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Review

Influenza is now a preventable disease

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Abstract

The world is waiting with apprehension for the predicted pandemic of H5N1 (avian) influenza as an increasing number of countries in Asia, Europe and Africa report cases of influenza in migrating birds. All is not 'despondency', however. Targeted and controlled administration of antiviral drugs, alone or in combination, to contacts and cases, together with well tried public health measures, should slow down the spread of the infection and allow time for vaccines to be developed, thus preventing a worldwide pandemic of the type that occurred in 1918.

Keywords: Influenza virus; Antiviral agents

Nature is a powerfully capricious killer and on the Richter scale of disasters must be near the top, capable of exceeding by many times the killing power of the two 20th century wars in Europe as well as the atomic bomb attacks on Japan. Nowhere is this unrepentant power more obvious than in the world of infection, and at the top of the infection list is pandemic influenza 1918 [1–2].

A recent study of the reproductive number (RO) of the 1918 influenza virus suggests that, unexpectedly, it may have been quite low, not exceeding three persons infected from a single case. This would place pandemic influenza not far above smallpox and Severe Acute Respiratory Syndrome (SARS). However, this unexpected theoretical analysis, if it is not flawed, gives us more practical opportunities to break the chain of infection of a pandemic using antiviral drugs and vaccines in association with well tried techniques such as quarantine (social distancing) basic hygiene and masks. Fortunately, there are now two classes of antiviral drugs, the neuraminidase inhibitors (NIs) such as oseltamivir and zanamivir, and the older M2 blockers such as amantadine and rimantadine [3–8].

The World Health Organization (WHO) has recently predicted that the world is on the brink of a global outbreak of influenza. At the same time there is an opportunity to prepare thoroughly for the pandemic and the chance must not be missed. Certainly the current situation looks dangerous, with the influenza A virus H5N1 present in poultry in 13 countries in Southeast Asia as well as in Turkey, Russia, Greece, Italy and Romania, and in Africa. There have been a total of 192 human hospitalised cases and 105 deaths in Southeast Asia and Turkey.

Molecular analysis of over 2000 avian influenza virus genes has identified gene 8,NS1 as an important determinant of virulence [9] in addition to HA gene.

The current anti-pandemic strategy is to identify new outbreaks of infection in chickens and to ring-fence the area, killing all birds. In China, some 15 billion doses of vaccine are also being used for poultry and in addition to date 200 million birds have been killed. These approaches reduce human and infected bird contact. Targeted use of oseltamivir, or another NI, in a post-exposure or straightforward prophylactic manner in human contacts, once the virus shows clear signs of human-to-human spread, could prevent a pandemic emerging from its source [10].

The latter analysis has shown that in a modelled pandemic epicentre in Thailand, the geographical application of 3 million doses of oseltamivir, or another NI, could prevent spread, but only if started within 10–14 days of the outbreak when the number of human cases would be ca. 50 and the RO of the virus would be low.

To understand the disease, we have to go back to the last Ice Age 12 000 years ago. At that time the human population

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density was too low to sustain influenza, which requires a continual person-to-person spread. At that point in our history, influenza was a disease of birds. Only in the next 1000 years or so would there be sufficient people in the world for the virus to spread, and at this stage we believe it jumped from birds to humans. Ever since then the main reservoir of the virus has been birds, mainly the continent-crossing and migrating, geese and ducks. Often the virus causes a silent infection in the birds with no disease, i.e. they are silent carriers. Unlike in humans, in birds the virus infects the gut as well as most other organs in addition to the lungs, and birds excrete the virus in droppings.

At present, H5N1 presents the greatest threat since it has proven lethality for humans, domestic chickens, ducks, geese cats and tigers [11,12]. It has spread to 13 nations in Southeast Asia and to Europe and Turkey as well as to Africa. The WHO has urged all 250 countries in the world to recognise the threat to public health, to produce an action plan and then to invest in a stockpile of the old [11] and newer antivirals [13–18] as well as H5N1 vaccine. However, fewer than one-half of the countries of the world have an influenza action plan. Most European Union (EU) nations have a plan of some description, whilst nearly one-half have stockpiled antiviral agents or are seriously considering an investment in these drugs.

It is expected that antiviral agents will have their main role for the first wave of influenza, of what is expected to be a multiwave attack. This should buy time for the production of vaccines. H5N1 vaccines are already under development. Most EU governments that have stockpiled NIs have chosen oseltamivir, but other options include zanamivir and the M2 blocker amantadine. Strategic stocks will be held for one-quarter of the population on the basis that a 25% clinical attack rate was typical of the later pandemics of the last century. Both the NIs and amantadine can also be used to prevent infection, and an additional sensible approach is to use post-exposure prophylaxis. When the virus is introduced into a family or workplace, the index case is treated (two 75 mg tablets per day), whilst contacts are given prophylaxis (one 75 mg tablet per day).

Clinical trials have shown a protective efficacy of ca. 80% for both NIs [8,14]. However, in the UK the strategic stockpile will be used almost exclusively for therapy and administered within 24–36 h of the onset of symptoms, at which time NIs have been shown to reduce symptoms, virus excretion and complications of influenza [8,15–18].

One potential plan in the UK to enable rapid access to antiviral agents, and therefore successful clinical use of the drug, is to bypass doctors' surgeries (offices), which could become a source of infection and also transmission, and to distribute the antiviral drugs at special pharmacies. This plan could also utilise a rapid diagnostic kit to ensure that the drugs are not wasted on non-influenza patients. The NIs could also be used prophylactically for a small percentage of frontline healthcare staff who may be exposed repeatedly to the virus in the course of their work.

The first treatment of patients suffering from life-threatening H5N1 infections in Vietnam [19] showed that oseltamivir can significantly reduce the quantity of virus in patients, even when given late in the course of infection, and patients with diarrhoea where the drug may be poorly absorbed and that the lowered virus titres correlate with survival. A drug-resistant mutant was identified in two of eight treated patients, but studies with other NI-resistant mutants have shown that they are less pathogenic and less contagious, at least in animal models. Not unexpectedly, the whole class of NIs are an acknowledged and major component of Europe's influenza pandemic plans, but the plethora of NI compounds together with the M2 blockers indicate that drug combinations could provide a back-up during widespread use in a pandemic.

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