INFLUENZA: WHAT ARE THE LIKELY THREATS OF FLU FOR THE UK AND HOW CAN SCIENCE HELP AMELIORATE THE CONSEQUENCES?

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The meeting was organised with financial support from the Society for General Microbiology, and in collaboration with Dr Ron Fraser, SGM Chief Executive. Although the threatened H1N1 'swine flu' pandemic was less severe than feared, the influenza virus nevertheless poses a continuing and evolving long-term threat to human health. Preparedness for control of outbreaks is essential. This involves many types of research and development, to inform and facilitate good public health practices.

THE EMERGENCE OF INFLUENZA PANDEMICS

We have just lived through the first influenza pandemic of the 21st century. In early 2009 a novel influenza virus emerged from pigs in Mexico that had the capacity to infect and readily transmit between humans. The virus showed the hallmarks of a pandemic in that it spread rapidly across the world, had recently emerged from an animal source, and took its toll mainly in the young.

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Across the world WHO reported an excess of 20,000 laboratory confirmed deaths in the first wave of the pandemic although this is certainly an underestimate of the true numbers. In the UK 474 deaths were attributed to the virus as it spread through the summer and autumn of 2009. Even more people died the following winter as the virus re-emerged in 2010 and at Christmas time 2010 more than 200 intensive care beds were occupied with swine flu patients. Thankfully, for most people infection with the swine flu virus led to mild self limiting disease and in many ways we are fortunate to have had a chance to rehearse our pandemic response under circumstances that are forgiving of a few glitches. It is certain that there will be future influenza pandemics but predicting when and the extent of their severity is difficult. Understanding why this particular virus sparked a pandemic whereas other influenza viruses that circulate in swine or in the natural wild bird hosts do not, is key to being able to predict and ultimately control pandemic emergence at the source. This knowledge will allow us to focus surveillance, prioritise vaccine strategies, and modify any practices that might increase the likelihood of a pandemic emerging.

Influenza viruses of many different antigenic subtypes circulate in wild birds. Fortunately, avian influenza viruses replicate so poorly in human hosts that they usually do not spread. However avian viruses can become adapted for better replication and transmission in humans by mutations in their genomes. It has been proposed that this may occur when the virus finds its way into alternative hosts such as pigs or chickens, which might act as intermediates in its evolutionary pathway from wild birds to humans.

The avian influenza H5N1 known as 'bird 'flu' became notorious in the first decade of the 21st century when a new variant evolved that spread through birds across 3 continents. Although the virus remains largely an avian influenza strain that has killed millions upon millions of chickens, it has also infected a wider range of hosts than any other influenza virus before. Around 500 people have been infected with this virus after exposure to high doses such as during plucking feathers from contaminated poultry, and two thirds of them have died. Thus this virus has been the focus of our pandemic plans since the consequences of a pandemic caused by an H5N1 virus would be severe. However, despite the widespread geographical spread of the virus and the huge

number of infected hosts, no H5N1 bird 'flu pandemic has happened. It is clear that unlike typical avian influenza viruses, H5N1 is not deficient in its capacity to replicate in human cells. The people who have died from H5N1 carry huge viral burdens during their disease. Rather, the reason there is as yet no pandemic is that the virus does not spread from one infected person to another. In the laboratory setting we can study influenza transmission using animal models such as the ferret. If one animal is directly inoculated with infectious virus and then a day later another animal is exposed, the second animal can be tested to see if it has acquired infection from the first. Exposure can be by placing the animals in the same cage perhaps modelling direct contact transmission in a household situation, or by placing the cages side by side so that they share the same air, perhaps more like standing next to someone on the tube where respiratory droplet transmission would occur. Whereas the 2009 pandemic H1N1 swine flu virus transmits readily in these animals, H5N1 does not; even though the first directly inoculated animals become robustly infected with the H5N1 virus.

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In order to assess the real risk from H5N1 and other avian influenza viruses to the human population we need to understand how likely it is that this deadly virus can learn to spread between us. To consider where the block to H5N1 human transmission might lie, we need to consider the site where transmission takes place. Viruses are inert unless they find access to a host cell. On the outside in the environment they are rapidly inactivated by ultraviolet light and other environmental factors. Avian influenza viruses have evolved to infect the intestinal tract of their natural hosts whereas spread between people occurs through the air. The mammalian respiratory tract is a very different environment than the avian gut. The receptors that the virus can bind to in order to mediate cell entry are of a different biochemical linkage in humans than they are in birds.

We know that avian influenza viruses have mutated before to accommodate the human receptors. However if we study the genetic code for H5 we can see that it would require more extensive mutation to achieve this switch, an event that is 10,000 times less likely than for the creation of the H3N2 influenza virus that caused the Hong Kong pandemic in 1968. Moreover this receptor switch might not be the only change the virus has to make before it can survive in the human respiratory tract long enough to mediate transmission. The brackish water in which avian influenza viruses are exchanged between ducks is above pH7.5, whereas the mucus that lines the human nose is below pH6.0. Since proteins of the virus are inherently acid labile, especially the HA, mutations may be required that enhance the acid stability of the virus particle before human transmission can occur. Human influenza viruses cope with the respiratory mucus barrier by using a specialised neuraminidase enzyme to chew it up. However the activity of the equivalent enzyme in a virus like H5N1 is compromised. We don't know why, but in passing from ducks into the chicken host, the virus loses a chunk of the genetic code for a part of the enzyme. This must have an advantage for replication in poultry but it may mean that viruses like H5N1, that have become adapted for chickens,

are unlikely to be able to cope with the human mucus barrier. In other words chicken viruses may pose much less of a pandemic threat than viruses that have remained in wild birds or viruses that have adapted to other species such as the pig. Indeed there are many other avian influenza viruses circulating in wild birds that might have pandemic potential and we should be careful not to focus all our efforts on protecting ourselves from viruses like H5N1, rather we should remain prepared for other eventualities.

It was from the pig that the 2009 pandemic emerged. The H1N1 pandemic virus itself was a complex mixture of genetic material derived from viruses that previously circulated in swine on two different continents. The manner in which such viruses met and mixed is not clear and whether the mixing event itself was sufficient to spawn the pandemic or whether other mutations were also required before the pig to human transformation was complete is a matter of intense research at the moment.

However like the butterfly in Edward Lorenz's chaos theory that flapped its wings on one side of the world and caused a tornado of public health sequelae on the other, it seems likely that tiny changes in this highly mutable virus can lead to the emergence of novel microbial agents with gargantuan consequence.

UNIVERSAL INFLUENZA VACCINES

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At the end of the 20th and the beginning of the 21st centuries, influenza immunology had become an unfashionable research area. The procedures for monitoring influenza viruses, defining the composition of the trivalent vaccine (against H1N1, H3N2 and influenza B viruses) producing vaccine seed stocks, manufacturing and annual immunisations of specified groups within the population were well established. The newer, more urgent threat posed to human health by the Human Immunodeficiency Virus (HIV) virus drew many viral immunologists away from their research on influenza. Now the tide has turned, drugs to treat HIV infections have been developed, and the potential and actual harm caused by an influenza pandemic frequently makes news headlines.

Seasonal influenza vaccines have served us well, but are far from perfect. The efficacy of these vaccines varies between 50 and 90% in young adults, depending on the match between the vaccine and the circulating virus, but drops to 30 to 40% in older adults. In the 1997/1998 influenza season when the H3N2 vaccine component did not match the circulating H3N2 virus, 84% of the vaccinees over 75 years of age who were tested failed to develop a protective immune response. Testing of the new vaccine formulation each year takes place in healthy young adults, whereas the elderly are one of the main groups offered the vaccine. Influenza infection in the elderly accounts for a large number of deaths, but also high rates of hospitalisation, loss of physical function, loss of ability to live independently and exacerbation of cardiovascular and pulmonary symptoms. Although the annual vaccination campaign targets those aged over 65, and represents a considerable health care cost, in the best case scenario where there is a good match between the influenza strains in the vaccine and those in circulation, vaccination is estimated to prevent one in five cases of influenza-like illness, one in four hospitalisations for pneumonia and influenza and one in four deaths following hospitalisation for these conditions.

A further difficulty in producing influenza vaccines is that it is necessary to know the exact genetic sequence of the virus causing disease in humans before a vaccine can be produced, resulting in a six month lag between virus identification and widespread vaccine availability. Even after six months, there will not be enough vaccine for the whole world. Some biotech companies have therefore set out to produce recombinant protein vaccines that use newer technologies for influenza haemagglutinin (HA) production, shaving weeks off the

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production time. However any vaccine based on a specific HA sequence can only be produced after a new pandemic virus has been identified, and the requirements for testing prior to widespread use mean that there will always be a significant delay before people can begin to be vaccinated.

A more innovative approach is to target a different part of the virus surface. HA is the major highly polymorphic coat protein of the virus but a small part of the M2 protein, known as M2e, is well conserved, and is also on the surface of the virus and therefore susceptible to antibodies that can recognise it. Although antibodies to M2e do not appear to be part of the natural immune response to influenza, they can be induced by vaccination, and this has been achieved in clinical trials. It is not known whether antibodies against M2e can provide useful immunity to influenza in humans, and the pandemic H1N1 virus contains four differences in the amino acid sequence, (out of a total of 22) from seasonal viruses on which the vaccine is based. This unexpectedly large difference has halted efforts to develop an exclusively M2e-based vaccine, although it may be possible to include M2e as a component of a more complex vaccine.

An alternative method to induce cross-reactive immunity is to induce antibodies against only the conserved portion of HA, rather than the whole molecule. It is known that these antibodies form a small part of the natural immune response to flu, but the challenge will be to work out how to produce a vaccine that results in only the cross-reactive responses.

The other approach that is being taken is to harness the

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second arm of the immune system, the T cell response. Any cell in the body contains specialised molecules on the surface that display a sample of the cell's contents to passing T cells that move through the body on 'surveillance'. This display enables the immune system to recognise any virally infected cells, as portions of viral proteins will be displayed, and if detected by a T cell that recognises influenza proteins, the infected cell will be killed, along with the virus that is hiding inside it. Whereas the external proteins of the flu virus are highly diverse, the internal proteins, which are protected from attack by antibodies, are highly conserved. Thus once we have recovered from infection with one influenza A virus, we have a T cell response that is capable of protecting us against other influenza viruses even when the two viruses are not closely related. However, as a few years pass, the quantity of T cells patrolling the respiratory tract on the look-out for influenza virus-infected cells gradually decreases, and we become susceptible to influenza disease again. At the Jenner Institute in Oxford, new methods of vaccination originally developed to provide a strong T cell response against malaria are now being deployed to make a cross-reactive influenza vaccine using two highly conserved

influenza proteins, nucleoprotein (NP) and matrix protein 1 (M1).

Clinical trials of this new approach have demonstrated that it is possible to boost circulating T cell responses to these two proteins to a high level following a single immunisation. Importantly, when tested in older adults, there does not appear to be any decline in the immunogenicity of this new vaccine, known as MVA-NP+M1. In addition, the first efficacy testing in humans indicated that this approach to vaccination does indeed protect against the influenza A virus. More clinical development is now indicated.

The ultimate influenza vaccine will produce a broadly cross-reactive immune response employing both T cells and antibodies, and provide high efficacy in all sections of the population. This will take time, money and a willingness to try and then refine new approaches. Several new vaccines have entered early stage clinical trials, but many years of increasingly large and expensive trials will be required before any of these will be ready to be licensed. Obtaining funding for this stage of vaccine development is particularly difficult, as charitable funders do not have deep enough pockets and large vaccine companies are reluctant to fund research that

they see as high risk. Companies wish to see sufficient evidence that a new type of vaccine will be highly effective before committing funds to late stage development and licensing, but it is not yet clear exactly what the new type of vaccine should be. There is a global public health need for improved influenza vaccines, and consideration should be given to committing public funds to advance research in this area. Once we understand how to achieve broadly protective immunity by vaccination in all sections of the population, vaccine companies will be willing to develop their own versions, which will have the potential to achieve major improvements in public health.

I think it is unlikely that we will ever have an influenza vaccine that gives protection for life, but it will be possible to make a vaccine that is given perhaps every five years to maintain immunity. This would result in a complete change to vaccine deployment and would make it possible to protect the whole population against all subtypes of influenza A, removing both the threat of a new influenza pandemic and the major economic losses currently caused by seasonal influenza.

GOOD SCIENCE TO SUPPORT PUBLIC HEALTH POLICY

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"In this world, nothing can be said to be certain, except death and taxes" (Benjamin Franklin 1789). To this we could reasonably add the emergence of infectious disease threats. The uncertainty and unpredictability of influenza, and the devastating impact that a pandemic can cause, underlies the description of influenza as the "last great plague of man", and ensures that it remains close to the top of the threat list for United Kingdom in 2011.

We now recognise that interventions can be applied to control epidemics of infectious disease, and that planning and maintaining a response capability will reduce the toll of human misery. Interventions include hygiene and use of protective equipment, quarantine, social distancing and more specific measures involving vaccination, and antiviral therapy. Intelligent and timely use of accurate communications about the nature of risk and the type of precautions that can be used supports operational responses and ensures that policy decisions are understood.

Translation of scientific knowledge and experience underlies the application of specific control measures, public health practice and accurate communication. Detailed analysis of the epidemiology of infectious diseases provides a framework for understanding which interventions will control particular epidemics. Two parameters, the basic transmissibility of infection and the ability to transmit when an individual is asymptomatic, do affect the way in which interventions are applied. In pandemic influenza, transmission predominantly occurs when individuals are beginning to be symptomatic and early in illness. Children have the lowest immunity to influenza and therefore have the highest viral replication and viral load. They are therefore particularly important in transmitting infection. This indicates that quarantine and travel restrictions will not be effective in preventing the spread of an epidemic. Key control measures for influenza involve the use of vaccines to induce development of protective antibodies, intended to reduce the impact of infection in the individual rather than eliminate transmission altogether, and the use of antiviral drugs.

Having a detailed understanding of the characteristics of individual infectious diseases provides much better information for operational decision support, during nationally coordinated response. This is provided by

• Intelligence about clinical illness case numbers and age attack profile, rate of growth of epidemic, risk factors associated with severe disease.

• The development of specific diagnostics to confirm cases identified by clinical diagnosis.

• Estimates of the total burden of infection in the community, cumulated from all cases of infection, mild, moderate and severe, so as to provide an estimate of severity of pandemic using case fatality index or hospitalisation ratios.

Estimations of case numbers of a widespread infection, which is transmitted easily, derived through surveillance, can be fraught with uncertainty. Indeed, surveillance indicators are only usually used during seasonal influenza to provide a picture of trends in illness in the community rather than absolute numbers of cases. Accurate confirmation of a new viral infection requires that, within a national laboratory infrastructure, there is scientific expertise to develop, validate and disseminate appropriate diagnostics within a matter of weeks, as part of an operational response. In 2009, from the identification of first case on 27th April, it was six weeks before regional NHS laboratories had a diagnostic capability on 1st June. During this period, intensive work at the HPA Centre for Infections in Colindale produced specifications for robust diagnostic tests for the NHS. This is a significant undertaking, which can be likened to the 100 metres sprint, an event for which extensive training and preparation are

required in order to achieve the most explosive launch.

As an epidemic unfolds, the application of laboratory diagnostics switches from confirming cases in the community to confirming cases being admitted to hospital, a key measure of disease severity. Understanding the extent and duration of virus shedding in an individual is also important. If the new virus has similar shedding patterns to seasonal influenza, normal infection control advice can be applied, enabling health care resources to be directed in the most effective way.

In a newly emerging pandemic of influenza, where the countermeasures may be in short supply, it is important to delay epidemic progression if possible. For our first pandemic of the 21st century, we had antivirals to treat and prevent (prophylax) infection, a significant development over all previous pandemics. A new class of specific influenza antivirals, neuraminidase inhibitors (NI), were first licensed in 1999/2000. The use of antivirals can now be planned for, with recognition that efficient targeting of antivirals is operationally extremely complex. Antivirals can be used in a variety of different ways. They can be used to prevent the acquisition of infection following contact with an infected person (prophylaxis) or to treat individuals who are unwell. Antivirals are most effective when taken early, within 48 hours of illness onset. Arrangements for antiviral treatment need to focus on rapid, efficient delivery, when

they are likely to be most effective. This requires that we can accurately identify clinical cases, treat them and then prophylax household and community contacts. Mass prophylaxis (containment) is a mammoth undertaking within any health system and does lead to the use of drugs in exposed but apparently healthy households and communities. In the United Kingdom in the 2009 epidemic a containment phase lasted for approximately eight weeks until there was sustained community transmission. Analysis of the outcome of antiviral prophylaxis in the first few hundred cases in the United Kingdom clearly indicated that prophylaxis slowed household transmission, reducing the likelihood of cases arising when index cases were treated within 48 hours. This confirmed the scientific advice underlying the policy decision to try to slow the epidemic growth and buy time for vaccine development.

Vaccines are clearly the key measure to be used against pandemic influenza. Much work has been done in the last decade, as a result of the H5 bird flu threats in South East Asia, to improve the licensure process for pandemic vaccines. The time to develop pandemic strain vaccines is anywhere between four and six months and is critically dependent on the generation of candidate vaccine strains. These are normally prepared in expert public sector institutes, and given to manufacturers for preparation of bulk vaccines. The first vaccines were available in the UK mid-October 2009, and approximately 80% of all the candidate vaccine strains supplied to manufacturers globally were from HPA National Institute for Biological Standards and Controls, another demonstration of the value of rehearsal and planning of response capability undertaken in the last few years.

As a pandemic unfolds and time to apply vaccine comes closer, the key questions arise as to the major risk groups for vaccination and the greatest susceptibility in the population. These questions are answered by analysis of confirmed cases. The analysis of susceptibility of remaining population needs to be approached in a different way, requiring that we have measurable immune correlates of protection or suitable surrogate. This will help estimate the residual population susceptibility, which in turn will influence whether vaccination should be applied selectively or universally.

Work in the last ten years had established the type of comparative data necessary to support decisions about how to deploy different vaccines in a pandemic. Head to head vaccine trials were conducted in children and adults using the available licensed vaccine in the United Kingdom. This demonstrated that the stockpiled vaccines generated good immune responses. Further monitoring demonstrated that the vaccine which was most extensively used had an efficacy comparable to or better than seasonal influenza vaccines. Key data used by the Joint Committee on Vaccination and Immunisation (JCVI) to recommend which groups receive vaccination and in which order, an important operating constraint when vaccines are in very short supply, were dependent on knowledge of the susceptible and risk groups in the population, the attack rates by age and measures of vaccine effectiveness. Stocks of available vaccine then determined the rate at which mass vaccination could proceed.

Individuals aged six months to 65 years were targeted for vaccination as a result of the data cumulated during the first few months of the pandemic, which showed most infection in younger age groups. Pregnant women were at particular risk of

severe outcome and all pregnant women were advised vaccination. The over 65 in clinical risk groups were the next target group. This vaccination policy is in reverse to the normal seasonal influenza vaccine policy where over 65s are usually targeted first, but was appropriate given the observed patterns of greatest clinical risk.

Whilst much excellent communication was undertaken during the pandemic, there are still opportunities to improve this. Terminology to describe modelling estimates of severity described within bounds of statistical uncertainty gave rise to misleading communications, such as "UK prepares for 65,000 deaths from swine flu". It is now recognised that this is an area where more attention needs to be given to find better descriptions of results of early statistical and modelling analyses as epidemic unfolds.

We can conclude a few things about our use of scientific information to guide the response to 2009 pandemic. The independent Hine review praised the overall public health response "I heard nothing but praise for the public health officials". The areas which had benefited from most planning and preparation: diagnostics and vaccine seed development, antiviral distribution, design of head to head vaccine studies and estimation of vaccine efficacy, were well executed. The linkage between case counting and estimates of severity requires further attention, a problem recognised at global as well as national level. Providing better estimates of case numbers through seroepidemiology needs further development, and may be best accomplished by developing this activity as part of the overall seasonal influenza response, so as to improve our ability to use different data sources to make predictions about population susceptibility.

We are left with a scientific agenda where key development requirements include the improvement of seroepidemiology, application of more user friendly alternative laboratory tests which tell us about exposure rather than immunity and better ways of assessing overall disease severity. Alternative vaccines and increasing the repertoire of antiviral drugs and their delivery mechanisms are long-term scientific aspirations which the 2009 operational response confirms continue to be worthy goals.

The 2009 pandemic influenza demonstrated the dearth of systematic prospective patient orientated clinical research. The ability to undertake high quality R&D at the same time as responding to the pandemic should be more explicitly embedded in operational response. Emergency use of new drugs and novel therapeutic options, where there is not time to go through lengthy protracted RCT study design, may be an important countermeasure for treatment of severe cases in a more virulent infection. This requires thoughtful planning in light of the increasing regulatory burden for clinical research, where guidelines intended to help regulate drug trials have spilled over into observational, clinical studies, acting as barrier to the conduct of high quality observational research during unforeseen natural events.

In completing this article, I would like to acknowledge the contribution, help, companionship, support and sheer professionalism of my Health Protection Agency colleagues during the response to the 2009 influenza pandemic, the first, but probably not the last pandemic of the 21st century.