either died from the disease or were culled in order to control the outbreak.

Mode Of Transmission

Wild ducks and geese are regarded as refractory to disease, but wild ducks probably represent the most important reservoir of bird flu viruses. Among domestic birds, chickens and turkeys are the species most likely to develop disease, but pheasant, quail, guinea fowl, and ostriches also develop clinical illness[8].

Influenza viruses replicate in the respiratory and intestinal tracts of infected birds

therefore, infected birds shed the virus in their saliva, nasal secretions and faeces. Bird-to-bird transmission would appear to occur through virus in droplets or aerosols from the respiratory tract or through feaces, either directly or in contaminated water and food [2, 13] . The faeco-oral route maybe the main route of spread and all available evidence suggest that primary introduction of bird flu viruses into an area is as a result of waterfowl activity [2].

In most recorded outbreaks of influenza virus infection of poultry, secondary spread has been primarily considered to be by the agency of humans[6]. Direct or indirect contacts of domestic flocks with migratory waterfowl have been implicated as a frequent cause of epidemics and also live bird markets are known to play an important role in spreading the disease. Apart from being highly contagious, avian influenza viruses are readily transmitted from farm to farm by mechanical means, such as by contaminated equipment, vehicles, feed, cages, or clothing.

It is believed that most cases of bird flu infection in humans have resulted from contact with infected poultry or contaminated surfaces. The spread of avian influenza viruses from one ill person to another has been reported rarely, and transmission has not been observed to continue beyond one person [2].

One characteristic of great epidemiological value and public health concern is the constant mutation of all type A influenza viruses, and the other is their high affinity for reassortment of genetic materials when different subtypes from different species are co-infected. This antigenic shift has historically resulted in highly lethal pandemics. For this to happen, the novel subtype needs to have genes from human influenza viruses that make it readily transmissible from person to person for a sustainable period.

Conditions favourable for the emergence of antigenic shift have long been thought to involve humans living in close proximity to domestic poultry and pigs. Because pigs are susceptible to infection with both avian and mammalian viruses, including human strains, they can serve as a "mixing vessel" for the scrambling of genetic material from human and avian viruses, resulting in the emergence of a novel subtype. Resent events, however, have identified a second possible mechanism. Evidence is mounting that, for some of the 15 avian influenza virus subtypes circulating in bird population, humans themselves can serve as the "mixing vessel" [23].

Virus Subtype H5N1

This virus subtype occurs mainly in birds. It was first isolated from birds in South Africa in 1961[12]. Like all bird flu viruses, H5N1 virus circulate among birds worldwide, is very contagious among birds and can be deadly. Of the 15 bird flu virus subtypes, H5N1 is of particular concern for several reasons. H5N1 mutates rapidly and has a documented propensity to acquire genes from viruses infecting other animal species. Its ability to

cause severe disease in humans has now been documented [6]. Also, birds that survive infection excrete the virus for at least 10 days, orally and in feaces, thus facilitating further spread at live poultry markets and by migratory birds.

Seasonal Variation

As with other viral respiratory infections, influenza is a seasonal disease[13]. In the Northern Hemisphere and in countries with temperate climates, influenza is most likely to occur from November to April, and in the Southern Hemisphere, from May to October. In tropical regions, it is more endemic with peak incidence during harmattan [13]. A continuous person-to-person chain of transmission must exist for maintenance of infection in between the bird flu epidemics.

High Risk Groups

School-age children are the predominant vectors of bird flu transmission. Crowding in school favours the aerosol transmission of the virus, and children take the virus home to the family. All sexes are equally susceptible to bird flu.

Veterinarians, poultry cullers and workers, including health care workers and patient's family members and visitors are at high risk.

Immunity to Infection

Immunity to bird flu is long-lived and subtype-specific[6]. Resistance to initiation of infection is related to antibody against the HA, whereas decreased severity of disease and decreased ability to transmit virus to contacts are related to antibody directed against the NA. Antibodies against the ribonucleoprotein are type-specific and are useful in typing viral isolates. Protection correlates with both serum antibodies and secretory IgA in nasal secretions. The local secretory antibody is probably important in preventing infection. Immunity can be incomplete, as re-infection with the same virus can occur.

PATHOGENICITY AND PATHOGENESIS OF AVIAN INFLUENZA

The pathogenicity for man and animal differ with the virus species and within species, and it also depends on the virulence of the virus strain. The pathogenesis follows when infected birds shed flu virus in their saliva, nasal secretion, and feaces. Susceptible birds become infected when they come in contact with contaminated excretion or surfaces that are contaminated with excretion.

Within infections with virulent strains of bird flu, viraemia may occur with pathological lesions in the liver, spleen, heart, and kidney. Haemorrhagic lesions may occur. Again, bird flu is often complicated by secondary bacterial infection or mixed viral infections.

Low Pathogenic Versus Highly Pathogenic Avian Influenza Viruses

H5 and H7 subtype of avian influenza A viruses can be further classified as either highly pathogenic avian influenza (HPAI) or low pathogenic avian influenza (LPAI). This

distinction is made on the basis of genetic features of the virus. HPAI is usually associated with high mortality in poultry. It is not certain how the distinction between ''low pathogenic'' and ''highly pathogenic'' is related to the risk of disease in people. HPAI viruses can kill 90 to 100% of infected chickens, whereas LPAI viruses cause less severe or no illness if they infect chickens. Because LPAI viruses can evolve into HPAI viruses, animal health officials should closely monitor outbreaks of H5 and H7 LPAI. [2, 24] .

How Influenza Viruses Change: Drift And Shift

Influenza viruses change in two different ways 'anitigenic drift' and 'antigenic shift'

Antigenic drift: Antigenic drift occurs through small changes in the virus that happen continually over time. Antigenic drift produces new virus strains that may not be recognised by antibodies to earlier influenza strains. This process works as follows: a person infected with a particular flu virus strain develops antibody against that virus. As newer virus strains appear, the antibodies against the older strains no longer recognise the 'newer' virus. Infection with a new strain can also occur. This is one of the main reasons why people can get the flu more than one time. In most years, one or two of the three virus strains in the influenza vaccine are updated to keep up with the changes in circulating flu viruses. For this reason, people who want to be immunised against influenza need to receive a flu vaccination every year [12].

Antigenic shift: Antigenic shift is an abrupt, major change in the influenza A viruses, resulting in a new influenza virus that can infect humans and has a haemagglutinin protein or haemagglutinin and neuraminidase protein combination that has not been seen in humans for many years. Antigenic shift results in a new influenza A subtype. If a new subtype of influenza A virus is introduced into the human population, if most people have little or no protection against the new virus, and if the virus can spread easily from person to person, a pandemic may occur[12].

Influenza viruses are changing by antigenic drift all the time, but antigenic shift happens only occasionally. Influenza type A viruses undergo both kinds of change. Influenza type B viruses change only by the more gradual process of antigenic drift [12].

CLINICAL FEATURES OF AVIAN INFLUENZA

Clinical Features in Birds

All birds are thought to be susceptible to infection with bird flu, though some species are more resistant to the infection than others. 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, domesticated 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.

. Infection causes a wide spectrum of symptoms in birds, ranging from mild illness to a highly contagious and rapidly fatal disease resulting in severe epidemics. The later is characterized by sudden onset, severe illness, and rapid death, with about 100% mortality[24]

Clinical Features in Human

The incubation period for human influenza viruses is short 2 to 3 days (range 1 to 7 days). However with influenza A (H5N1) the median time between exposure and onset of illness is 3 days-range 2 to 4 days depending on the source, route and infecting dose of the causal agent and the susceptibility of the victim to the disease[4, 25]. The symptoms of bird flu may depend on which virus caused the infection.

The reported symptoms of bird flu in humans ranged from typical influenza-like symptoms (e.g. an insidious onset of fever, malaise, muscle pains, sore throat, difficulty in swallowing, cough, vomiting, headache, chest muscular aches) to eye infections, pneumonia, severe respiratory distress and other severe and life-threatening complications. The cough is harsh and unproductive. There may be pancytopenia, leucopenia and raised liver enzymes. [2, 25]

Criteria for suspecting a human case of avian influenza [26]

A person presenting a severe respiratory illness (regardless to documented contact with poultry or another flu case)

OR

Fever ≥38.0 ^{o}C

AND

At least, one of the following Symptoms

Cough

Shortness of breath (Difficulty in breathing)

Sore throat

AND

Close contact* in the past 7 days with either

Any sick or dead poultry

Or

Any person hospitalised or died from flu-like symptoms (such as fever and cough or shortness of breath etc)

**Examples of close contact with poultry: cared for them, petting, touched them; killed them, prepared them, gut them; cleaned the cage/pen or birds living areas etc*

Examples of close contact with a flu case: cared for the person; lived in the same household; ate with the person etc.

LABORATORY DIAGNOSIS

Respiratory virus diagnosis depends on the collection of high quality specimens, their rapid transport to the laboratory and appropriate storage before laboratory testing. Virus is best detected in specimen containing infected cells and secretions. Specimens for the direct

detection of viral antigens or nucleic acids and virus isolation in cell cultures should be taken preferably within the first three days after onset of clinical symptoms[27]

Specimens: Types, Collection, Transportation And Preservation

Specimen for the laboratory diagnosis for avian influenza A should be collected in the following order of priority: nasopharyngeal aspirate, acute serum and convalescent serum.

Standard precautions should always be followed and barrier protection (gowns, gloves) applied whenever samples are obtained from patients. In addition to these standard precautions, eyes should be protected [27].

Nasopharyngeal aspirate: Nasopharyngeal secretions are aspirated through a catheter connected to a mucus trap and fitted to a vacuum source. The catheter is inserted into the nostril parallel to the palate. The vacuum is applied and the catheter is slowly withdrawn with a rotating motion. Mucus from the other nostril is collected with the same catheter in a similar manner. After mucus has been collected from both nostrils, the catheter is flushed with 3mls of transport medium [27].

Sera: An acute-phase serum specimen (3-5 ml of whole blood) should be taken soon after onset of clinical symptoms and not later than 7 days after onset. A convalescent-phase serum specimen should be collected 14 days after the onset of symptoms. Where patients are near death, a second ante-mortem specimen should be collected[27]. Clinical specimens transported in transport media are accompanied with forms that contain general patient information, type of specimens, date of collection and contact information of person completing the form etc

Specimens for direct detection of viral antigens by immunofluorescence staining of infected cells should be refrigerated and processed within 1-2 hours[27].

Specimens for use with commercial near-patient tests should be stored in accordance with the manufacturer's instructions

Specimens for virus isolation should be refrigerated immediately after collection and inoculated into susceptible cell cultures as soon as possible. If specimens cannot be processed within 48-72 hours, they should be kept frozen at below-70oC

Laboratory methods

Good microbiological technique is fundamental to laboratory safety. The use of safety equipment, combined with good procedures and practices, will help to reduce the risks involved in dealing with biosafety hazards. Basic containment- Biosafety Level 2 (BSL2)-practices and procedures should be the minimum requirement for handling specimens [28].

Personal protective equipment (PEP) which consist of gowns, gloves and eye protection should be worn in the laboratory when handling and processing specimens and performing diagnostic testing [28].

Tests for diagnosing all influenza strains of animals and humans vary in sensitivity and specificity depending on the timing of specimen collection and type of test used.

A confirmed case definition of influenza A/H5 bird flu infection is an individual with an acute respiratory febrile illness for whom laboratory testing demonstrates one or more of the following[22]:

a. Positive viral culture for influenza A/H5;

b. Positive polymerase chain reaction (PCR) for influenza A/H5;

c. Positive immuno-fluorescence antibody (IFA) test to A/H5;

d. Enzyme immunoassay

e. Other antigens using H5 monoclonal antibodies;

f. 4-fold rise in H5 specific antibody titre in paired serum samples.

The current laboratory confirmation of bird flu is the detection and quantification of these antibodies using Fluorescent Antibody Technique (FAT) or any of the above definitional methods. In places where facilities are available, Electron Microscopy could be employed for the detection of the viral particle or the virus could be grown in susceptible cell/ tissue culture (Madin-Darby Canine Kidney cells – MDCK) and the characteristic cyto-pathic effect (CPE) on the cell observed.

TREATMENT

Treat with neuraminidase inhibitor zanimivir and oseltamivir (75mg orally, twice daily for 5 days) as early in the clinical course as possible [29].

If clinically indicated, hospitalise patients under appropriate infection control precautions. If a case is assessed as not requiring hospitalisation, 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). Instruct the patient to seek prompt medical care if the condition worsens. Follow up non-hospitalised patients by home visits or telephone contact as resources permit. Provide supportive care. Monitor oxygen saturation and treat desaturation with supplemental oxygen as required [29]. Take respiratory and blood specimens serially to check for possible bacterial infection. Consider intravenous antibiotic therapy to control secondary bacterial infections as required.

Do not use amantadine or rimantadine because preliminary reports from WHO collaborating centres suggest resistance of H5N1 to these drugs with the risk of increasing the selective pressure for development of a resistant influenza virus with pandemic potential Avoid administration of salicylates (e.g. aspirin) in children less than 18 years of age because of the risk of Reye syndrome [29].

Do not use ribavirin because there is no evidence to support its effectiveness [29].

Immunomodulators such as corticorsteroids should be used only in the context of clinical trials. Interferon and immune plasma have been employed with appreciable success[23].

PREVENTION AND CONTROL

The use of quarantine for infected farms and destruction of infected or potentially exposed flocks are standard control measures aimed at preventing spread of the virus in a poultry population. Stringent sanitary measures on farms can confer some degree of protection[4].

Ensuring that farms are situated away from migratory waterfowl routes and not developed in the clusters frequently seen in countries with established industries. Where possible, birds should be reared in confinement in wild bird-proofed houses. Movement of people between farms and flocks should be kept to a minimum and disinfectant baths used for vehicles and other equipment. In areas of high risk, the most stringent methods of biosecurity must be imposed and these should include changing of clothes and showering for staff working with poultry[20].

When outbreaks occur, control can be achieved by culling or depopulation of even the less-virulent virus infections (infected and exposed birds) should be considered in the absence of any statutory requirement. After "stamping out" all poultry and products, including feaces, should be buried or incinerated on site, and restocking should not take place until at least 2 weeks after thorough cleansing and disinfection[30]. The virus is inactivated by 70% alcohol and by chlorine (1% sodium hypochlorite, bleaching powder7g/litre), therefore cleaning of environmental surfaces with neutral detergent followed by a disinfectant solution is recommended[4].

In the absence of prompt control measures backed by good surveillance, epidemics can last for years. For example, an epidemic of H5N2 avian influenza, which began in Mexico in 1992 started with low pathogenicity, evolved to the highly fatal form and was not controlled until 1995.WHO regards any case of transmission of an avian influenza virus to humans as a cause for heightened vigilance and surveillance[4].

Standard precautions: Treating all patients in health care facilities with the same basic level of 'standard' precautions involves work practices that are essential to provide a high level of protection to patients, health care workers and visitors. These include: hand washing and antisepsis (hand hygiene), use of personal protective equipment (PPE) when handling blood, body substance excretions and secretions; appropriate handling of patient care equipment and soiled linen, prevention of needle stick sharp injuries, environmental cleaning and spills-management and appropriate handling of waste [4]. The patient should be placed in an air bone isolation room (i.e. monitored negative air pressure in relation to the surrounding areas with 6 to 12 air changes per hour). Also the use of a fit-tested respirator, at least as protective as a

NIOSH-approved N-95 filtering face piece respirator when entering the room.

Any healthcare worker who has had potential contact with respiratory secretions or droplets from a patient with confirmed influenza A (H5N1), or for whom an influenza A (H5N1) virus diagnostic test results is pending, should be considered for prophylaxis or treatment with a neuraminidase inhibitor such as oseltamivir[4]

Vaccine- There is currently no commercially available vaccine to protect humans against the H5N1 virus that is being seen in Asia and Europe. However, vaccine development efforts are taking place. Research studies to test a vaccine to protect humans against H5N1 virus began in April 2005 and a series of clinical trials are underway[31].

CONCLUSION

The world is indeed at the verge of another influenza pandemic. This is no doubt a global problem and requires a global solution. Therefore, there is an urgent need to get each country of every continent on the same level of preparedness. Dr David Nabarro, the United Nations system senior coordinator for avian influenza in calling for openness and joint action within and between countries and within scientific institutions concluded that 'The preparedness of the world depends not so much on who is strong but on who is weak'

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