Veterinary Laboratories Agency

SUBMISSION FOR ROYAL SOCIETY/ACADEMY OF MEDICAL SCIENCES STUDY ON AVIAN AND PANDEMIC INFLUENZA

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The scientific data from which the following bullet point conclusions/information are drawn can be found in the bibliography list appended to this document.

INFLUENZA PANDEMICS

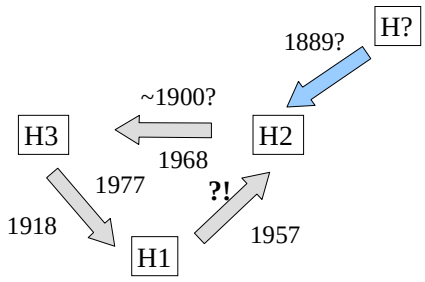
- Influenza pandemics are very distinct episodes that can be traced by their unmistakable descriptions as far back as 200 BC. Since 1700 there appear to have been 12 pandemics, for which we have at least some evidence of the causative virus for the last six. In this period the mean occurrence has been every 22.3 years, with the longest period between two pandemics of 49 years and the shortest 9 years.
- In the 20th Century there were 4 pandemics: H1N1 in 1918; H2N2 in 1957, H3N2 in 1968 and H1N1 in 1977. Many people consider only the first three to be true pandemics as the 1977 virus appears to have escaped from a laboratory. However, this virus caused a pandemic in that it spread world wide infecting many millions of people and continues to circulate in the population today. The pandemic beginning in 1977 is a fact and its origin seems irrelevant.

MECHANISMS FOR THE EMERGENCE OF PANDEMIC VIRUS

- The viruses responsible for these 4 pandemics appear to have arisen by 3 different mechanisms. Evidence suggested that the 1957 and the 1968 viruses had arisen when genes of the prevailing human virus re-assorted with genes of an avian influenza virus, resulting in a virus that had the genes coding for the internal proteins that allowed transmission in humans, but with the gene coding for the surface haemagglutinin protein (or genes for both the haemagglutinin and neuraminidase) derived from the avian virus. The human population would then be immunologically naive as far as that virus was concerned and a pandemic ensued. The second mechanism has been mentioned already – the 1977 virus was a human influenza virus that escaped from a laboratory. The third mechanism was proposed by Taubenberger *et al* after their reconstruction of the 1918 pandemic viruses entire genome. "*Here we present sequence and phylogenetic analyses of the complete genome of the 1918 influenza virus, and propose that the 1918 virus was not a reassortant virus (like those of the 1957 and 1968 pandemics), but more likely an entirely avian-like virus that adapted to humans*." This view has had some criticism, because the virus was compared to a consensus avian virus sequence rather than those of contemporaneous viruses and does not explain why/how the genes of later human H1N1 viruses diverged from avian genes.
- Two hypotheses have been proposed for the rhythm of occurrence of pandemic influenza viruses, these were termed by Shortridge as an influenza circle (or cycle) and an influenza spiral. The *circulation theory* suggests there is simply a recycling of H1, H2 and H3 subtypes. If this is so, the HA subtype of the next pandemic virus would be H2. The *spiral theory* assumes that humans are capable of being infected with all HA subtypes of influenza A viruses providing the receptor demands are met and a specific constellation of the other genes is present and thus it may not be possible to predict which of the 16 H subtypes will

emerge next by re-assortment, unless there is careful monitoring and surveillance. The theories are not mutually exclusive and since the circulation theory does not state how the next pandemic virus will arise, it could be by reassortment.

- The circle or circulation theory is largely ignored, but it is worth considering it in more detail. The reasoning is summed up in the following diagram.



Human influenza - circulation of subtype theory

Based on data obtained from archived sera and other studies some evidence is available on the outbreaks occurring prior to the 1918 pandemic and when this is added to the 4 pandemics in the 20th Century it appears that H1, H2 and H3 influenza virus subtypes seem to be circulating. However, why there should be such a restriction to a limited number of subtypes is not clear.

INFLUENZA A VIRUSES IN OTHER MAMMALS

- Influenza A viruses have been reported to infect mammals other than humans and isolates have been obtained from natural infections of pigs [subtypes H1N1, H3N2, H1N2, H3N1, H1N7, H4N6, H9N2, H7N7, H5N1]; horses [subtypes H7N7; H3N8]; harbour seals [H7N7; H4N5]; whales [H13N2; H13N9; H1N3]; mink [H10N4]; Felidae species [H5N1]; dogs [H3N8 and possibly H5N1]. Most of the viruses appear to of avian origin.
- Of these other mammals influenza A viruses appear to have become *established* and *readily transmissible between individuals* only in horses and pigs. Surprisingly, especially for pigs, the subtypes that have become established are very few. The viruses that have circulated in the pig population have been restricted to H1N1 and H3N2 [recently the reassortant H1N2 also appears to be circulating]. Further, when these viruses are subjected to phylogenetic analysis it appears that the H1N1 viruses may be of swine, human or avian origin or contain reassorted genes from these distinguishable lineages; while the H3N2 viruses may be of human or avian origin, or reassortments of the two. In horses the H7N7 and H3N8 viruses appear to form equine lineages, but it is interesting that when outbreaks in horses in Jilin Province in China were shown to be caused by a virus genetically identifiable as an avian virus of the subtype was H3N8.
- Thus in other mammals the range of subtypes that can become established does appear to be limited, although we do not understand why that should be. It is especially surprising that this is the case for pigs as it has been demonstrated experimentally that pigs are readily infected with avian influenza A viruses of all subtypes and that reassortment with viruses already established in pigs occurs readily. If this is a rule it is difficult to see why it should not also apply to humans

AVIAN INFLUENZA CURRENT SITUATION

- Surveillance studies since the 1970s have demonstrated the huge reservoirs of influenza viruses in wild birds, especially migratory waterfowl and to a lesser extent shorebirds. All 16 recognised haemagglutinin subtypes and all 9 neuraminidase subtypes have been recorded in wild birds in most possible combinations. Influenza viruses from wild birds spread to poultry [occasionally in some circumstances regularly in others] some, but not all, of those of H5 and H7 subtypes, may mutate in poultry so that they become extremely virulent for susceptible species. The disease caused by such virulent viruses had been termed “fowl plague” in the past, but is currently called “highly pathogenic avian influenza” (HPAI).
- Although it is difficult to quantify properly, the impression is that avian influenza infections of poultry seem to have increased in recent years. Certainly there have been more primary outbreaks of HPAI and when these have occurred there is a tendency for them to involve far more birds than they did in the past. This may well be the result of changes in poultry production that have tended to establish densely populated poultry areas. Two subtypes of virus, H9N2 and H5N1, appear to have become established in the poultry populations in Asia and other areas of the World, where they can now be considered endemic.
- During the last 10 years or so, outbreaks, due to **H9N2** subtype had been reported in Germany, Italy, Ireland, South Africa, USA, Korea, China other countries in SE Asia, throughout the Middle East, Iran and Pakistan and this virus continues to spread. It is now essentially endemic throughout Asia.
- HPAI **H5N1** viruses appear to have been present in E. Asia since 1996, the apparent low-level, but probably endemic, situation changed dramatically in December 2003 to February 2004 when suddenly eight countries in E and SE Asia reported outbreaks of HPAI H5N1. Since then the virus has spread across Asia into Europe and to Africa. Like the H9N2 subtype it appears to be endemic in poultry (especially free range ducks and village chickens) in many countries.

HUMAN INFECTIONS WITH AVIAN INFLUENZA VIRUSES

- Although 3 isolations of avian influenza viruses of H7N7 subtype from humans [one of unknown origin, two laboratory accidents] had been recorded earlier, the first isolation of a natural infection was from a woman in Oxford, England, who kept ducks, in 1996. This virus was also of the H7N7 subtype.
- Since 1997 infections of humans with HPAI H5N1 virus have dominated the scientific literature and media. To date over 200 human infections have been confirmed and in these the mortality rate was about 50%.
- There were reports of 7 human infections with H9N2 in 1998-99 in Hong Kong and mainland China. In addition there have been two reported H7N2 subtype infections of humans in the USA in 2002-2003. Two H7N3 HPAI infections of humans were associated with the HPAI outbreaks in Canada. In The Netherlands H7N7 HPAI virus was isolated from 83 people during the widespread epidemic in chickens in 2003, one person died. However, The Netherlands situation was of interest, since subsequent serological testing of humans in contact with diseased birds suggested that >1000 people had been infected.
- To date, all AI viruses isolated from humans have had a full set of avian genes – indicating no reassortment has taken place so far. All viruses have shown an avian receptor preference. There has been limited drift in HA of human H5N1 isolates between 2004-6. However, the concern still remains that if one of these

cases had also been infected with a human influenza virus reassortment could have occurred - with the potential emergence of a new pandemic virus.

- No results of surveillance studies of people in contact with infected poultry in SE Asia have been released. But, from the evidence of the infections in The Netherlands, there must have been 1000s of people subclinically infected in Asia with H9N2 and H5N1 over the last 10 years, but a pandemic has not yet occurred.
- This fact may offer some assurance that an H5N1 pandemic may never occur. But if the suggestion that the 1918 pandemic was the result of an avian virus jumping without reassortment from birds to humans is true, the more people infected the more likely this mechanism may be likely to occur again.
- The spread of the current HPAI H5N1 virus is often described as "unprecedented", but from the 1870s to 1930s "fowl plague" [H7 HPAI] virus was considered to be endemic in Italy, Germany, & Egypt and outbreaks occurred in Austria, Hungary, Switzerland, France, Belgium, Holland, England, Indonesia, China, Japan, USA, Argentina & Brazil. These represent just about every country able to identify outbreaks. In many ways the situation must have been similar to that seen with H5N1, but the human pandemic strains in this period were: H2 [1889], H3 [~1900], H1 [1918].
- It is 28 years since the last human pandemic, the expected occurrence is every 22 years with a range of 9-49 years. A new influenza pandemic in the near future seems inevitable, but will the subtype be H5? H9? Or perhaps H2?
- These three seem the most likely candidates, but it would seem injudicious to choose between them with our current understanding or to rule out any of the other subtypes as potential pandemic viruses.

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