**Eur Ing Dr Royston Flude** has received his first degree in Physics from the University of Manchester and has more than 25 years experience in a broad range of technologies and social economics with particular expertise at identifying commercially viable IPs. He has held senior positions with Shell Chemicals, Reed International, Lafarge Coppeé, Philips, and Manpower, among others. He has directed projects in Germany, the Netherlands, France, and the USA, as well as the UK. He has also been a Visiting Fellow at Manchester Business School. More recently, he has contributed to a new approach to Corporate Governance & Social Responsibility and sits on the Steering group of the UNECE, Geneva and is actively involved in the activities of the United Nations. Residing now in Switzerland, he has extensive contact networks within the international financial sector and has developed senior level links with governments in the USA, the European Union and the Pacific Rim including the computer hardware sectors of China and Taiwan. He is a specialist in understanding the dynamics of purchasing through multi-media, including the Internet, and in the development of specialized customer service interventions that prompt repeat purchases. He is also a researcher focused on the development of nanotechnology solutions for major world challenges.

**Dr Pete Moore** became a freelance science communicator after performing post-doctoral research in the physiology of fetal development, working at UCL, London. Over the last decade he has authored 10 books that reflect on the way that science and technology has had an impact on humanity. His latest book "The New Killer Germs" was published this week. His journalistic work includes contributions to national and international publications, including 'Nature' and the 'Journal of Biology'. He is developing a line in public speaking and has appeared on radio and television. He has won 6 awards for his work. Pete is a fellow of the Royal Society of Arts and has worked as a rapporteur at private meetings in the House of Lords, and at St George's House, Windsor Castle. He is a visiting lecture in ethics at Trinity College Bristol, and a Course Tutor on the Science Communication MSc course at the University of the West of England, Bristol. He is the immediate past Chairman of the Medical Journalists' Association.

Dear DK and Colleagues:

**Avian Influenza Infection Scenario**

The 1918 viral influenza called "Spanish Flu" (Spain was hardest hit) resulted in an estimated 1 billion people (world's population estimated at 1.8 billion) around the world being infected before it disappeared two years later. Symptoms were sore throats, fevers and muscular aches with autopsies revealing swollen lungs filled with enormous quantities of thin bloody fluid. Sufferers began to drown from the fluids in their lungs, and rapidly became cyanotic, turning blue due to oxygen starvation. Unlike more normal 'flu', which attacks the elderly, the Spanish Flu particularly affected young people because they produced the greatest quantities of fluids in their lungs. From the first reported case on March 4, 1918 at Camp Fuston in Kansas the influenza rapidly spread to Europe. By the autumn, the virus had mutated to a highly virulent form and killed twenty to forty million people worldwide.

**The virus**

Influenza viruses fall into three types; the A type similar to the 1918 pandemic; B type more likely in confined residential communities; C type normally associated with the 'common cold'. Influenza viruses are composed of enough DNA to build just 8 genes, packaged inside a spherical capsule covered with two spike-like proteins. The hemagglutinins (H) help the virus enter the 'host cell' and the neuraminidases (N) facilitate exit. In the A type virus there are twelve different H types and nine different N types. Flu viruses evolve and develop over time by mixing and matching their genes and their H and N types. "Spanish Flu" (H1N1) emerged in 1918. "Asian Flu" (H2N2) emerged in 1957 and then "Hong Kong Flu" H3N2 evolved later in 1968. Recently the Avian Influenza (H5N1) has developed with the same N type as the Spanish Flu and it is highly pathogenic, just as the Spanish Flu was.

The eight genes in the Highly Pathogenic Avian Influenza H5N1 virus from Hong Kong (1997) descended from viruses that were hosted by an extensive 'family of animals':

**H5 gene**: Chicken, Turkey, Duck, Tern, Emu, Ruddy Turnstone

**N1 gene:** Chicken, Swine, Parrot

**Nonstructural gene:** Chicken, Swine, Turkey, Gull, Horse, Duck, Oystercatcher, Herring Gull, Mallard, Pintail, Tern, Emu, Northern pintail, Shearwater, Mynah

**Nucleoprotein gene:** Chicken, Swine, Turkey, Gull, Horse, Duck, Mallard, Budge, Parrot, Mink, Oystercatcher, Whale (Atlantic Ocean), Shearwater, Whale (Pacific Ocean)

**Matrix Gene:** Chicken, Swine, Turkey, Gull, Horse, Duck, Nudge, Oystercatcher, Turnstone, Mallard, Shearwater, Northern pintail

**PB1 Gene:** Chicken, Turkey, Swine, Gull, Horse, Mallard

**PB2 Gene:** Chicken, Swine, Turkey, Gull, Horse, Ruddy Turnstone, Budge, Seal

**PA Gene:** Chicken, Swine, Turkey, Gull, Horse, Duck, Pintail, Ruddy Turnstone

**Routes of passage from animal to human**

Research into the 1918 pandemic has concluded that the virus most probably moved first from birds to 'pig incubators', and then into humans. Pigs often live side-by-side with domestic poultry

and wild fowl, and pig physiologically is remarkably similar to that of humans. The risk of this is being recognised by some policy makers, and under a European directive on dealing with the disease, the movement of pigs is to be restricted on farms where an avian flu outbreak has been detected – there is also talk of slaughtering pigs on infected farms.

The type A virus is widespread in the migratory and domestic bird populations and has the opportunity to cross the species barrier when pigs ingest virus-laden faeces or water contaminated from infected birds. In 1997 the H5N1 virus emerged in Hong Kong, jumping from poultry to the first known human cases, killing six (6) people. By 2004, the H5N1 virus killed more than 40,000 birds in Vietnam and rapidly spread to the Philippines and Thailand. In Vietnam, human mortality rates, primarily of adolescents and young adults, were 80% of those infected. Since then bird migration has brought H5N1 to India, Iran, Iraq, Turkey, Nigeria, Sardinia, Italy, France, Switzerland, Austria and Germany.

Whilst most attention has been focussed on this virus' presence in poultry, H5NI has extended its reach to the dog and cat population of Thailand (Nature Feb 16, 2006). In a Thai village that had already removed all their bird flu infected poultry, ~15% of the dogs tested positive for a previous H5N1 infection and one dog was still spreading the H5N1 virus. It is probable that contact of the cats and dogs with local poultry, pigs, and migratory birds resulted in their infections. At the end of February 06 reports came that the H5N1 virus had also killed a cat in Germany.

This raises the possibility of additional pathways for the virus to move to humans. Regarding pigs, traditional roasting on coals and spits does not always raise pig meat to the 70 degrees centigrade required to disable viruses. Thus, residual virus-contaminated pig meat consumed by humans could pose a major risk of the development of a virulent human-to-human form. Further, pets such as dogs and cats coming into contact with domestic farm animals or migratory birds such as ducks and geese can become infected with H5N1 and potentially spread the disease to humans.

The H5N1 virus can persist for long periods of time in faeces, animal tissues, and in water. This ability of the virus to survive long periods outside a living host may explain the recent human H5N1 infections reported in China, in areas long since thought to have been decontaminated by removal of infected birds.

The great fear is that the H5N1 virus currently in the animal populations will mutate in such a way that it acquires the ability not only to infect humans, but to readily jump from human to human – normally in the showers of airborne droplets released when a person coughs or sneezes. If it ever evolves to this 'air-borne' form then an epidemic or pandemic could be hard to prevent. If that happens, then the next question is whether it is possible to predict where that new variant might appear, and how it would spread?

One potential scenario is that a single strain of Avian Influenza will acquire this ability in the Far East. An alternative is that multiple human-to-human variants will appear, each coming from different parts of the world where the virus is becoming endemic in wild birds. This possibility is strengthened by the recent establishment of multiple sub lineages of H5N1 virus in Asia (PNSA 103(8):2845).

A paper published in Nature on 23 March showed that in the few humans that the current version of the H5N1 virus has already infected, it preferentially binds to cells deep down in the airways. This contrasts with other more normal forms of human flu, where the virus binds high in the airway. The researchers say that a possible implication of this is that the current version of H5N1 will not spread easily by coughing, so it will not readily spread from human to human. They point

out that gaining an ability to bind higher in the airways could be a necessary requirement before the virus could trigger a pandemic.

**Movement of virus if it ever acquires human-to-human capability**

Wherever the mutation(s) occur(s) to an air-borne form, the human to human variant is likely to come to Europe via a human carrier. In March 2003 a single passenger suffering from severe acute respiratory syndrome (SARS) infected 22 fellow passengers on a three-hour flight from Hong Kong to Beijing. While symptoms of influenza will probably take up to three days to manifest, the carrier will be contagious before symptoms can be observed. This will reduce the effectiveness of the infra-red forehead scanners installed to check passengers before they board. They also will do nothing to prevent human-to-human transmission within crowded airport check-in facilities. Once checked-in there are plenty of opportunities for transmission within the departure lounges and on board aircraft which do not have effective viral filtration systems in the air-conditioning units. Furthermore since smoking has been banned, air circulation through existing filter systems has been reduced to save cost.

Human carriers of highly pathogenic avian influenza are likely to arrive and first infect high-density business or residential populations of metropolitan areas. If uncontrolled, panic movement of peoples to friends and relatives in the country will then distribute it rapidly. The spread of the infection is likely to be in a number of waves. Unlike 1918, with a 'matured' mutation the first wave is likely to have a high mortality rate that could be as high as 50% of those infected. Advances in data availability (both epidemiological and molecular) coupled with high performance computational capacity make it possible, using mathematical models, to predict and qualitify alternative infection paths and review the impact of treatment and containment strategies. Current models predict nearing 100% infection within 240 days.

Mortality is likely to be highest in young healthy adults with the healthiest immune systems, as those people would produce the greatest amounts of fluid in their lungs, thereby drowning to death internally. Those under 12 months and over 60 years, as well as others whose immune response has been lowered, would also be highly susceptible. Lifestyle behaviours of smoking, binge drinking and substance abuse are also likely to increase risk. The current human infections from H5N1 show that young people with good immune systems appear also to be the most vulnerable, in a similar way to the 1918 pandemic.

**The Human Factor**

Currently, populations are largely unaware or unconcerned about the impact of Avian Influenza. Confirmed cases could result in a number of classically observed behaviours, depending on the 'perceived' magnitude of the threat.

- The more affluent moving out of metropolitan areas causing difficulties for rural communities
- Families sealing themselves off in their own homes after having stockpiled food and provisions (Panic buying? Requires controlled & secure distribution)
- Lawlessness as elements of fringe communities use the situation as an opportunity for theft and self-gratification.
- There is a high probability that major transit routes would become 'gridlocked'
- Bringing critical resources to metropolitan centres are likely to be disrupted due to road congestion and a reduced number of drivers and staff to operate outlets.
- If Biological warfare counter-measures are applied they require containment of affected populations and movement restricted to treatment/ decontamination centres
- Emergency services are likely to be depleted and demoralised (families at risk?)

- Communication technology is likely to be strained with mobile phone services restricted to Emergency Workers or service times and usage limits.

The extent to which negative behaviours are apparent is dependent on people 'believing' that there is a viable alternative for 'survival' for themselves and their extended family.

**Treatment and Containment**

The anticipated waves are likely to be of approximately six weeks duration with at least three waves before the surviving population has developed an effective immune response. As a consequence, any prophylactic intervention would need to last at least 12 weeks. The treatment of infected subjects would need to be through the medical profession, probably utilising containment areas and specialist facilities. All non-emergency medical interventions would need to be cancelled and treatment allocated based on the best prognosis.

In reality, Western medical facilities would be unable to cope and **'containment in the community'** would be the most likely option. This would be a 'survival of the fittest' scenario with high mortality rates and maximum economic disruption.

A critical question will be at what point would the movement of humans be banned? In 1918 the virus spread so rapidly around the world because there were massive war-associated movements of troops and refugees. In Mediaeval times plague similarly spread as peoples fled from areas of outbreak.

An exercise conducted in the US looked at the likely outcome of a deliberate terror-driven introduction of smallpox has relevance to planning. Called Dark Winter, it followed politicians and other senior officials as they made decisions to designate some areas and hospitals as disease zones to which people with the disease would be sent, and to employ the military to enforce movement bans. The model exercise anticipated considerable violence and unrest as people started to act against this loss of what has always been considered a basic civil liberty – i.e. the ability to travel when you want to. There are many ethical questions as to the precise circumstances where 'lethal force' becomes acceptable.

This sort of action would have to be considered if a highly infectious disease that causes high levels of mortality ever did break out. It does, however, introduce a serious ethical debate: At what point do you curtail the rights of an individual to flea a disease-ridden area, in order to protect other populations living in disease-clear areas? In the West we have a rhetoric suggesting that the rights of the individual over-ride community-driven rights, but this is one area where the needs to protect the community would have to be taken into consideration.

This is not entirely new. In the US, for example, communicable disease confinement procedures give legal powers to, if necessary, forcibly confine individuals with diseases that cause a serious disease and can be passed from human-to-human. Similarly, under UK law there is also provision to detain people who pose a serious risk of infecting others. But neither of these pieces of legislation gives permission to detain people who may simply be living near to an infected person. To gain that power you have to declare one form or another of 'martial law'.

With just-in-time delivery being the main stay of food and energy supply industries, a 6-8 week movement ban would have severe consequences.

There are three other possible treatment strategies:

**Vaccination** would require at least six months to create a vaccine response to the human-to-human form then to produce, distribute and administer the human vaccine. Generic vaccination is unlikely to be effective. The big fear with animal vaccination is that you may create a population of animals that are infected with the virus but do not display any symptoms. These would be perfect incubators of the next generation of the virus. One possible solution to this is to leave somewhere around one in 100 birds in each flock not vaccinated, as they can then act as markers of any circulating infection. A similar problem exists for human vaccines, if they do not cause vaccinated people to eradicate the virus from their bodies.

If there is a decision to vaccinate the human population then, as with all viral diseases, you need to administer the vaccine to around 80% of the population before the vaccination campaign will have any sustainable success.

**Antivirals** such as Tamiflu and Relenza that reduce only the viral cycle may be limited in their effectiveness with H5N1. There are reports that the current H5N1 virus is already immune to these drugs. (There are also calls to restrict use of these drugs in 'normal' 'flu to slow down the rate at which these other viruses build immunity.)

**New technologies** may provide a solution. One is Hydronanon ™ technology which consists of particulate nanodevices suspended in ultra-pure water. These particulate devices are nano-sized spheres of various metals, which can be tuned by the production process to emit an assortment of antimicrobial wavelengths, including inactivating wavelengths against viruses, bacteria, fungi and parasites.

Laboratory studies have indicated that Hydronanon ™ solutions proved effective against H1N1 and H3N2 with further studies on H5N1 in progress. No cytotoxicity and rapidly scalable production, capable of producing 17 million treatments per week from a 1000 tank facility that could be constructed within 90 days, make this a very realistic potential solution. Dr Flude is a research facilitator in this field and has commercial interests in the development of Hydronanon ™ technology.

ATCA: The Asymmetric Threats Contingency Alliance is a philanthropic initiative founded in 2001 to understand and to address complex global challenges. ATCA conducts collective dialogue on opportunities and threats arising from climate change, radical poverty, organised crime, extremism, informatics, nanotechnology, robotics, genetics, artificial intelligence and financial systems.

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