

**T5.3: The Threat of Epidemic and
Pandemic Influenza A**

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Abstract:

In the years ahead, infectious diseases will increase globally as the population of the world expands and, in parallel, farming and tourism move into previously uncultivated areas. The very marked increase of tourist and business travel by air will ensure that newly emerged and re-emerged microbes will spread quickly. On the other hand global viral surveillance has increased recently and the national plans to combat chicken influenza H5N1 has shown that it is possible to galvanise even reluctant governments into action. Soon after the discovery of pathogenic waterborne bacteria, the cities of the world were torn apart to introduce sewage and clean water systems. Such practical application of scientific knowledge now needs to be matched both in terms of preventing new infectious diseases and in the current preparations for a chicken H5N1 global outbreak. Such a focus will form an excellent example of the pattern of political and public health behaviour and investment in a new century.

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Introduction

When the influenza A virus first emerged from a presumed avian reservoir at the end of the ice age 10,000 or so years ago, there was a distinct difficulty in finding new human victims. For example, at that time only a few hundred settlers were in the London region near our hospital, now a community of four million people. At that time a traveller would have to walk 100 miles to find another small settlement, perhaps near Salisbury.

Nowadays we have a truly global community of six billion people, linked so that two million people are moving each day by plane whilst perhaps 100 million are journeying in their homelands. Influenza, like all viruses, is opportunistic. In 1918 it had the unprecedented opportunity to spread at the end of the first global war. Ten million soldiers began the move homewards and every steamship was packed as they fanned out from France to England, Europe, the US, Canada, Australia, India and SE Asia. How perfect for a virus spread by aerosol droplet, close contact and contamination of towels, cups and everyday utensils. A virgin population which had never before encountered the virus was on the stage of this theatre of infection. Perhaps a billion people were infected in the next 18 months, and 40 million died. ⁽¹⁻⁸⁾

The same happened in the other pandemic years of 1957 and 1968, aided in these two outbreaks by air travel. ⁽⁹⁾

The influenza virus looks like a football, with two sorts of protein spikes protruding through the lipid outer membrane, the Toblerone-shaped haemagglutinin (HA) and the mushroom-shaped neuraminidase (NA). This negative stranded RNA virus is one of the most changeable and mutable of human viruses because of the low fidelity of the viral RNA replicase enzyme. The virus is transmitted from person to person in coughs and sneezes as a droplet infection but there is significant transmission from virus-contaminated surfaces, shared cups, towels and handshaking. The clinical signs are classical, with very rapid onset of headache, aches and pains, cough and general malaise. In younger people the illness lasts 4-8 days but in the elderly, the virus may move deeper into the airways to cause bronchopneumonia and open the way to super-infection by bacteria.

1 Current influenza vaccines and antivirals

At present the main clinical management of influenza as a disease is centred upon the use of prophylactic vaccine, mainly a subunit preparation of haemagglutinin (HA) and neuraminidase (NA) spikes. Most European countries and the US try to target at least 70 per cent of their 'at risk' group. No country has a wide immunisation strategy across all sectors of the community, for two reasons. Firstly, the world production capacity for influenza vaccine (200 million doses) is not large enough at present to cope with the changes to the vaccine required to keep up to date with the yearly antigenic changes of the virus itself and to produce virus for a mass vaccination campaign each year.^(10, 11) Secondly, a large-scale vaccination programme would pressurise the virus to change faster. Therefore, the 10-15 per cent of the population over the age of 65 (in the EU, but over the age of 50 in the USA) are the targets of vaccinators in normal inter-pandemic years, as well as persons of any age with asthma, chronic heart disease or diabetes. These are termed the 'at risk' group because they more often succumb to post-viral complications.

It is clear that age alone is a risk factor for influenza. But the vaccination strategy would need to be radically different should the world be faced with a pandemic, either natural or deliberate. As was noted in 1918, a pandemic virus can target a particular age group. In this latter year the 25-35 year olds were at risk. In the re-emergence of the H1N1 virus in 1977, under 25s were vulnerable because they had no prior immunity whereas older persons had experienced the same virus 25 years or so before. The older community group often finds itself more susceptible to virus-induced bronchitis and bronchopneumonia, and hence hospitalisation and death.^(12, 13) The vaccine has been shown very clearly in large clinical trials conducted over several seasons⁽¹³⁾ to reduce both hospitalisation and death by all causes including heart attack and stroke.⁽¹⁴⁾

It should be appreciated that there are large numbers of influenza deaths in most countries of the world in most years among unvaccinated 'at risk' individuals. In the UK over the millennium period there were nearly 20,000 deaths from pneumonia and bronchitis in a period of 4-5 weeks.

There is an alternative management strategy involving the influenza vaccine but to date it has been little explored and at first sight seems tenuous in its practicability. There is clear evidence that influenza is predominantly a disease of childhood. An innovative approach, therefore, is to immunise children and thereby break the chain of influenza transmission to parents and grandparents. A re-analysis of such vaccine data from Japan⁽¹⁵⁾ in the 1980s and to a lesser extent from towns in the US⁽¹⁶⁾ has shown some validity for this approach. But could modern parents be persuaded of this benefit and agree to have their child immunised with yet another vaccine? They might be more receptive to the use of an intranasally delivered spray of live-attenuated vaccine⁽¹⁷⁾ or of one of the new inactivated vaccines⁽¹⁸⁾. This could have a comparable effect to vaccination and at the same time avert parental

concerns about conventional vaccines. This may be considered as a public health tactic during a pandemic or threat situation.

Meanwhile, we are left with the clear observation that 85 per cent or so of the population are outside the classical at-risk group but remain vulnerable to influenza infection each year. Most of these people will be ill for 5-7 days and then recover, but there are still many deaths of people not regarded as being at risk. It has been estimated that 40-50 per cent of the 20,000 deaths in the UK at the time of the millennium were not in the at-risk groups. Therefore there is a clear need for an extra intervention with vaccines or antivirals in the wider community. Such increased targeting would simultaneously build up vaccine production capacity and the quantities of antivirals available for use in an emerging pandemic or threat. Although the scientific community, along with pharmaceutical companies, has developed vaccines and antiviral drugs over the last half century, there is not the capacity to deal with a sudden outbreak.

A quarter of a century ago a group of scientists began to explore the much-understudied NA protein of influenza. The NA had already been identified as a separate gene product⁽¹⁹⁾ and antibodies to NA were known to reduce viral spread in cell culture. X-ray crystallography revealed the positions of enzyme-active sites and the antigenic epitopes of NA.^(20, 21)

A group of chemists actively interested in the discovery of antivirals took Neu5Ac2en as the basic inhibitor and substituted a guanidinyll group for a hydroxyl carbon atom to make Zanamivir (Relenza), the first anti NA drug,⁽²²⁾ Another group of chemists designed a cyclohexene ring and replaced a polar glycerol with lipophilic side chains⁽²³⁾ creating the drug oseltamivir (Tamiflu). The bioavailable drug is an ethyl ester that is converted into the active carboxylate by esterases in the liver. A third set of chemists designed a cyclopentane derivative with a guanidinyll group and lipophilic chains -^(24, 25) the drug RWJ-270201 (also known as BCX-1812 or peramivir). All three drugs (zanamivir, Oseltamivir and peramivir) were shown to be powerful inhibitors of influenza A and B virus NAs in enzyme tests, viral replication in cell culture and, importantly, in animal model infections in mice and ferrets⁽²⁶⁾ and later humans.⁽²⁷⁾ As expected, in drug-treated mammalian cell cultures, large viral aggregates can be detected at the cell surface by electron microscopy. All nine influenza A NA subtypes including the NA from the 1918 virus and the recent H5N1 chicken flu are inhibited at a micromolar level.⁽²⁸⁾

2 Clinical management of influenza

The original investigations with the first anti-influenza drugs, amantadine and rimantadine, now known as M2 blockers, showed clearly that antivirals could be used to prevent infection in the workplace or family,⁽²⁹⁾ or to treat already established infection. The idea that any antiviral drug could reduce the symptoms of influenza was strongly contested at the time but it became clear that intervention with amantadine 24-48 hours after the onset of symptoms could reduce time in bed, cough and viral titre in the throat. Less controversial at the time were studies showing that judicious use of the drug in the family after identification of a member with influenza - the index case - could reduce

the spread in the family by 80 per cent or more. This sensible intervention is now called post-exposure prophylaxis⁽³⁰⁾ because it is recognised that most family members would have already been infected by the index case even before drug intervention. Undoubtedly drugs would be used in this way in the face of a pandemic or threat.

Overall, the protective effect of both the zanamivir and Oseltamivir drugs, the new NIs, varies between 60 and 90 per cent, showing that these drugs can be used effectively in the community during an influenza outbreak. There is less evidence at present of their value in vulnerable settings such as homes for the elderly, but there is no clear reason why the new inhibitors should not be very effective in this setting too.

Clinical studies in the community showed that administration of the inhaled or oral NI drug within 48 hours of natural influenza A or B infection reduced the duration of symptomatic illness by one day from 5 to 4 days. The drugs reduced the impact of influenza virus infection on a patient's productivity and health status and also the number of contacts made with healthcare professionals.⁽³⁰⁻³⁴⁾

To illustrate the therapeutic effects we will analyse two studies in more detail. To study the therapeutic effect of zanamivir⁽³⁵⁾, Monto et al (1999) analysed the overall intent to treat (ITT) population and showed that the drug reduced the median number of days to the alleviation of clinically significant symptoms by one day compared with a placebo. For patients who began treatment more than 30 hours after the onset of symptoms, the difference between zanamivir and placebo groups, although still present, was reduced to 0.5-1 day. This difference was not statistically significant. Zanamivir reduced the time to symptom alleviation in both febrile and non-febrile patients but had a greater effect on febrile patients. Zanamivir given twice daily reduced the median time for alleviation of symptoms by 0.75 days in the non-febrile groups ($P=0.049$) and by 1.5 days in the febrile group ($P=0.049$). Similar differences were seen when zanamivir was administered four times daily, compared with a placebo. Similar benefits regarding symptom alleviation were also seen in the corresponding analyses of the influenza positive population. A reduction of 1.5 days in the time to symptom alleviation was seen in both the groups given zanamivir twice and four times per day in the total influenza-positive population, although the differences were not statistically significant.

In comparable studies of Oseltamivir in the community⁽³⁶⁾ a total of 629 healthy, unimmunized adults aged 18-65 presenting within 36 hours of onset and with a temperature of 38°C or more, with at least one respiratory symptom and one constitutional symptom were enrolled. Individuals were randomised to one of three treatment groups: Oseltamivir 75mg twice daily, 150mg twice daily or placebo, for five days. A total of 374 participants were confirmed to have influenza (60 per cent). The duration of illness from the initiation of therapy was reduced by approximately 30 per cent in the Oseltamivir groups. In the 75mg twice daily group, the median duration of illness was reduced to three days compared with 4.3 days in the placebo group ($P=0.001$) and in the 150mg twice-daily group the duration was reduced to 2.9 days ($P=0.001$). There was also a significant decrease in the symptom

score AUC as a measure of the severity of illness. Volunteers treated with Oseltamivir reported a more rapid return to normal health and usual activities. Additionally, the incidence of secondary complications, predefined as pneumonia, bronchitis, sinusitis and otitis media in subjects with influenza was reduced from 15 per cent in placebo recipients to 5-9 per cent in the two Oseltamivir-treated groups. Antibiotic prescriptions for these complications were also reduced. This is a most important observation for use in a pandemic and bioterrorist threat. It is not known yet whether the NIs prevent death but this would be anticipated by analysis of the strong effects in antiviral animal models.

More recently, the clinical data with Oseltamivir has been extended in children⁽³⁷⁾ and it is clear that the public health community has a strengthened range of new anti-influenza drugs. The important practical question is how to use antivirals in the most effective manner.

Drug resistant mutants can be selected against the NIs⁽³⁸⁾ but, at least to the present day, they have been shown to reduce virulence and transmissibility in animal models and are less likely to spread in the community than the wild type, drug-sensitive parent (see below). A European laboratory network has now been established to search for and characterise influenza viruses resistant to NIs or the M2 blockers. (www.virgil.).

Amantadine (also called 1-adamantanamine hydrochloride, Symmetrel or, more recently, Lysovir) has significant antiviral effects against all influenza A viruses in cell culture, including H5 viruses, in animal model infections in mice, and, most importantly, in humans.⁽³⁹⁻⁴⁰⁾

Its method of action has been well characterised and consists of blocking the viral acidification function of the viral M2 channel.⁽⁴¹⁾ Analysis of rare biopsy material established that the drug was concentrated, to higher levels than simple tissue distribution models predicted, in the upper respiratory tract.⁽⁴⁰⁾ However, the most significant discovery was that amantadine, and its molecular relative rimantadine, had prophylactic and therapeutic activity in human infection with influenza A H1N1, H2N2 and H3N2 viruses. At the start of this work 40 years ago, amantadine was most studied in the UK, continental Europe and Japan, while rimantadine was investigated in very large trials in Russia, the USA and, to a lesser extent, Eastern Europe. These extensive studies will not be further summarised briefly but can easily be consulted in reviews.⁽⁴⁰⁾ The prophylactic activity, around 80-90 per cent, is similar to that of the recent discovered neuraminidase (NA) inhibitors, as is the therapeutic activity, reducing illness by approximately 1.5 days if the drug is used within 36 to 48 hours of symptoms appearing. In fact, the scientific community did not accept that an anti-influenza drug could have any therapeutic activity until the first studies with amantadine proved otherwise.

In commercial terms, in view of the investment of some €500 million needed to develop any new drug, pharmaceutical companies need to be assured of a market. However, the history of the under-use of amantadine and rimantadine and more recently of the NIs illustrates the difficulty of introducing antivirals

into the management of influenza in the community in the event of a pandemic. An entirely new plan of approach is required.

Amantadine and rimantadine have been licensed as anti-influenza A drugs for four decades, but their application in the community has been bedevilled by two factors - the emergence of drug resistance, and fear of toxicity. As regards toxicity, most earlier clinical studies employed a dosage of 200mg per day of amantadine. Some 'jitteriness' was noted in about 10 per cent of patients, particularly the elderly. Subsequent studies indicated that the dose could be halved to 100mg daily with continued effectiveness. At this level no toxicologic problems would be expected, but the dosage can still be adjusted downwards for the frail elderly, who could be underweight. We will return to this important low-dose application below.

The problem of drug resistance is more difficult to resolve, but is not unique to amantadine. Amantadine-resistant mutants can be generated among experimentally infected mice, but only after the use of very high drug concentrations.⁽⁴²⁾ It is not known whether these viruses are less pathogenic or virulent than the wild-type viruses, such as viruses resistant to the NI drugs, but the low frequency of detection in the field does suggest this. Mutations which confer resistance to amantadine can be clearly identified in the viral M2 gene, and such viruses are cross-resistant to all the M2 proton channel inhibitors.

3 New mammalian cell culture techniques to rapidly cultivate influenza virus for vaccines

We know that current vaccine production and administration need to be increased both in the inter-pandemic year and for a pandemic. Influenza virus for vaccine production has been grown in embryonated hens' eggs for 60 years. The technology is well automated and usually produces one vaccine dose (3 x 15µg HA and NA protein) from the virus-containing allantoic fluid of a single embryonated hen's egg. The influenza A viruses are normally reassortant with the HA and NA genes from the wild epidemic strain of H3N2 and H1N1 viruses and with the remaining six genes from a classic egg-adapted virus called A/PR/8/34 (H1N1). This latter virus has been extensively passaged in eggs and produces ten times higher virus yields than a wild type unadapted virus. Therefore, the new reassortant vaccine virus has the same growth capacity in eggs of A/PR/8/34 and the appropriate HA and NA as the wild type virus.

However, the potential problem from the viewpoint of a sudden pandemic or bioterrorist event is lack of production surge capacity using eggs. The eggs are fertilised, and have to be ordered, six months in advance from specialised farms. Commonly, an influenza vaccine production plant is built to infect 40,000 eggs each time and then, two days later, to harvest allantoic fluid from these eggs. Therefore, the production capacity cannot suddenly be increased five or ten fold. Obviously the overall surge would not be necessary if all countries had an inter-pandemic strategy and vaccinated each year the 15 per cent of the 50 per cent of the population at risk of complications,

hospitalisation and death following an attack of influenza, mainly the over-65s. If every country produced such a recommended quantity of influenza trivalent vaccine, producing a monovalent pandemic vaccine rather than a trivalent epidemic vaccine would allow 45% per cent coverage in the same populations. Such production coverage could be even extended should a whole virus pandemic vaccine be used. This would give a more powerful immune response and could even allow dilution to less than 15µg dose, thus extending further the number of potential vaccinees.

But more recent laboratory experience of cultivating influenza viruses in mammalian cells rather than eggs has encouraged two manufacturers at least to invest in cell culture fermenters.^(43,44) Here capacity can be increased to cope with a surge in demand for a pandemic virus vaccine. Moreover, the final vaccine has the theoretical advantage of the absence of egg proteins. A minority of the population are allergic to hens' egg protein. The cell culture virus is also easier to purify. Where clinical isolates of influenza viruses are cultivated on mammalian cells and eggs in parallel, different antigenic variants are selected.⁽⁴⁵⁾ The biological variants have amino acid substitutions in the receptor binding site in proximity to an antigenic site on the HA and, therefore, an amino acid change in this region can alter antigenicity. Of the two subpopulations that can be selected, the virus which is grown on MDCK (or Vero) cells rather than in eggs appears more closely related to the wild type clinical virus. There is some indication that cell-grown virus vaccines offer greater protection in animal models than the corresponding egg-grown vaccine. These are powerful arguments in favour of the new generation of influenza vaccines being cultivated in Vero or MDCK cells.

4 New influenza vaccines that could induce protection across the different subtypes

There are 16 known subtypes of the HA of influenza A virus, distinguished by their antigenicity. Only three subtypes have caused pandemics in humans, namely H1, H2 and H3 whilst H5, H7 and H9, predominantly circulating in birds, have crossed the species barrier into humans and caused localised outbreaks.^(46,47) We do not know whether these latter three subtypes could mutate into human-to-human transmitters and thereby acquire pandemic potential. At present H5N1 is causing considerable concern in SE Asia. An important question is whether there is any way that a vaccine could be engineered to give so called heterotypic or cross-subtype immunity. It is well known that the internal proteins of influenza A virus such as M1, M2 and NP are shared by all influenza A viruses. These internally situated proteins are certainly immunogenic (particularly NP) but could the immunity induced, either T cell or antibody, be broadly reacting?

To back up the central core of this approach it has been known for 40 years that mice infected with an influenza A H1N1 virus would later resist a lethal challenge from an influenza A H3N2 virus. Given the lack of genetic and antigenic relatedness between the H1 and H3 proteins, or indeed the corresponding N1 and N2 proteins, this strong cross-immunity was attributed

to an internal protein such as NP or M. However, it has been difficult to construct a solid database and there has been a lingering doubt about this so-called cross-protective immunity. Most virologists deduced, virtually by elimination, that a cross-reactive portion of the HA (HA2) could have provided the cross protection. Furthermore, this cross protection is particularly seen in the mouse model, leading some to conclude that the mouse recognised cross protection epitopes that perhaps humans did not.

Fundamental studies to correlate the genetics and immunology of NP established the cytotoxic T cell response to portions of this protein. However, the work clearly showed that M2 could be a cross-reactive immunogen, although a relatively weak one.⁽⁴⁸⁾ The M2 protein is an integral membrane protein of influenza A viruses that is expressed at the plasma membrane of virus infected cells and is also present in small amounts on virions. It is some 96 amino acids in length, with a 23 amino acid extra-cellular domain, a trans domain of 19 amino acids and a 54 amino acid cytoplasmic tail. The important extracellular domain, potentially targeted by antibodies and T cells, is conserved by virtually all influenza A viruses. Even the 1918 pandemic virus differs only in one amino acid. The first indication that the M2 was immunologically active was the observation that an anti-M2 monoclonal antibody reduced the spread of virus in cell culture. Not unexpectedly, the antibody reacted with the extracellular domain of M2. Even more excitingly, the antibody reduced the replication of virus in mouse lungs. Immunisation studies with M2 constructs, however, have given more mixed results. Immunisation of mice with a DNA plasmid of M1 and M2 genes gave protection mainly via T helper cell activity had already showed that a hepatitis B core in M2 fusion protein gave protection in a mouse model⁽⁴⁹⁾ coupled a peptide of the external portion of M2 to the immuno dominant region of the core antigen of hepatitis B virus. The same group later investigated the immunological mechanism and found that the cross protection resided in antibodies, although the M2 specific antibodies did not neutralise the virus *in vitro*. The authors concluded that the protection was mediated by an indirect mechanism such as complement-mediated cytotoxicity or antibody-dependent cytotoxicity. But importantly, the protection induced in the mouse model was considerably less than that induced by conventional sub unit HA/NA vaccine.

It could be argued that weak heterotypic immunity may be present already in the community and that this is helping to prevent the emergence of chicken influenza A (H5N1) in SE Asia. Certainly with evidence of tens of millions of birds infected since late 2003 in 13 countries in SE Asia, with only a handful of human infections and only human to human transmission in family groups, there is a possibility that the unique co-circulation since 1977 of two influenza A viruses (H1N1 and H3N2) may have enhanced heterotypic immunity in most communities, which in turn abrogates the emergence of chicken influenza A (H5N1) into humans. It would be foolhardy, though, to take this argument to a fuller conclusion and relax the pressure to prepare for a new pandemic influenza A virus.

5 National planning for a pandemic

The first sections of this review represent the crucial points of preventative medicine for influenza using antivirals and vaccines. The communities of the world now have newly-developed antivirals and potent vaccines for influenza that would blunt a serious outbreak. But exactly how prevalent are these new influenza viruses and is a pandemic or threat expected? Where will it come from and how long will it take to spread around the world? How long would the warning period be? Table 1 summarises the global outbreaks of influenza during the present and last centuries. It is immediately obvious that these global outbreaks are intermittent and there is an unpredictable time frame.

Influenza is a unique virus in that it has two epidemiologic forms, epidemics and pandemics, and management of community illness needs to be different in each case. It is quite clear that effective utilisation of antiviral drugs to combat a pandemic virus or bioterrorist threat will depend upon the prior widespread use of the drugs during inter-pandemic years. Most people of any age would be vulnerable to infection with a new pandemic or bioterrorist virus. During epidemic years those over 65 years of age are most vulnerable to medical complications. It is unreasonable to deduce that antivirals can be stored during inter-pandemic years and only used in a pandemic or in a threat situation. In contrast, the best approach would be consistent and detailed clinical use of antivirals and vaccines to reduce the year-to-year medical and economic impact of influenza. This would also allow physicians and nurses to become familiar with influenza and build up knowledge of use during a pandemic or an influenza threat.

Given the unpredictability of a date for a new pandemic and the existence of more pressing medical problems, there is a tendency to forget influenza. The WHO has requested each member state to produce a pandemic plan, but abysmally few governments have responded to date. On a more positive note, European countries are now considering a strategy of stockpiling anti-influenza drugs. This alongside more clinical use of vaccines and antivirals could be a significant investment in future community healthcare in Europe.

The essential objectives of a pandemic plan are to alert scientific, medical and political groups and to reduce the morbidity and mortality from influenza illness. This would increase the ability of a community to cope with large numbers of people who are ill and dying, at home and in hospital, and it would ensure that essential services are maintained. Such a strategy can also be used as plan for a bioterrorist attack. Indeed the UK influenza pandemic plan has been modified to cope with either a deliberate or natural potential outbreak.

Tables 4 and 5 summarise the preparedness levels and some scenarios for vaccine or drug use during a pandemic. A simple mathematical calculation identifies 29, 39 and 10 years between recorded pandemics while 36 years have now elapsed since the 1968 pandemic. The pessimists could conclude that a new pandemic of influenza A virus is now overdue.

Although a natural influenza pandemic would seem to be almost inescapable, the likelihood of a deliberate terrorist-caused outbreak would seem minuscule, at least at present. But preparations for a pandemic would cover both possibilities.

The WHO has issued a consultation document about pandemic influenza, which places the responsibility for management of risk with national authorities. It urges them to take the initiative to discuss new issues such as how scarce supplies of vaccines can be shared when the next outbreak comes and whether public gatherings should be cancelled to slow the spread of infection. The same plan can be modified for a deliberate attack.

The document reiterates that in spite of medical and scientific advance since the 1918 pandemic, unparalleled tolls of illness and death would be expected in a new influenza A outbreak, with air travel speeding up the global spread of infection. There is also a very real problem of the build-up of fear in a population about the possibility of an outbreak. To better cope with false alarms and public fear, WHO has designated some warning levels.

Possibly the most important phase is the pre- or inter-pandemic period designated phase 0. More attention to vaccinating the at-risk group by year, will lead to a greater awareness of influenza as a public health threat as well as directly benefiting those who are at risk of complications of influenza, because of age or underlying chronic medical conditions. Without this experience there will be no chance whatsoever of serious and effective clinical management during a pandemic or bioterrorist attack. Another vital aspect of this phase is surveillance, which is now accurate and speedy because of molecular diagnostics. To give two examples, the SARS virus genome was sequenced in a matter of weeks and a diagnostic kit supplied within this time frame to SE Asia. Similarly the 1999 and the recent (2004) outbreak of influenza A H5N1 in SE Asia and the H7N7 outbreaks in the Netherlands^(50,51) were intensively and very rapidly investigated using PCR based tests. However, the extreme sensitivity of the test can be a problem, leading to overhasty deductions about transfer of the virus to other species simply by a detection of viral genes in the respiratory tree where they may not be causing overt disease.

Recent experience of the H5N1 chicken influenza outbreak in SE Asia shows an absence of coordination between human and veterinary virologists. Taubenberger⁽⁵²⁾ has defined a physician as 'a veterinarian who only manages to deal with diseases of one species' and there is more than an element of truth here. One of the problems faced recently is the 'ownership' of new viruses, the competition between groups of scientists to have hands on experience with the new virus. Traditionally a virus emerging from birds or animals is a veterinary virus and in many countries the Ministry of Agriculture may refuse permission for the virus to be brought into the country unless to a veterinary institute. Obviously a contradictory viewpoint is that once an avian virus is recovered from a human then it could be viewed as a human virus. These apparently small questions of ownership can impede research.

Mathematical models can be developed during this inter-pandemic time and these have proved their worth in attempts to avert large outbreaks of SARS. Where countries are contiguous with open borders, as in the EU, it is important for national pandemic plans to be exchanged. A new factor is the growing recognition by WHO that it can exert huge economic pressure on countries to take zoonotic outbreaks of influenza seriously. Scientists and virologists took a non-interventionist approach to the pandemics of the 20th century. However, the WHO is now acting very quickly and the central hypothesis is that unless a pandemic can be stopped very early it will never be stopped. This explains the huge interventions in SE Asia in 2003-2005 to kill over 100 million chickens to prevent an emergence of chicken influenza A H5N1 virus, and the killing of 20 million chickens in the Netherlands in 2003 to prevent influenza A H7N7. Should a policy of encircling vaccination of chickens also be carried out together with human distancing or quarantine it is possible that a potential outbreak in humans could be aborted or at least delayed, which would allow time for a vaccine to be manufactured.

Probably the most important contribution to public health is the build up and stockpiling of antiviral drugs, which can be used to blunt the effects of the first wave of an outbreak and give opportunities for a new vaccine to be made. It is not widely appreciated that there could be a long delay in the manufacture of a stock of antiviral drugs. The new NIs have a lifespan, in bulk, of 10 years or more and so chemical stability is not a problem. The problem is the complex chemical synthesis. Without a designated factory to produce the drug beforehand, the world production capacity will remain minuscule and totally inadequate in a world, or even national, threat. It could be argued very strongly that the single biggest investment in public health at present would be the establishment of a reserve of all three anti-influenza drugs. To give some urgency to planners the situation can be viewed from another direction.

Since there are only 16 subtypes of influenza A virus, it would also seem sensible and strategic to prepare this number of experimental vaccines using a representative virus strain of each subtype and to obtain preliminary evidence of their immunogenicity. Such virus vaccines could be used, at the very least, as early release vaccines for healthcare workers, nurses and doctors. They could be viewed as community 'priming' vaccines. The practical experience from the 1918, 1957, and 1968 influenza pandemics, and more recently the SARS outbreak, showed how vulnerable the healthcare sector is to infection. An initial vaccine, made even in small quantities to immunise the most vulnerable 5-10 per cent of the population would ameliorate the otherwise devastating effects in hospitals.

As to the later phases, the recent isolation of a new influenza A H5N1 in humans triggered phase preparedness (PP) at level 2 but no human-to-human transmission was detected. At PP trigger level 3, vaccine manufacturing will start. Experience from the past has shown that phase 3 can last as long as 9-12 months. The objective during the pandemic phase itself is to organise distribution of vaccines and antivirals.

6 Mortality and morbidity during a pandemic

The 1918 pandemic dominates the records of infectious disease during the 20th century, and indeed for the previous five centuries, for both numbers of afflicted persons and deaths. The worst-case scenarios of a new pandemic or deliberate outbreak indicate that mortality and hospitalisation in a new pandemic could easily exceed that of 1918. New factors at work include a higher world population, the rapidity of transport and the much larger number of immunosuppressed persons. In 1957, when the illness was milder than the 1918 pandemic, more than 30,000 deaths occurred in England and Wales. Estimates ranged from 1.3 to 3.5 deaths per 1000 cases, and two-thirds of the deaths were of people aged over 55 years. In a pandemic, the number of new general practice consultations for influenza-like illness could be expected to exceed 500 per 100,000 population per week. A medical practice of 10,000 patients would therefore expect to see at least 50 new patients per week. Pandemics also have a marked effect on hospital admissions. During September and October 1957, between 25,000 and 30,000 more cases of acute respiratory infection were admitted to hospitals in England and Wales than would have been expected at that time of year.

It is easy to see that the healthcare system of most countries would be quickly overwhelmed in any future outbreak. In recent years there has been no provision of spare beds for such emergencies. As the outbreak of SARS in SE Asia and Canada showed, modern healthcare systems can be more easily disrupted than in the past.

7 The impact of pandemics on the economy

Pandemics have a serious effect on the economy. In 1957 in the UK, new sickness benefit claims by those working and aged 15-64 years increased by 2.5 million out of 17.5 million insured. Among the uninsured, an additional 1.5 million work absences were estimated. Of the insured population, 8-10 per cent were estimated to have lost three working days during the epidemic. In the pandemic of 1968, just over one million excess sickness claims were received in England over five months. Modern estimates of the cost of an epidemic in the US assume attack rates in the community from 15 to 35 per cent, and vary between \$71 and \$166 billion.

8 Conclusions

Influenza A virus has a proven record as a life-threatening virus driven by the vast unfathomable laws of nature and emergence, re-emergence, and resurgence of natural disease. Indeed, the ever-inquisitive nature of scientists seems to be poor in comparison to the virus they are studying, although molecular virology is at the edge of important new discoveries using reverse genetics.

Picasso gave us his picture of the caring scientist and doctor in his painting 'Science'. We would do well to reflect on his vision and abide by the ancient

tradition of science which is not to be used under any pretext in a harmful way whether to our potential enemies or anyone else. The new technologies of reverse genetics allow RNA viruses to be manipulated for the first time.^(53, 54, 55) Many emergent and threatening viruses such as Ebola, HIV, Lassa fever, West Nile fever, influenza and SARS have RNA genomes. The potential to deliberately, or more likely accidentally, create a hyper-virulent virus is now with us. The answer is not to close this area of scientific exploration.

But there is an extraordinarily clear message emerging which tells us to build our public health infrastructure, and to expand our epidemiological vigilance and surveillance against all these infectious viruses and bacteria. For instance, we need both a detailed and practical plan and a supply of antiviral drugs and new vaccines to hand. We would then be 'at the end of the beginning' as regards the protection of all citizens of the new world of the 21st century. Influenza was the twentieth century's weapon of mass destruction, killing more than the Nazis, more than the atomic bomb and more than the First World War. Nature is the greatest bioterrorist of our world and we should concentrate and expand our efforts in public health with this in mind. Emerging viruses could do for us all, as easily and as quickly, or even more so, than the Great Influenza of 1918.

Table 1: *The global impact of pandemic or potential pandemics of influenza in the 19th, 20th and 21st centuries*

Year	Colloquial name and subtype	Source	Impact
1889	Russian flu	Emerged in Eastern Russia and spread westwards.	Less than 1918 pandemic. Possibly mortality similar to 1957 H2N2 virus?
1918	'Spanish flu' (H1N1)	Possibly emerged from swine or avian host of a mutated H1N1 virus in Europe.	Pandemic with 50 million deaths globally.
1957	'Asian flu' (H2N2)	Mixed infection of an animal with human N1N1 and avian H2N2 virus strains in Asia.	Substantial pandemic. 5 million deaths. The 1918 H1N1 virus disappeared.
1968	'Hong Kong flu' (H3N2)	Mixed infection of an animal with human H2N2 and avian H3Nx virus strains in Asia.	Substantial pandemic. 2 million deaths. The 1957 H2N2 virus disappeared.
1977	'Russian flu' (H1N1)	Source unknown, but virus is almost identical to human epidemic strains from 1950. Reappearance detected at almost the same time in China and Siberia. Probably a laboratory escape.	Benign pandemic, primarily involving persons born after the 1950s. H1N1 virus has co-circulated with H3N2 virus in humans since 1977. This combination could prevent a new pandemic but this should not be relied on.
1976	'Swine flu' (H1N1)	US/New Jersey. Virus enzootic in US swine herds since at least 1930.	Localised outbreak in military training camp, with one fatal case.
1986	H1N1	The Netherlands. Swine virus derived from avian source.	One adult with severe pneumonia.
1988	'Swine flu' (H1N1)	US/Wisconsin, Swine virus.	Pregnant women died after exposure to sick pig'

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