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Journal of Hospital Infection (2007) **65**(S2) 10–13

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Avian influenza and the threat of the next human pandemic

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KEYWORDS Influenza; Avian; Pandemic

Avian influenza or 'bird flu' is causing increasing concern across the world as experts prepare for the possibility of the next human influenza pandemic. It is 38 years since the last influenza pandemic in 1968; a period of time close to the longest recorded interval (39 years) between the 1918 and 1957 pandemics.

In inter-pandemic periods, influenza is predominantly a winter disease in both the northern and southern hemispheres.[1-7] The emergence of a pandemic virus is not controlled by seasonality to the same extent.

Of the three types of influenza virus, only influenza A has ever been shown to have the capacity to cause pandemics. Influenza A viruses exist as many antigenically distinct subtypes in nature. Influenza B is mainly responsible for outbreaks of respiratory illness among school children or in nursing homes, and influenza C is but one of the 150 or so viruses which are responsible for the common cold.

Influenza A caused three well-documented pandemics in the twentieth century, in 1918–19 (subtype A/H1N1[8,9]), 1957–58 (A/H2N2[10]) and 1968–69 (A/H3N2[11]). Retrospective serological analysis has indicated that A/H2N2 is likely to have been responsible for a pandemic which began in 1889, and that a mild pandemic in 1900 may have been caused by A/H3N8.

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In order for an influenza A virus to be capable of causing a pandemic it must fulfil four criteria: to represent a new A subtype where either the haemagglutinin antigen is unrelated to its immediate (pre-pandemic) predecessor (e.g. H2) or it is almost entirely novel to humans (e.g. H5); there must be little or no pre-existing immunity in the population; it must cause significant clinical illness; and be able to spread efficiently from person to person.

Analysis of the excess- and age-specific mortality caused by the 20th-century pandemics reveals a pattern so variable it is impossible to predict these features for a subsequent pandemic. Excess mortality varied from an estimated 40–50 million worldwide in 1918–19 to 1 million worldwide in 1957–58 and 1968–69.[12] In terms of excess mortality, the latter two pandemics were similar to later years (e.g. 1976) when severe seasonal influenza activity occurred over the winter season.[13,14]

The majority of influenza deaths in inter-pandemic years are in the elderly, with some in infants and young children.[15,16] This pattern occurred in England and Wales during the first wave of the 1918 pandemic, however during the second wave of that pandemic the greatest mortality was in 25–29 year-olds.[17] Similar trends were observed during the 1957–58 and 1968–69 pandemics, although to a far lesser degree. While the majority of excess deaths during these two pandemics occurred among elderly persons, the relative increase in deaths was greatest among young adults.[18-21]

Currently highly pathogenic avian influenza (HPAI) A/H5N1 has infected and killed poultry and

wild waterfowl across Southeast Asia, parts of Africa and Eastern Europe, with some associated human infections.[22,23] At the time of writing, HPAI A/H5N1 has been responsible for over 260 human infections, of which over 150 were fatal. While it is by no means certain that this virus will cause the next human influenza pandemic, most experts predict that the most likely source of the next pandemic will be Southeast Asia and that A/H5N1 is currently a strong contender.

The viruses responsible for the previous five pandemics have all been of H1, H2 or H3 subtypes, and while there is evidence that the 1918 pandemic was due to an influenza virus of avian origin,[24] there is no evidence to date that the influenza A/H5 haemagglutinin protein has ever been responsible for a previous influenza pandemic.

The first human cases associated with the current outbreaks were reported in Vietnam in December 2003. Subsequently, a pre-dated case was reported in China, in a 24-year-old member of the military based in Beijing in November 2003.[25] Human cases of A/H5N1 in increasing number have since been reported from countries across the world with the majority of cases in Indonesia and Thailand. Almost all such cases have been attributed to direct exposure to infected birds, although limited, unsustained person-to-person spread cannot be excluded in a few cases in Indonesia and Thailand.[26,27] All confirmed cases are reported on the website of the World Health Organization [http://www.who.int/csr/disease/avian_influenza/en/].

These features mean the world is in World Health Organization (WHO) Pandemic Alert Phase 3: human infection(s) with a new subtype, but no person-to-person spread, or at most rare instances of spread to a close contact. Progression to Phases 4 and 5 will be triggered by small and then larger clusters of human cases, with limited and localised person-to-person spread. Phase 5 indicates a substantial pandemic risk and is followed by Phase 6 when there is "increased and sustained transmission of a pandemic virus in the general population".[28]

Countries across the world are preparing for cases of A/H5N1 in poultry or wild birds, human cases of A/H5N1 and for the next pandemic (whatever the eventual subtype). The over-arching UK pandemic contingency plan has been developed by the Department of Health, based upon the global WHO plan.[28] It describes the UK strategy of considering a broad range of measures: antivirals (of which the UK has now acquired 14.6 million treatment courses); non-pharmaceutical interventions such as hand washing; voluntary isolation of cases; effective handling of contacts; and limiting non-essential travel and mass gatherings of people to minimise the impact of the pandemic while a vaccine is developed against the pandemic virus.[29]

The UK pandemic contingency plan (available at http://www.dh.gov.uk) is supplemented by many other plans specific to other organisations and government departments, such as the Health Protection Agency (available on the HPA website at http://www.hpa.org.uk), and by specific guidelines for care settings. Guidance is also being developed for non-medical care settings, such as schools, local authority domiciliary services, prisons, the emergency services and care homes. These pieces of guidance and others are considered as 'living documents' to be reviewed and updated as the situation develops and as knowledge and understanding about the threat posed by A/H5N1 advances.

The main defence against pandemic influenza is a vaccine matched to the pandemic strain. Development of such a vaccine would take at best four months from identification of the strain responsible for the pandemic, and more realistically six months until there were sufficient stocks available to start using the vaccine. Even then, vaccine supplies are likely to be limited for several further months.

While the pandemic vaccine is being developed, other interventions, such as neuraminidase inhibitor antivirals, will be used to try to mitigate the impact of the virus. The UK currently has a stockpile of oseltamivir (Tamiflu®) sufficient to treat one quarter of its population. The World Health Organisation also has a stock of oseltamivir available to use to try to contain the first outbreaks of human pandemic influenza at the source, likely to be in Southeast Asia.[30] Neuraminidase inhibitors inhibit viral replication, in particular the release of newly formed virions from an infected host cell, therefore they must be taken as early as possible following infection, certainly within the first 48 hours of becoming infected, in order to be effective.

In addition to antivirals there are a variety of different non-pharmaceutical interventions which are being considered, such as travel restrictions, school closures and community isolation. These measures will not prevent a pandemic, but may delay its spread.

Imposing international travel restrictions would intuitively seem like an effective means to reduce and/or delay spread of a pandemic virus. However, modelling has indicated that such measures are unlikely to delay an epidemic significantly.[30,31] Border restrictions and/or internal travel restrictions

are unlikely to delay spread of the pandemic by more than 1–2 weeks if 90% effective, and by only 2–3 weeks unless more than 99% effective.[30]

Interventions to reduce local transmission of influenza are likely to be more effective at reducing the rate of global spread and less vulnerable to implementation delays than air travel restrictions.[31] Furthermore, entrance screening at airports is unlikely to be effective at preventing or delaying an epidemic, as most of those who board a flight incubating influenza would not display symptoms until after arrival and so would not be prevented from entering the country.[32]

Implementation of school closures is also being considered by many governments. Although this has had varied success in the past, recent modelling work indicates that while school closure during the peak of a pandemic might reduce clinical peak attack rates in children by up to 40% and slow the epidemic spread to some degree, it has little impact on overall attack rates across other age groups.[30] Even with school closure it is important to ensure that children do not then meet in informal networks outside of school, thereby negating any positive effect.

Most experts agree that influenza is transmitted predominantly via large droplet spread and contact spread.[33,34] However, opinions are sharply divided over the additional role which might be played by aerosol spread. The evidence base around this particular aspect of influenza biology is scanty and in need of further definitive work, a feature which makes preparing for a pandemic of influenza particularly challenging.

The discussion about the use of surgical facemasks and respirators by healthcare workers and the general public is ongoing across the globe. Current UK guidance advises the use of surgical masks for healthcare workers dealing with symptomatic patients and respirators (standard FFP3) when undertaking aerosol-generating procedures.[35] Additionally it is recommended that, in some circumstances (e.g. in hospital waiting areas), symptomatic patients wear surgical masks.

Although the human cases of infection with influenza A/H5N1 which started in Southeast Asia are of concern, it is the risk that the same virus might evolve to produce the next pandemic which is the major public health threat. Pandemic planning continues to evolve, develop and be modified as more information on the developing A/H5N1 situation and our understanding of influenza becomes available. We will never be able to truly predict which interventions are going to be most effective, until we use them during a pandemic.

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