The threat of a new influenza pandemic – are we doing enough?

Avian influenza is the most recent of a series of pandemic diseases that have terrified the world over the centuries. Advances in medical science have, however, given both the medical community and the public at large a feeling of invulnerability – a feeling that is misguided to say the least. The 1918 pandemic killed 20 - 40 million, more than died in World War I or in 4 years of the 'Black Death' plague of 1347 - 1351.[1] If H5N1 becomes pandemic it has the potential to kill millions of people in weeks to months, more even than have died from AIDS over the last 15 years. It is an event for which we in South Africa are grossly under-prepared and against which will have little defence.

Intermittent pandemics of influenza A virus, caused by antigenic shift (in which humans are exposed to a novel strain against which we have no immunity), have been documented since the 12th century.[2] These are classified according to their haemagglutinin (H) and neuraminidase (N) side-chains (of which there are 16 and 9 respectively), and according to their 'formidableness', a term used to describe the threat that this virus represents to the community.[2] Whether it is formidable or not is determined by its transmissibility, its pathogenicity and its ability to evade immune defences.

Most avian strains are of low pathogenicity, and the H7N7 strain that recently emerged in Holland is an example of this type.[3] In contrast H5N1, which first appeared in Hong Kong in 1997, is a highly pathogenic variety. In the 1997 outbreak 18 previously healthy young adults were infected; 14 presented with acute viral pneumonia and 6 (30%) subsequently died.[4] At that time a pandemic was probably delayed by the destruction of the entire domestic bird population of Hong Kong. In 2003 the Z-strain of H5N1 appeared. It has increased virulence, inducing 10 times the pulmonary inflammatory response of H1N1, is pathogenic to a larger number of species and is resistant to amantidine and rimantidine.[5] H5N1 has now been isolated from both domestic and wild bird populations and has most recently been identified in Turkey and Romania, probably spread by migratory geese, moving it firmly out of the South-East Asian arena and increasing world concern about a pandemic.

The prerequisites for the development of a pandemic are that there should be a novel virus, that it should be able to cross the species barrier and cause virulent infection, and finally that there should be efficient human-to-human transmission.[6] The first two criteria have been met and the next, mutation to a form that readily attaches to human respiratory tract receptors, would occur as a result of spontaneous mutation or gene reassortment from co-infection of a pig or human with H5N1 and human influenza. Genetic sampling of virus isolated from Turkish victims show that it has already mutated the haemagglutinin protein responsible for attaching to cells prior to infection. This allows it to bind more easily to sialic acid moieties on cell surfaces and in so doing confers enhanced ability to attach to human cells.[7,8]

At the time of writing (30 January 2006) there have been 152 confirmed cases with 83 (54.6%) deaths in China, Indonesia, Vietnam, Cambodia, Thailand and Turkey.[9] In the event of a pandemic, global mortality estimates vary from 40 million to in excess of 200 million, affecting not only the traditionally vulnerable groups, the old, sick and very young, but also the fittest, most economically active portion of the population. In the 1918 pandemic half of those who died were aged between 18 and 40 years and the age-specific mortality was highest for those in their teens to the 3rd decade.[10] The Centers for Disease Control estimates that 30% of the world's population will be infected, 8% of these will require hospitalisation and 1% will die. This is a conservative estimate based on the assumption that sufficient hospital beds and antiviral medication will be available, that health care workers will not succumb and will remain on duty and that at least a portion of the population will have access to vaccine. Considering that South Africa's health system is already overloaded, that a large proportion of our population is immunosuppressed and that no plans have been made for the protection of health care workers, the mortality is more likely to be similar to or in excess of the estimated 2.5% mortality rate in 1918, translating to the death of 1 000 000 South Africans.[11]

Vaccine is, according to the World Health Organization, the single most important intervention, but no country will have adequate supplies initially. The yearly global capacity of 300 million doses of regular influenza vaccine is inadequate to meet expected needs during a pandemic and cannot be rapidly augmented.

It would be necessary to vaccinate 25 - 30% of the population to have an impact on the spread of the disease, and vaccine is unlikely to be available early in South Africa given that 90% of production capacity for all influenza vaccine is concentrated in Europe and North America in countries that account for only 10% of the world's population. Whereas the USA has contracted two companies, Chiron Corporation and Sanofi Aventis, to develop and produce vaccine for the US market, South Africa has no vaccine production capacity and no intention to rectify this situation despite the availability of the necessary expertise locally.

The situation with regard to antivirals is equally dismal. The neuraminidase inhibitors, oseltamivir and rimantivir, reduce

the period of symptomatic illness of seasonal influenza, are active *in vitro* against H5N1 and are likely to be of benefit if taken within 12 - 24 hours after the onset of symptoms or if used for prophylaxis by high-risk groups such as health care workers.[12,13] Mathematical models indicate that a stockpile capable of treating 20% of the world's population would result in a mortality reduction of 53%.[14,15] While the rest of the world's nations scramble to purchase huge stockpiles of the orally available oseltamivir from Roche, it has not even been registered by the Medicines Control Council in South Africa. So-called 'fast tracking' only reduces the delay prior to registration to 9 - 12 months, so order-to-delivery time, already more than 18 months, will be enormously extended. Roche will not guarantee supplies to countries that do not order and stockpile prior to a pandemic.

The WHO has produced a valuable document detailing how nations should prepare for the pandemic.[16] The USA has allocated some $7.1 billion to prepare for the pandemic, only $250 million of which is to be used to assist foreign nations. It is likely that most of this would be diverted to South-East Asia, the most likely site for a pandemic to begin. In contrast, South Africa's current level of preparedness is virtually zero and virtually no funds have been made available.

What needs to be done? First and foremost in importance is political commitment in the form of finance directed towards access to and production of both vaccine and antivirals and towards education of a blissfully unaware medical community and public at large. Protocols should be developed for the distribution of available antivirals, similar to planned rationing and distribution of vaccine in the USA. First on that list, anticipating a high level of social disruption and heavy demands on health care services, would be police, military, front-line health care workers and mortuary attendants.

Plans must be developed to limit spread in the community. Containment similar to that of SARS will not be possible; influenza is far more infectious and transmission occurs before the development of symptoms. Preparations should be made for school closures, restriction of human-to-human contact and limitation of mobility within communities and the country as a whole. It is possible that transmission may be limited by wide distribution of masks, preferably the N95 type, and these should be stockpiled now. Preparations must be made for stopping all 'cold' procedures and the training of all medical staff must be directed toward self-protection, management of patients and limitation of the effects of the disease. It is not ethical to abandon patients despite the grave danger faced by all front-line health care workers; however, it is likewise incumbent upon government and the Department of Health to do all in their power to ensure that staff are protected.

Given government's proven lethargy with regard to the AIDS crisis, large employers should consider protecting their own employees by developing response plans similar to the national recommendations of the WHO.

Because we are so defenceless at present, if the pandemic were to occur soon consideration should be given to the practice of a '*cordon sanitaire*', so successfully utilised in medieval times in city-states such as Venice and Genoa. The economic consequences of isolation, in particular the closure of international airports, would be negligible in comparison to the effects of a full-blown pandemic. This is not as unrealistic as it may seem. Australian foreign minister Alexander Dowling has already stated that his country might have to close its borders to protect itself from a pandemic.[17] This is not a call to panic; it is a call to action, directed specifically at our health authorities.[18] Their prompt action has the potential to save hundreds of thousands of lives, perhaps even their own, as no one will be spared the scourge of this new plague.

Many of these thoughts have been expressed previously in an article published in the *Adler Museum Bulletin* (2005; **31:** 5-8).

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