Pandemic influenza

A note from John Godfrey
(a director of European Research into Consumer Affairs, but written as an individual)
Submitted to the Royal Society's study, 6 April 2006, modified 27 April.

Is a bird flu pandemic likely in people?

As viruses mutate so readily a human pandemic should now be considered probable, as a spur to precautionary action. If the problem is underestimated counter-measures may well turn out to be inadequate. It would be good if COBRA, the UK government's civil contingencies committee, took this precautionary approach as it considers what should be done. With the recent increase in the rate of spread of AI the total population of the virus in the world has grown dramatically, and with it the opportunity for mutation and evolution. However, it is impossible to predict with accuracy if or when a human pandemic may begin. It is possible that a genetic change allowing infectivity between humans will not occur; it is also quite likely that mutation will lead to a less lethal virus. If a human AI pandemic does begin, the number of human deaths will depend on the virulence of the new virus, as well as how prepared we are.

Some practical steps that might reduce the risk of a pandemic arising.

1. An AI pandemic among birds is already upon us. It has posed a great challenge to the veterinary, poultry, ornithological and farming communities. Two hundred million or more poultry and wild birds have already died or been killed, and the appropriateness of vaccination has still to be resolved. There is a possibility that high viral load in animals might lead to a higher risk of reassortment in a pandemic virus. Pigs are susceptible to human influenza, and also to H5N1 which may not make them ill. H5N1 has been found in pigs in Java. Felids, mustelids and other carnivores offer similar scope for viral adaptation to a mammalian environment. As cats have been naturally infected by wild or domestic birds and by experiment, and then been found to excrete virus that could infect others. So they may not be dead-end hosts. These species may offer an opportunity for viral evolution in mammals. There is a serious risk that this could lead to an epidemic of the resulting strain in humans.

2. Transmissibility between people might arise by genetic re-assortment between avian and ordinary seasonal flu, as well as by mutation. Different pandemics in the past seem to have arisen by each route. Re-assortment is most likely to happen among those most exposed to bird flu, if someone happened to catch avian and seasonal flu simultaneously. This risk for facilitating the evolution of the disease towards the capacity for it to infect from one person to another is greatest among those who are in

close contact with birds. I suggest that regulations, perhaps at a European level, should make vaccination against seasonal flu obligatory for people working with poultry, including vets, in the interest of the public at large. A pandemic virus for humans is obviously most likely to originate where people and sick birds are in close proximity, such as Southeast Asia, or Africa, rather than in Europe. However, good practice here would reduce the risk here somewhat. More importantly it might encourage similar precautions to be taken elsewhere. The ethical case for medical intervention for public rather than individual benefit was well made by Dame Onora O'Neill at the Royal Society's "Emerging infections: what have we learned from SARS?

3. The greatest protection for any country against pandemic bird flu is to contain and eradicate infectivity at its source, wherever in the world that may occur. This should be the highest priority for all countries, but governments will be under pressure to devote the scarce resources of antiviral drugs and of vaccines directly to their own populations. There is a strong case that common action would be in the enlightened self-interest of each country involved.

Vaccination for humans

There cannot be, at present, an optimum vaccine for the virus that may cause the putative pandemic. Vaccines for "ordinary" seasonal flu that are produced and used each year for the current genetic variants of the virus, but these will be no direct defence against AI. However, people who work with poultry should be protected against seasonal flu to reduce the risk of simultaneous infection with AI that would allow genetic reassortment between the two viruses and hence a greater risk to the general population. Because viruses are constantly changing, the precise virus that may attack the human population will need to be identified fully before reliable production of the necessary vaccine can begin. At present, a vaccine for the current genetic variant of H5N1 can be made but it is unlikely to be effective against the variant of any pandemic in humans. Therefore, it is essential that national, regional and international laboratories work together closely to identify any mutations that are occurring in the H5N1 virus (or any other HPAI virus).

Once a new virus has been identified, three to six months may be the minimum time that would be required to develop a new vaccine, using the existing techniques where the vaccine is produced by incubated eggs. The supply of eggs could itself be put at risk by AI. Potential methods for more rapid production, on a cellular or molecular basis, are being investigated and doing this research and development should be a top priority. Clearly, a vaccine will not be available for the first wave of an AI pandemic; and there is the further possibility that there might be further changes in the virus which would necessitate the development of a new vaccine.

A vaccine for the current genetic variants of H5N1 could be produced now, and its use would probably mitigate the severity of the disease in the event of a pandemic in humans.

So it is essential that national, regional and international laboratories work together closely to identify any mutations that are occurring in the H5N1 virus.

Might avian influenza be transmitted in food?

Food is probably not a likely route of infection, but I attempt to act as the devil's advocate on this question. The Food Standards Agency dismisses a risk, but advises proper cooking. But what is a proper, and accepted, practice for some dishes does not involve a high temperature.

The European Food Safety Authority's carefully nuanced statement about cooking poultry properly and on the possibility that eggs could be a problem, have provoked unwise and intemperate attack. The vested interests from which the attacks came should remember (as should the FSA also) that raw egg is a key ingredient of some traditional European cooking. Real mayonnaise, steak tartare, puddings such as zabaglione, iles flottante, and sabayon, and some sauces, including Hollandaise, demand uncooked, or but slightly cooked, egg.

It seems to me possible that the avian flu virus in food could pose some risk for consumers, though the virus is heat sensitive and would not survive cooking at more than a moderate temperature. However, not all table birds are well cooked. As chickens become severely ill at an early stage, and most potentially infected birds will be slaughtered as a precaution, few will be sold to consumers. Ducks are susceptible, but they do not show infection so promptly or severely. Fragments of lung tissue that may be left in the body cavity of a duck following evisceration might pose a potential risk if cooking were insufficient; perhaps more likely if the bird's body cavity had been filled with stuffing. Foie gras cannot be heated very much as, if it were, its fat would flow out. It is sometimes eaten raw.

Even if food is not a danger to people, consumers become alarmed if avian flu infects farm stocks in their own countries. Even the prospect that bird flu might arrive depressed sales of chickens in Italy for instance.

PS. I attach as appendices a note in response to an EU initiative on avian influenza; and an earlier note on the problem from an evolutionary perspective, which was critical of the plan that Defra had lain before Parliament.

Appendix 1

Comments from John Godfrey[1] on a proposal for a Directive on Community controls for avian influenza[2]

1. The proposals are a most welcome response to the highly variable risk[3] posed by avian influenza, which has become more severe[4] since the proposal was issued on 28.4.2005. These comments focus on the threat from highly pathogenic strains of avian influenza (HPAI); to humans, rather than to birds. There are clearly threats to farming, but also to other, even larger, human interests such as general economic activity[5].

2. Three months for consultation seems an excessively long period in view of the life threatening nature of this problem to the general population. In such cases the time allowed for the legitimate concerns of other interested parties to be expressed should reduced in order to be proportionate.

3. As the risk to public heath is so variable, "due to rapid virus mutation and possible reassortment of the genetic material between different strains"[6], more attention needs to be focussed on those environments that may encourage natural selection for mutant strains likely to become adapted to humans; and that provide conditions favouring reassortment. As the virus has the capacity to change rapidly it will be difficult to have the most appropriate vaccine ready in time. Research into novel methods for speeding up the preparation of the optimum vaccine once a dangerous virus variant has evolved is urgently needed (Lipatov,A.S. *et al. J. Infect. Dis*., **191**, 1216-1 (2005) provides an example of the sort of innovation that may be appropriate). It is equally important to scale up the capacity for manufacture once the best vaccine to use has been identified.

3.1 HPAI can infect mammals other than man. If it does so evolutionary adaptation to this new environment has to be expected. Such adaptation to a mammal is likely to confer improved adaptation to man. So pigs, for instance, should be kept separate from birds, and particularly stringent measures should be taken to eliminate infected pigs.

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[2] COM(2005) 171 final

[3] Proposal, p. 10(6) and (10) and p. 12(28)

[4] For instance: H. Chen et al. Avian flu: H5N1 virus outbreak in migratory waterfowl. *Nature* **436**, 191, 14 July 2005; and "A virulent outbreak of avian flu among migrating geese at a wildlife refuge in China has raised fears that the disease could spread to India and Europe, according to studies published this week by the journals *Science* and *Nature*." (telegrah.co.uk, filed: 09/07/2005)

[5] As an example: 'Preparing for the next Pandemic'. *Foreign Affairs* July/August 2005

[6] Proposal, p. 10(6)

3.2 Reassortment will be favoured if the HPAI virus coexists with one of the strains of human influenza. This may occur in man if someone has an overlapping infection with human and with avian influenza. So far all, or almost all, people who have caught HPAI recently have done so through close association with sick birds. So the risk of reassortment would be reduced if bird handlers, including veterinary personnel, were to be given whatever vaccine to human influenza is appropriate to the strain that is a current risk. As the evolutionary hazard is to the general population rather than to those people close to sick birds, there is a compelling case for the vaccination to be mandatory as an "appropriate precaution"[7]

3.3There is another promising precaution against reassortment, other than in humans. Domestic ducks can become infected by bird flu without being acutely ill as soon as chickens are. As they are also susceptible to human flu they could be a receptacle for reassortment. Similarly pigs[8] have become infected with HPAI and can also catch human flu. So they pose a similar risk. As they are mammals evolutionary adaptation of a virus in them could also lead to genetic change pre-adapting the bird virus to humans.

4. In the chapter on vaccination[9] the conditions for general prohibition of avian influenza vaccination, and for emergency vaccination in birds, are given generally acceptable consideration. However, vaccination as opposed to slaughter does pose a worse risk that some humans may catch bird flu. This will tend to encourage reassortment and hence a not improbable pandemic among the human population. In my opinion this chapter therefore needs detailed re-examination with reassortment in mind.

5. A number of these considerations in these comments are more fully covered in my earlier note, added as an appendix.

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[7] p.43. art. 47.1
[8] p. 43, art. 48
[9] p. 48 et seq.

Appendix 2

Zoonotic Evolution and Avian Influenza

From John Godfrey, 24th of June 2005 (modified note of 16th June 2004)

"We are in a situation where we simply have to deal with uncertainties on when this will happen — not whether this will happen or not."
Dr Klaus Stöhr, project leader for the WHO Global Influenza Program, 19 May 2005.

1. The present outbreak of avian influenza is severe for birds, but the threat it poses to people depends upon it evolving the ability to pass from person to person. The report from the World Health Organisation's meeting of 6th of May 2005 in Manila indicates that in northern Vietnam recent human cases of avian flu have an epidemiological pattern and virological features different from those in cases studied during 2004. While this is a concern, it is not surprising. In general diseases tend to evolve an increased capacity for transmission, and also tend to become less lethal.

2. It was fortunate that the Royal Society held a scientific discussion meeting on emerging infections in their topical series on the 13th of January 2004. They can scarcely have known how topical it would be, coming as it did just when the outbreak of bird flu was being recognized. The meeting brought together research and public health virologists and epidemiologists from around the world, including experts directly involved with action to control Severe Acute Respiratory Syndrome from Hong Kong, China, Canada and from the WHO. The focus was on viral infections but some of the considerations apply to infections by bacteria and by metazoan parasites. The proceedings are published.

The problem

3. Both the corona virus of SARS and the bird flu virus are problems derived from animals eaten as food. Each is an RNA virus. These viruses mutate much more rapidly than do DNA viruses[10] and, possibly related to this, they have very small genomes. So they change unpredictably, but between a limited range of genetic and serological variants[1]. The origin of such new variation has been best studied in the human influenza virus.

4. SARS has been controlled because infected people fall ill shortly after they become infectious, and before the peak of infectivity occurs. So the isolation of patients is far more effective than in the case of influenza, where the virus is being passed on for a long period before it has become apparent that someone has the disease. The SARS virus has been found in civet cats (a viverrid rather than a true cat) that are caught, and then bred in captivity, in some parts of China. The scale is surprising, with specialist markets and restaurants. Workers with these exotic species have not been found to be susceptible SARS. This suggests that they have been previously exposed to a closely related but non-lethal virus that has induced immunity. So SARS may be due to a novel mutant that has occurred recently[2]. It is striking that children have been found less prone to becoming

infected than are adults. However, the SARS story with respect to mutation is very difficult to pin down. The latest data are not sufficiently informative, since they deal with evolution after the outbreak[3,4].

5. The current avian influenza is not very infectious to humans but we have no immunity to it. It has been caught by people closely associated with ill birds, although the virus can persist for some days on chicken meat and for a while on frozen chicken. As 11 of the 14 people first infected died quickly the virus has not yet had much opportunity to mutate so as to become more infectious. The problem will become severe if, but only if, its infectivity to man increases. If some patients live for longer then natural selection will have more generations of the virus to favour any variant that is better suited to the environment provided by the human population. Should someone catch both bird and human flu then genetic recombination between them could result in a virus with some of the characteristics of each. If the present avian flu (H5N1, named for subtypes of its key surface proteins) were to become as transmissible between people as are our usual flu variants, but to retain its virulence, then a severe pandemic would be likely: often lethal, and very hard to control. The 1918 pandemic that killed around 40 million people had its origin in birds[5].

6. Human history records transformation of infectious disease patterns at times of rapid ecological change: during the agrarian settlements, Eurasian interactions and European empire building. A fourth transition is in progress caused by, for instance, more rapid and widespread transport and by modern medicine.

7. Many human diseases are zoonotic in origin. In the fossil record, periods of rapid extinction have been associated with rapid evolution. It is a reasonable hypothesis that this has included rapid evolution among disease organisms. While it may have been particularly fast in them due to the short generation time most of them have, we have little evidence on the point. They fossilise too poorly. Changed diseases could have contributed to further extinction among their hosts. As we change our environment and our climate in particular, extinction follows apace. For instance, many species of mammals are dying out, probably often together with the microorganisms peculiar to them. As generalists are replacing ecological specialists there are new openings for evolution by microbes. We should anticipate rapid change among the disease organisms of our time. Some of them, but only some, will be food borne. Infections that were initially food born will become far more dangerous if they evolve the capacity to cause infection from person to person.

8. Diseases are becoming increasingly global as humans travel ever more freely. The UN World Health Organisation has been acting to good effect on SARS and, more recently, on bird flu[4]. It needs extended powers where states are reluctant to cooperate. This will be difficult to achieve. Some states simply lack the facilities to monitor viruses or to protect public heath because of poverty. The Royal Society meeting ended with an argument that, while individual health care is like a consumer good requiring individual consent, freedom from infection is a public good. There is therefore a need to think through which public health interventions may or must be provided on a compulsory basis.

An example from the UK: the response to the problem by DEFRA

9. A document of the Department of the Environment, Food and Rural Affairs: "Avian Influenza and Newcastle Disease Contingency Plan" sets out the organisations, structures and systems to be used for an outbreak in the UK. This looks in the main sensible, although I am out of my depth on the likely effectiveness of the particular measures that are proposed.

10. However, the introduction headed 'background' starts: **"Avian influenza (highly pathogenic) affects poultry and other birds. Infection in humans is rare but when it does occur, usually presents as a mild to moderate conjunctivitis, with more rarely, mild to moderate flu-like signs. In exceptional circumstances it may be fatal."**

    In my opinion this could be dangerously misleading as the death rate among the rather few people who have been infected in the present outbreak is very high. The WHO reports 53 deaths among 97 confirmed cases of H5N1 infection by 19 May 2005. There is a realistic possibility that infectivity may evolve so that humans are more readily infected from birds and possibly from non-human mammals. A paper in *Proc. Nat. Acad. Sci.*[1] studied 21 samples of H5N1 flu virus from different dates. Later samples were found to be more infectious to mice, and thus more likely to be a hazard to humans. If wild mammals come to harbour the disease then the virus may adapt to infection from mammal to mammal. The virus will also be very much harder to eradicate than if it were confined to birds. The capacity of the virus to infect from person to person will then be more likely to evolve. If so, then in the UK it would become primarily a DoH matter rather than one for DEFRA. In my opinion it is possible that food could pose some risk, that the Food Standards Agency needs to consider (see paragraph 15 below). Meanwhile DEFRA should surely not base its plans on a false premise?

In the EU the question is one for DG SANCO, its timely new European Centre for Disease Prevention and Control, and possibly for the EFSA.

Conclusions

12. **The potential pandemic of avian influenza may possibly be averted, but there will certainly be further zoonotic problems of this kind[12]. There is a need for effective precautionary measures, particularly for better facilities to produce appropriate vaccines quickly, and on a sufficient scale[7]. This is a lesson we should learn from bird flu as well as from SARS.**

13. **Contingency planning should meanwhile take into account the known evolutionary potential of animal viruses and other pathogens to adapt to the environment of humans. If the probable adaptation of the avian influenza virus is taken into account the scope of planed measures need prompt reconsideration[9].**

14. **The most worrying risk from avian flu is that someone may be infected by one of the human influenza viruses together with H5N1 avian influenza. H9N2 is another threatening strain[9]. A genetic trait might then readily go from the human to the bird virus so that avian influenza acquired the capacity to pass from person to person. With this risk in mind it would advisable to consider any method to reduce the probability of this happening. One measure would be for bird handlers including veterinary personnel, to be given vaccination for any current human influenza virus on a routine basis.**

15. **It is possible that avian flu in food could be a problem, though the virus is heat sensitive and would not survive proper cooking. As chickens become severely ill at an early stage, infected birds may well not be sold to consumers. Ducks are susceptible, but they do not show infection so promptly. Fragments of lung tissue that may be left in the body cavity of a duck following evisceration might pose a potential risk if cooking were insufficient; perhaps more likely if the bird had been stuffed. These risks are amplified now that 178 bar-headed geese have been reported (23 May 2005) to have died from the H5N1 strain of avian flu in Northwestern China having just migrated from India. Wild birds of other species of have also died[14] in the same region, so that the infection may well have taken place in China. There are unconfirmed reports of human cases in this remote area[13, 14], with 6, perhaps as many as 121, deaths. Parts of China are in the midst of the human flu season, so genetic interchange may become possible. Even if food is not a danger to people, consumers in the west will become alarmed if avian flu infects farm stocks in their own countries.**

16. **Pigs are susceptible to human influenza, and also to H5N1 which may not make them ill. So they may offer an opportunity for gene exchange, leading to an epidemic of the resulting strain in humans. H5N1 has been found recently in pigs in Java.**

17. **Michael Osterholm, director of the University of Minnesota's Center for Infectious Disease Research and Policy, has just warned in *Nature*[8] of the economic consequences of a major pandemic. "The world today is much more vulnerable to the collapse of trade than it was in 1918," he wrote. An H5N1 pandemic strain could rival the devastation of the 1918 pandemic. Industrialised nations reliant on "just in time" delivery of health care goods do not have enough medical supplies to care for the sick. Osterholm said the world's leading economic powers need to confront the problem directly at the forthcoming G8 meeting in Scotland. He calculates that, with the world population swollen to 6.5 billion, a flu strain as lethal as the one in 1918 could kill 180 million to 360 million people worldwide.**

18. **The present world capacity for vaccine production is enough for only about 450 million doses. This is far from adequate even for the inhabitants of the rich countries that manufacture them. Reacting to infection at source, probably in Asia, rather than awaiting its arrival at home might even best mitigate the risk for**

countries with advanced medical facilities. If a pandemic strain differs much from strains already tested then a new vaccine will be essential. This may be possible in four weeks[10]. The promising new technique of reverse genetics[11] that enables such speed has been patented, which poses a potentially serious problem of cost and delay. Research on this, and on alternative methods to speed up the production of an optimal vaccine once a dangerous virus variant has evolved, is urgently needed. Antivirals[7], too, are not yet produced on a scale to meet the likely need.

19. **The rest of the world is in more immediate danger. The WHO is struggling to cope and may be hampered by poor support from some countries. The UK, and the EU collectively, together with the USA and Japan, need to lead an extremely robust response[10] to the challenge[15]. The G8 meeting this July, or a special international initiative thereafter, should address this problem. The cost will be very large, but the value may well be incalculably greater.**

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1. H. Chen *et al. Proc. Nat. Acad. Sci*.doi:10.1073/pnas.0403212101: (2004)

2. The rate of variation differs markedly between viruses. New strains are continually emerging in the case of influenza. This field has been discussed by D B Smith and S Inglis, *The mutation rate and variability of eukariotic viruses: an analytical review*. J. Gen. Virol. (1987), 68,2729-2740. They mention that influenza virus has a high rate of functionally silent nucleotide substitution as well as rapid mutation.

3. Viruses are prone to jump from one host species to another, but this may not involve an adaptive genetic change in the virus, probably due to their simple genetic architecture. However, the Coxsackie B5 virus of man does seem to have evolved adaptively when it moved to pigs, so as to become Swine Vesicular Disease virus (G. Zhang *et al* 1993, J. Gen. Virology 74, 845-853). It is clear however that viruses, with their high mutation rates and rapid replication, are able quickly to optimise their interaction with a novel host. For the latest SVD adaptation data, see: Crystal structure of Swine vesicular disease virus and implications for host adaptation. Fry EE, Knowles NJ, Newman JW, Wilsden G, Rao Z, King AM, Stuart DI. *J.Virol*. 2003 May; **77**(9): 5475-86.

4. Since the meeting it has been reported by Chung-I Wu and colleagues of Chicago University that the virus causing SARS was originally very similar genetically to that found in animals, and that it infected about 3 per cent of people in contact with it. Some months later a changed form infected around 70 per cent. The new variant spread from person to person.

5. Molecular evolution of the SARS coronavirus during the course of the SARS epidemic in China. *Science*. 2004 Mar 12; **303**(5664):1666-9. Epub 2004 Jan 29. Chinese SARS Molecular Epidemiology Consortium. This paper strengthens the argument for an animal origin of the human SARS epidemic.

6. It was reported (*Nature* **427**, 472-473, 5 February 2004) that the WHO has been working with laboratories in the USA and the UK to produce a vaccine if there is an

outbreak. It was then estimated that this might take 2 months, with 2 more for testing. Mass production would take around four to six further months. At present the facilities for rapid production on a sufficient scale to meet the challenge of a major pandemic are not in place. It is highly unlikely that private investment would fund the precautions essential in the public interest, so immediate public investment must be made at national, EU and international levels as appropriate.

7. Were a pandemic to start before an appropriate vaccine is available, a new anti-viral agent (oseltamivir) that would act against an enzyme in the H5N1 virus would be valuable, but it is in short supply and is expensive. The USA, Japan and some European countries are getting supplies of the drug, but it would seem wise for this to be a model followed by others. However a case of drug resistance to oseltamivir has been reported in the *New Scientist*, 19th May 2005.

8. *Nature* **435**, 385, and news features 390 and 399-409, 26 May 2005 for current and helpful articles on the problem.

9. *Nature* online: 25 May 2005; doi:10.1038/435404a.

10. Webby, R.J. *et al. Lancet* **363**, 1099-1103 (2004)

11. Lipatov,A.S. *et al. J. Infect. Dis*., **191**, 1216-1 (2005)

12. For instance, the related Ebola and Marburg viruses are probably zoonoses, the latter coming from green monkeys. Suzuki, Y. and Gojobori, T. *Molecular Biology and Evolution*, 14, 800-806 (1997)

13. Reported, but denied by the Chinese authorities, on promed@promedmail.org of the International Society of Infectious Diseases, who seem to have good sources in China: they were the first to report the SARS outbreak in China, initially denied.

14. News items, *Nature* **435**, 542-543, 2 June, 2005

15. The WHO website reports, 16 June 2005, that there have been in all 54 deaths among 103confirmed cases, but there are at present a further 6 cases in Hanoi hospital together with a health care worker who was presumably infected by them.

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