

OPINION

THE DRAMATIC AVIAN INFLUENZA EPIDEMIC AND THE PIG CONNECTION

The Asian Avian Influenza Epidemic

During late 2003 and early 2004 avian influenza (AI) ravaged East Asia (Japan, China, Korea) and South East Asia (Vietnam, Thailand, Indonesia), killing millions of chickens and infecting humans, some of them fatal: 79 infected, 49 deaths (62% !). The virus responsible for the epidemic is known as the H5N1 strain of subtype A Avian Influenza virus, a highly pathogenic avian influenza (HPAI) virus. Many subtypes AI virus are of low pathogenicity (low pathogenic influenza virus, LPAI), giving no symptoms (subclinical) or only local mild symptoms, but some, including the H5N1 subtype, trigger a severe systemic symptoms resulting in a high death rate. The H5N1 notation pertains to two viral surface proteins that the virus used to bind and enter host cells, namely: haemagglutinine (H) and neuraminidase (N). There are 15 different H alleles (H1 → H15) and 9 different N alleles (N1 → N9).

The highly pathogenic H5N1 was first detected in 1997 in Hongkong and Guandong (China), killing poultry and infecting 18 people, 6 of which died. Due to aggressive killing of chicken the epidemic seemed to be contained but reappears in 2001 and 2002, due to mutation in different genes, which is quickly stamped out. Influenza virus is an RNA virus belonging to the orthomyxoviridae. RNA viruses, unlike DNA viruses, are known for their high mutation rate. In 2003, the virus suddenly re-emerge hitting China, and spreading to Korea, Japan, and South East Asia. In term of lost poultry, Vietnam and Thailand were the hardest hit (36 millions each), followed by Indonesia (9 millions). The epidemic last until the first half of 2004 and seemed to subside after that. However, small outbreaks still occurs notably in Vietnam and also in Indonesia (South Sulawesi 2005). There are even some indications that it has spread to India, although not as yet confirmed by Indian authorities.

AI epidemic in Indonesia

Beginning at the second half of 2003, a spate of epidemics, ultimately killing several millions of chickens, begins to appear in some provinces located at Java, Sumatra, Bali and Kalimantan. These epidemics were at first not recognized to be due to AI, but to another virus, the New Castle Disease (NCD) virus, a viral infection often affecting small poultry farms. It was not until 3 February 2004 that the Minister of Agriculture officially announced the presence of AI in Indonesia causing epidemics in a number of provinces.

What is not generally known is the role of two Airlangga University staff in the discovery of AI in Indonesia. These two staff members will, for the sake of distinguishing their identity, only be designed by their initials namely: KS of the School of Medicine and CAN from the School of Veterinary Medicine and the Tropical Disease Center (TDC)

Early in August 2003, KS who also worked in the Electron Microscopy Facility, received several tissue samples originating from poultry farms located in East Java. Upon studying the electron micrographs, he (KS) reported to the Animal Health Authority that judging only from the morphological aspects, several of the samples contain a virus that he could positively identify as being NCD virus, but some of the other samples contain a different virus which he suspected might be the AI virus, a much more dangerous virus. His suspicion was ignored by the authorities, and the official press release stated that the epidemic was due to NCD, a virus known often to affect small, traditional poultry farms.

However, when the epidemics began to spread alarmingly, the Department of Agriculture formed a Special Task Force (STF) to further investigate the cause of the poultry epidemics, of which CAN is one of the members. As the result of investigation by the STF, a special release by The Animal Health Authorities stated that the poultry epidemics was due to an especially vicious strain of NCD called velogenic-viscerotropic NCD (vv NCD), but it was admitted that another, still unknown virus might be responsible for at least some of the cases. Several members of the STF (including CAN.) were however convinced that the virus responsible for the epidemics was actually AI and not vv NCD.

Taking a personal initiative, CAN in early November 2003 obtained (unofficially) several tissue samples. Working at TDC's DNA laboratory, he was then able to positively identify the offending virus as being AI subtype H5N1, using a technique called "reverse transcriptase-polymerase chain reaction" (RT-PCR) followed by DNA sequencing. Unfortunately, the identity of AI as the cause of the epidemics ravaging poultry farms was prematurely publicized by

the mass media before it was officially reported, thus stirring a lot of fuss among the responsible Animal Health officials.

Perhaps due to increasing public pressure, on January 2004, the Department of Agriculture finally admit that the unknown virus accompanying vv NCD was in fact AI of as yet unknown subtype, followed on 3 February 2004, by the official statement of the Minister of Agriculture as stated above, again not mentioning the AI subtype. It seems that the authorities "higher up" were reluctant to publicly admit the presence of the AI H5N1 subtype, although the report of the STF clearly indicated that the subtype was H5N1. The presence of AI, especially the highly pathogenic H5N1 must be reported to International Health Authorities notably WHO and the Office Internationale des Epizootics (OIE). This is perhaps one of the reasons why the presence of AI-H5N1 was not announced earlier, since at that time Indonesia was still declared as being AI-free.

For whatever reasons, it was ultimately decided to test the sample by serological methods using anti-sera and reagents imported from abroad (Holland, England and Australia). The serological test confirmed the presence of AI subtype H5N1. It was on early February 2004 that the Indonesian Government finally filed a report to OIE announcing the presence of AI-H5N1, 3 months after the detection of the offending virus by CAN and 8 months after KS related his suspicion on the presence of AI to Animal Health Authorities.

Transmission to humans, the pig connection

AI virus normally does not infect humans and, vice-versa, human influenza (HI) virus does not normally infect chickens or fowls. This is because the two related viruses use different receptor molecules to bind and enter their host cells. AI binds to a molecule called 2,3 α sialic acid (acetyl neuraminic acid 2,3 α galactoside, abbreviated: NeuAc 2,3 α Gal), whereas HI binds to a related molecule 2,6 α sialic acid. Chickens and other fowl express only the 2,3 α molecule, while humans only express the 2,6 α molecules. That is why normally AI virus does not infect humans.

However, as stated above, the H5N1 virus infects and kills people in Vietnam and Thailand. How is that possible? Still more perplexing is the fact that the virus isolated from the Vietnamese victims still retains its 2,3 α specificity! There is no definite answer, but theoretically it is possible that the avian H gene acquire mutation which then made the avian hemagglutinin binds to 2,6 α albeit with low affinity. Thus, if someone, say, is exposed to a great concentration of H5N1 virus, then he (or she) can get infected by the virus. If this scenario is correct, then it would also explain why inter-human transmission does not occur.

Pigs are in a unique position, because their cells express both the 2,3 α and the 2,6 α sialic acid molecules. Thus, pigs can be infected by both AI and HI, and if a mixed AI and HI infection occurs, this may have dire consequences as we shall see. Viruses belonging to orthomyxoviridae are rather unique, because their RNA genome are fragmented into 9 genes, one of which code for haemagglutinin (H).

If a pig is infected by both AI and HI, there is the possibility of the formation of hybrid viruses containing both AI and HI genes. If then the HI gene happens to be the haemagglutinin gene (H gene), then the emerging virus will recognize and bind to the 2,6 α molecule, thus infecting humans and also making human to human transmission possible. Since the genetic make-up of this hybrid virus is different from the known HI viruses, our immune system will not be able to recognize the new virus, thus triggering a new flu epidemics.

Reasoning along this line and knowing that in Tangerang and surrounding pigs are raised near poultry farm recently ravaged by the AI epidemic, CAN again on his own initiative took throat swab samples from healthy pigs raised in that area, and was able to detect AI of H5N1 in 5 of 10 pigs tested. When he reported to the Authorities on February 2005, he (again) found no response. Accordingly he took his finding to the press and on April 9, a widely read local newspaper ran his story. Even more, on May 26, his discovery of the presence of H5N1 in pigs was also published in the prestigious scientific journal "Nature". Responding to the media attention, the Authorities finally ran their own survey, and found H5N1 in 3 out of 9 pigs tested. Even so, the ranking authorities within the Department of Agriculture seemed not to be completely aware of the possible consequences: when interviewed by Nature's correspondent a high ranking official told Nature that: "this is not an outbreak, it's just a finding" because the pigs are not sick or dying! This statement is of course true seen from the perspective of animal health officials: why worry, unlike chickens, the pigs are not sick!

A sense of false security prevailed because up till that time no one has been reported sick due to AI unlike what happened to Vietnam and Thailand. The feeling of security was further fostered because samples taken from people working at the poultry and pig farms around Tangerang all tested negative for H5N1. The "no action" stand still prevails even when in early March 2005 an outbreak occurred in South Sulawesi and one poultry farm worker tested positive for AI, although (or because ?) the said worker remained free of symptoms.

Then, like lightning striking on a sunny day, reports began to appear first in electronic media and then in printed media, about the death of 3 residents in Tangerang, a father and two daughters. The cause of death was officially reported as acute severe pneumonia, which immediately triggered speculation that the real cause of death could be either AI or SARS (severe acute respiratory syndrome). The allegation was at first denied by hospital officials until on July 15 the Minister of Health announced that samples from the father and one daughter tested positive for AI, while sample from the other daughter was not obtained because of early death (she died two days after admittance) and before suspicion occurred. The Minister also told the audience present on the meeting that there is no reason to panic because the virus can not be transmitted between humans.

Lesson learned

In retrospect one could only surmise what will happen if only the Government took early action when KS relates his suspicion on the presence of AI. At last count more than 9 million chickens were killed. How many of them could be saved? Even the death of the 3 Tangerang residents might not occur if early action was taken. We can only speculate on the Government tardiness to take action.

Is the Government's over-cautiousness due to their fear to trigger undue panic? Is it because of the fear of the impact on poultry industry so that they must be first pretty sure of the presence of AI before announcing it? Is it because of their reluctance to accept findings by research workers working outside the official surveillance system or in institutions unfamiliar to them, or is it because of "the father knows best" attitude often shown by many high ranking officials? We will never know! The damage has been done and we can only hope that these things will not happen again. Meanwhile, as of this day (July 20), the source of infection killing the 3 residents of Tangerang remains unknown. If, as stated by the Minister of Health, inter-human transmission is not possible, the 3 of them must be exposed to the same source at the same time and place. The only place where the 3 of them are together was in their home. But they reside at a middle class real estate housing far away from poultry farms and they (and their neighbors) do not keep chicken at their homes. So, where did the virus come from ? Wild, migrating birds? As of today there were no reports of en-masse death of wild birds.

The older daughter was admitted to the hospital on June 29, while her father and her infant sister were both admitted on July 7, more than a week later! Is it possible that the older daughter was the first infected and then transmitted the virus to her father and her infant sister? However, in a press conference the Minister of Health announced that test by WHO confirmed the previous finding: the samples sent contain AI H5N1 and so the possibility of inter-human transmission can be excluded. However, we cannot exclude this possibility in the future, because, inter-human transmission did occur. In 1994, an outbreak of flu occurred among children in an orphanage in Holland. Upon investigation, it was found that the outbreak was due to a hybrid between avian H1N1 and human H3N2 coming from pigs. It is thus important to be always aware of this possibility.

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