Scientific Summary of Pandemic Influenza & its Mitigation

Scientific Evidence Base Review

Science Summary

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Scientific Summary of Pandemic Influenza and its Mitigation

Scientific Evidence Base Review

Prepared by the Pandemic Influenza Preparedness Team, with expert input and advice from the Scientific Pandemic Influenza Advisory Committee (SPI). The objective of this paper is to synthesise the findings in all twelve of the specialised scientific evidence base papers developed by the Department of Health (see 'References') to inform and underpin the policy content of the 2011 UK Influenza Pandemic Preparedness Strategy. In most cases, these specialised evidence base papers only examined scientific literature published up until the end of June 2010. This document thus represents a contemporary summary of the evidence base for pandemic influenza and its mitigation as of July 2010. It is anticipated that further studies from the 2009 H1N1 pandemic will be published over the course of 2011 and 2012. The summary will therefore be updated periodically to reflect any additions to the scientific literature that might alter any its conclusions.

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Executive summary

Pandemic influenza

Influenza pandemics appear to have occurred rarely and randomly throughout human history (see Annex A). Historical evidence indicates that the timing, severity and duration of each episode can be variable and unpredictable. There have been four recorded pandemics of influenza during the past 100 years: in 1918, 1957, 1968 and 2009. 1918 was by far the most serious event, causing an estimated 200,000 deaths in England and Wales, and some 50-100 million worldwide (see Annex A).

Although much has been discovered about pandemic influenza, there remain considerable levels of uncertainty in the scientific evidence base. However, it is known is that influenza infection is usually caused by the 'influenza A' type of virus (see Annex B). Crucially, influenza viruses are also capable of infecting animals, including mammals, poultry and wild migratory birds. This provides both a large reservoir for influenza viruses, allowing novel strains to emerge, and a vehicle for the transport of such novel influenza strains around the globe.

Once a particular strain of influenza virus enters the human body during infection, the immune system attempts to use the three-dimensional structure of viral proteins to recognise it as "foreign" (see Annex C). As a result, the immune system can mount a defensive response against that particular viral strain, retaining the ability to react against that strain should it subsequently be encountered (see Annex D).

However, influenza viral strains are constantly changing and evolving in relatively subtle ways. This means that the human immune system may mount only imperfect immune responses to those previously-encountered strains as they continue to alter over time. The net result of this "cat-and-mouse game" is seasonal influenza, typically occurring in the winter months in temperate climates such as the UK (see Annex E).

Rarely, however, a radically-altered strain of an influenza virus emerges to which human populations have little or no immunity. Should that strain also be efficiently transmitted from human-to-human and have the ability to replicate and cause disease in humans, then conditions may favour the occurrence of a pandemic.

Box (i): Glossary

ANTIBODY: Proteins made by B-lymphoctyes that recognise and bind to viral antigens
ANTIGEN: 3D stretches of protein used by immune system to identify viral strains.
ANTIGENIC DRIFT: The accumulation over time of mutations in viral antigens that can lead to the immune system losing the ability to recognise those antigens as 'foreign'.
ANTIVIRAL DRUG: Pharmaceutical that inhibits viral replication and spread.
CASE FATALITY RATIO (CFR): the proportion of the population who develop symptoms during an influenza outbreak and who subsequently go on to die as a result of that infection.
CLINICAL ATTACK RATE (CAR): the proportion of the population who develop symptoms, ranging from severe to mild, during an influenza outbreak.
CYTOKINE STORM: Hyperactive immune response to a viral infection that can lead to death.
CONTAINMENT: The act of attempting to prevent a viral outbreak from spreading further.
CROSS-PROTECTION: The ability of an immune system response against one specific viral strain to target additionally other viral strains.
CROSS-REACTIVITY: The ability of an antigen to induce an immune response that interacts additionally with other antigens.
EXCESS MORTALITY: The number of deaths that occur during an outbreak and above that expected for the time of year.
GENOME: The genetic constitution of any organism, including viruses.
HAEMAGGLUTININ (HA or H): Viral surface protein used to gain entry to host cells.
HERD IMMUNITY: Protection from infection brought about when a high proportion of the population is immune.
HOUSEHOLD PROPHYLAXIS: Post-exposure prophylaxis of household contacts with antiviral drugs.
IMMUNE: The state of a person that is protected from a specific type of infection.
IMMUNE SYSTEM: Body's defense mechanism against 'foreign' antigens, including those from viruses, bacteria, fungi, parasites and cancer cells.
IMMUNISATION: Manipulation of the immune system to confer, or bolster, its ability to protect.
MODELLING: Theoretical system, based on complex mathematics, used to simulate pandemic scenarios.
MITIGATION: Strategy to delay the spread, or moderate the severity or extent, of a pandemic.
NEURAMINIDASE (NA or N): Viral surface protein used to release newly-synthesised viral particles from host cells.
OSELTAMIVIR: Antiviral drug, marketed by Roche Pharmaceuticals under the trade name Tamiflu®, that acts by inhibiting Neuraminidase activity and thus blocking viral spread.
PANDEMIC: Worldwide epidemic of a disease.
PANDEMIC-SPECIFIC VACCINE: Vaccine developed against the antigens of the specific viral strain responsible for the pandemic.
POLYMERASE (PB1): Protein of virus used to replicate new, additional copies of itself following infection of a host cell.
POST-EXPOSURE PROPHYLAXIS: Use of antiviral drugs to prevent infection *after* exposure to infected contacts.
PRE-EXPOSURE PROPHYLAXIS: Use of antiviral drugs to prevent infection *before* exposure to infected contacts.
PRE-PANDEMIC VACCINE: Vaccine developed, ahead of a pandemic, against antigens of a viral subtype.
PRIME-BOOST: Vaccination strategy whereby two different types of vaccine, both raised against the same antigen, are given sequentially in order to maximise the chances of inducing a robust immune response against that antigen.
PRIMING: Initial exposure of the immune system to an antigen, before subsequent exposure ('boosting') that leads to more robust immune system responses.
PROPHYLAXIS: The prevention of infection.
REASSORTMENT: The swapping of genomic segments between different subtypes during co-infection of a host to create a potentially-radically-altered novel viral subtype.
***R* (REPRODUCTION NUMBER):** The number of people that an infected individual goes on to infect.
SEROLOGY: The study or diagnosis of blood (eg assessment of antibodies circulating in the blood).
SHEDDING: Release of newly synthesised viral particles from an infected host.
SPI: Scientific Pandemic Influenza Advisory Committee; provides scientific advice to the UK Government on pandemic preparedness and related issues
SUBTYPE: Viral strain classified by the versions of Haemagglutinin and Neuraminidase that it possesses.
SURVEILLANCE: Capture of data to understand the characteristics and impact of an influenza outbreak.
TRANSMISSION: Viral spread via its replication in infected host cells following exposure to infected material.
VIRULENCE: The capacity of an infectious agent to infect and cause illness.
WHO: World Health Organization.
ZANAMIVIR: Antiviral drug, marketed by GSK Pharmaceuticals under the trade name Relenza® that inhibits Neuraminidase activity, thus blocking viral spread.

Mitigation strategies

Because a novel influenza viral strain could arise at any point in time and in any location; it is not considered feasible, at present, to prevent such a strain occurring in the first place. It is also considered highly unlikely to be able to "contain" such an outbreak at source, which would most likely be overseas, perhaps in Southeast Asia based on historical analyses (but see also Section 1). As would most likely be the case with a newly-arising pandemic that was spreading through the UK, multiple and parallel cases of infection would have already been imported from initial overseas epidemics.

There is, therefore, no scientific rationale to support the notion that such a pandemic in the UK could successfully be "contained" by currently-available interventions. This would be especially true where the severity of infection was mild, such that many infected people did not seek care and, if found by contact tracing, did not meet the case definition for laboratory testing, so were never diagnosed and, hence, never treated, nor their contacts traced.

Instead, once a pandemic is present in the UK and depending on its nature, there is scientific evidence to suggest that its impact might be somewhat suppressed, or mitigated, by the judicious use of a combination of behavioural and pharmaceutical interventions. Depending on the impact of the pandemic, a range of interventions are available. These vary considerably in their potential effectiveness and mode of action. Some impact on the disease by limiting spread of the virus, whilst others reduce the severity of clinical symptoms (see Sections 2 & 3).

Whilst any pandemic can be expected to exert effects across the UK, at any one point in time the outbreak will almost certainly be associated with regional and temporal variability. Therefore, it may be appropriate to deploy certain mitigation strategies in one region, but not others, at any one particular time during the pandemic.

Based on the scientific evidence base summarised in Sections 2 & 3, much of which is still characterised by uncertainty and extensive gaps in our knowledge, a strategy to mitigate the effects of an influenza pandemic would likely involve a diverse range of measures, referred to collectively as "defense-in-depth". This will include some, or potentially all, of the following:

(i) *effective communication to the public, including skills training, to promote habits of stringent respiratory etiquette and hand hygiene, particularly amongst children;*

(ii) *environmental restructuring to consolidate habits of stringent respiratory hand hygiene via cues, prompts and improved access to respiratory and hand hygiene facilities, such as tissues and soap;*

(iii) *increased cleaning of solid surfaces potentially contaminated with virus, such as door handles or light switches;*

(iv) *prophylactic use of antiviral drugs, especially in the earliest stages of the outbreak;*

(v) *widespread treatment using antiviral drugs, in combination with behavioural and communication interventions to encourage pharmaceutical uptake;*

(vi) *widespread antibiotic treatment of secondary bacterial infections;*

(vii) *pre-pandemic vaccination, should an appropriate vaccine exist as the pandemic commences;*

(viii) *pandemic-specific vaccination, initially targeted at at-risk groups, in conjunction with behavioural and communication interventions to encourage vaccine uptake;*

(ix) *the use of facemasks and respirators to protect healthcare workers and encourage their attendance at the workplace;*

(x) *school closures, especially when they can be instigated early in a pandemic that is severe and where transmission is disproportionately high amongst children; &*

(xi) *restrictions on mass gatherings, including travel, especially in the event of a severe pandemic.*

1. The nature of pandemic influenza

'Known knowns'

1.1 Our knowledge base for both pandemic and seasonal influenza can be characterised by (i) established facts ("known knowns"), (ii) recognised areas of uncertainty ("known unknowns") and (iii) complete gaps in our understanding ("unknown unknowns") (Nicoll *et al.* 2010). This knowledge base is continuously evolving and will require regular review, particularly in light of the anticipated publication of further studies of the 2009 H1N1 pandemic over the course of 2011 and 2012.

1.2 Of the "known knowns", seasonal influenza occurs in temperate regions, such as the UK, on an annual basis and predominantly during the winter months (see Annex E). Pandemic influenza, by contrast, is much rarer, but when it does occur, it can be at any time of year. Although there is no universally-agreed definition of what constitutes a pandemic, it is generally accepted that one can occur when:

(i) a novel viral strain appears, usually by genetic reassortment of multiple viral subtypes in an animal, or human, host [see Box (i) Glossary];
(ii) the population has no or low levels of immunity to that new strain;
(iii) the new strain can replicate in humans and cause human disease; &
(iv) the new strain can be efficiently transmitted from human to human.

1.3 Taubenberger and Morens (2009) have proposed that there were 13 pandemics in the last 500 years. Although unpredictable, uncertain and variable by their very nature, certain general trends can be extracted from an examination of previous pandemics and based on the nature of the influenza virus (see Annex A). As well as infecting humans, for example, the virus is regularly transmitted among and between a broad range of animal hosts, including horses, pigs, and birds (see Annex C). This pool of animal hosts supports the continued propagation of existing influenza viral strains. In addition, the capacity of some animals to become co-infected simultaneously with multiple strains of influenza virus provides a "mixing bowl" that can enable novel strains with pandemic potential to emerge.

1.4 In both seasonal and pandemic influenza, outbreaks happen when the Influenza virus alters, most notably, at two kinds of protein on its surface, known as Haemagluttinin (HA, or commonly H) and Neuraminidase (NA, or commonly N) [see Box (i) for Glossary]. These proteins are normally used by the virus to gain entry to and release from host cells during infection (see Annex B), but they also provide a means to classify particular strains of the virus [e.g. the "H1N1" strain was responsible for the 2009 pandemic].

1.5 In the case of seasonal influenza, the H and N proteins of a new strain of virus may have altered slightly in shape, or "mutated", since the previous influenza season. This is commonly known as "antigenic drift" (see Box (i) and Annex D). Consequently, the immune system may only poorly recognise that newly altered viral strain and mount an imperfect defensive response, leading to infection and illness in a proportion of the population. By contrast, in pandemic influenza, a radically altered version of influenza virus emerges, usually expected to be from animal hosts, whereby the human immune system has little or no ability to recognise the new viral strain. For most of the population, therefore, the immune system is likely offer minimal or no protection against that particular viral strain.

1.6 Transmission of influenza virus from human-to-human appears to occur via:

(i) *the respiratory route, for example from droplets and, potentially, aerosols caused by coughing and sneezing;*
(ii) *direct human contact such as handshaking or kissing;*
(iii) *contact with solid objects such as contaminated hard surfaces or tissues;*
(iv) *contact of the face with contaminated hands; &*
(v) *possibly via the eye* (Department of Health 2011 J).

Of these routes, the respiratory one, involving the production of infectious droplets and aerosols during coughing and sneezing, is probably the most significant in terms of terms of transmission (Department of Health 2011 J). Aerosols are gaseous suspensions of fine solid or liquid particles that can remain suspended in the air from prolonged periods; droplets, by contrast, are larger particles that rapidly drop on to the ground or other surfaces (Department of Health 2011 J). Aerosols can therefore travel over greater distances than droplets and, although they may contain less numbers of infectious viruses per particle than droplets, they can penetrate more deeply into the lungs upon inhalation (Department of Health 2011 J). Whilst there is clear evidence for

transmission of the virus via droplets, some evidence suggests that aerosols may represent another important route of transmission (Department of Health 2011 J).

1.7 Significant pandemics have Clinical Attack Rates, that is, the proportion of individuals infected who develop clinical symptoms, in the range of 20-60% (see Annex A and Box A1). By contrast, previous pandemics have showed more variation in their severity, with Case Fatality Ratios, that is the proportion of those infected that die from the disease, ranging from less than 0.01% to over 2% (see Annex A and Box A1). One can also expect significant levels of regional variation in pandemic outbreaks, in terms of dynamics, duration and, to some extent, severity.

1.8 In any influenza epidemic school children have the highest probability of being infected. Typically, for seasonal influenza, fatalities are concentrated in the elderly (see Annex E). By contrast, for pandemic influenza, the age distribution profiles for fatality rates can shift towards older children and younger adults. For example, in 1918 a strikingly high proportion of young adults developed illness and died (see Annex A). There are many possible explanations for this. The elderly may have had some pre-exposure to viral strains that are no longer in circulation, but which share similar antigens to the new pandemic strain, thus conferring some level of immune system protection. It also appears that the immune system of young adults can sometimes over-react to an infection, in a situation known as a “cytokine storm” (see Annex A).

1.9 Pandemics are also, in general, associated with multiple waves of infection. Later waves can be associated with more severe illness, for example 1918, 1957 and 1968 (see Annex A). Significant pandemic events in the historical record have included waves that last approximately 16 weeks, with the peak two weeks of each wave accounting for up to 50% of cases of infection. Historically, the interval between waves of infection has varied from weeks to months, depending on the pandemic and circumstances of the time (see Annex A).

1.10 Over the centuries, pandemics had tended to spread around the globe with increasing rapidity (Taubenberger & Morens 2009). For example, the pandemic of 1729 took three years to traverse the globe (see Annex A). In 2009, the H1N1 pandemic spread globally within eight weeks, reflecting the increased interconnectedness of modern societies and their heavy use of air transport. We can therefore expect any future pandemic to reach UK shores within weeks of the first outbreak anywhere in the world (SPI-M 2010).

1.11 The influenza strain responsible for the pandemic normally reverts to a persistently-circulating strain that causes seasonal influenza once a sufficient proportion of the population develop immunity against that strain (see Annexes D & F). Generally, the strain of influenza responsible for the most recent pandemic replaces the previously-dominant, circulating strain of influenza that has accounted for preceding epidemics of seasonal influenza (see Annex A). Thus, after 1957 the H2N2 strain responsible for that pandemic replaced the 1918 H1N1 strain as the dominant circulating strain of virus responsible for seasonal influenza; after 1968 the H3N2 strain replaced the 1957 H2N2 strain as the dominant circulating strain of virus responsible for seasonal influenza.

'Known unknowns'

1.12 Although it is possible to say that a future influenza strain with pandemic potential *will* develop at some point in future, it is not possible to predict *when* such an influenza pandemic might occur, nor how likely it would be for a pandemic to occur at given point in time.

1.13 A future pandemic could also arise in any location. Many of the previous pandemics through history appear to have originated in China or Southeast Asia. These regions may serve as efficient "incubators" for new influenza subtypes, with year-round circulation of influenza viruses coupled to the close living quarters of humans with swine and poultry. With such logic, they may represent the most likely locations for new influenza outbreaks. However, many potentially-pandemic events have taken place outside of these regions in recent years (see Box A1). Reassorted human-avian viruses have been detected in pigs, for example, in several regions of the world and H7 poultry outbreaks have been seen in Canada and Holland, where one human infection proved fatal (see Annex A). Importantly, the 2009 H1N1 pandemic apparently commenced in Mexico, an event and a location that were not predicted.

1.14 The particular type of influenza strain that will be responsible for a future pandemic also cannot be predicted. Since 1997, there has been much concern regarding H5N1 outbreaks in poultry, with concomitant infections and fatalities in humans, as they have become increasingly common in Indonesia, some parts of Southeast Asia and Egypt. The latter country had the greatest number of reported human H5N1 infections and fatalities in 2010 (World Health Organization data; see also Annex C). Like the "cytokine storms" believed to have been responsible for deaths amongst young adults in the 1918 pandemic, similar hyperactive immune

system responses have been observed in humans infected with H5N1 (see Annex A). Indeed, given the current Case Fatality Ratio of over 50% for H5N1, compared with around 2% for 1918, more severe pandemics than 1918 may be entirely feasible at present, even with 21st century improvements in healthcare and interventions. However, to date, there has been no evidence that Highly Pathogenic Avian Influenza (HPAI; see Annex C), such as H5N1, can convert into a strain capable of readily causing human-to-human transmission, let alone a pandemic. However, there remains a possibility that this situation could arise at any time and so H5N1 remains a major contemporary cause for public health concern.

1.15 In addition, numerous other novel subtypes of influenza could have as great a pandemic potential as H5N1, for example H9N2, H2N2, H7N7 or H7N3 (Taubenberger, Morens & Fauci 2007). Indeed, after H1N1 emerged from swine in 2009, there was renewed recognition of the range of animal reservoirs available to influenza, in addition to the much-publicised avian ones. For example, we still do not understand the origins of the 1918 H1N1 pandemic strain, but there is speculation in the scientific literature that the virus may have emerged from an as-yet unidentified animal host. In addition, given that the viral strains responsible for seasonal influenza tend to replaced by new pandemic strains, future pandemics may well arise from the regeneration of previous pandemic strains that had subsequently disappeared from circulation in humans.

1.16 Despite the relatively "mild" nature of the most recent 2009 H1N1 pandemic, overall threat levels from pandemic influenza have not diminished. Indeed, it is not clear that 2009-like events would show up in the historical record; there may have been many such events. Therefore, the likelihood that a highly virulent human influenza strain could appear has still not changed (Taubenberger, Morens and Fauci 2007). When a future pandemic does arise, uncertainty and unpredictability will be prevalent features, especially during the first few weeks, when surveillance data will be extremely limited. Emerging influenza pandemics will thus be characterised by "known unknowns" (Nicoll *et al.*, 2010) which will require elucidation as soon as possible during an unfolding pandemic. However, some of these "known unknowns" may only be resolved months, even years, after an event and include, but are not restricted to:

(i) genetic and antigenic characterisation of the novel influenza viral strain;

(ii) symptomology of disease caused by the new virus;

(iii) the extent and age profile of pre-existing immunity in the population;

(iv) any differences between age groups in contributing to the spread the virus;

(v) *the rate of asymptomatic infection, based on serological analyses;*

(vi) *the infectivity of the virus;*

(vii) *characteristic secondary bacterial infections;*

(viii) *the identification of "at-risk" groups who, once infected, have poorer outcomes than the rest of the population;*

(ix) *the Clinical Attack Rate;*

(x) *the Case Fatality Ratio;*

(xi) *excess mortality as a result of the outbreak;*

(xii) *the appearance of regional "hotspots" that will shift location over the course of the pandemic;*

(xiii) *the safety, efficacy and effectiveness of pharmaceutical interventions; &*

(xiv) *public acceptance and uptake of behavioural and pharmaceutical interventions; &*

(xv) *the severity, extent and impact of the virus on healthcare, the economy and society.*

'Unknown unknowns'

1.17 Finally, it is worth noting that, based of historical precedence and given the complex nature of pandemic influenza, new events are also likely to feature "unknown unknowns"; elements of the outbreak that had not been anticipated from theoretical considerations, mathematical modelling or analyses of previous pandemic events (cf. Annex A).

2. Behavioural interventions

Behavioural responses in emergencies

2.1 Attitudes and behavioural responses can play a key role in how a pandemic progresses. Behavioural interventions can affect the development of pandemic influenza and are of crucial importance in mitigating the spread and impact of pandemic influenza (Department of Health 2011 D). However, their impact is not uniform across society. Older age, being female, belonging to a non-white ethnic group and higher levels of education, for example, are all associated with a greater chance of protective and avoidance behaviours (Department of Health 2011 D).

2.2 Behavioural science revels that some key principles in communicating risk to the public (Department of Health 2011 C). These involve:

(i) being open and transparent;

(ii) clear and simple communication, including sensitivities to cultural differences;

(iii) acknowledgement of uncertainty;

(iv) using absolute, as well as relative, risk;

(vi) framing ambiguous messages negatively [e.g. 1 in 100 will develop disease; not 99 in 100 will not]; &

(vii) using visual aids wherever possible.

Infection control

2.3 As discussed in Section 1, transmission of influenza virus from human-to-human may occur via the respiratory route via droplets and, potentially, via aerosols; direct human contact; contact with contaminated solid objects; contact of the face with contaminated hands; and the eye (Department of Health 2011 J; Wilschut, McElhaney & Palache 2006; Enstone 2010). The strength of evidence in support of the contribution from each of these routes of transmission for the influenza virus varies and it is also possible that different infected individuals will differ in their transmission abilities (Department of Health 2011 J). For example, infected children or immunocompromised patients may shed much higher amounts of virus than infected adults and so offer greater opportunity for transmission via routes that might not always be used, such as aerosols (Department of Health 2011 J).

2.4 It is possible to limit physically the spread of the influenza virus by appropriate infection control measures. In general, voluntary domestic isolation when a person develops influenza-like symptoms should decrease the number of contacts between that infected person and other susceptible people and thereby reduce spread of infection (SPI-M 2010). It is also possible to curtail the spread of the influenza virus in other situations. In the hospital setting, for example, this can be done by "cohort nursing" those patients believed to be infected with influenza all together in one area (Enstone 2010).

2.5 In the domestic setting, the risk of transmission can be reduced by environmental cleaning of solid surfaces (Greatorex *et al*. 2010). Active ingredients in common household cleaning products, such as bleach, soap or detergent, can disrupt protein or lipid components of the envelope (see Annex B), so that the virus is unable to survive as an infectious agent. In a similar regard, appropriate hand hygiene is an important way to control the spread of infection (Department of Health 2011 H).

2.6 Stringent respiratory etiquette should also be employed to prevent transmission of the virus via coughing and sneezing (Department of Health 2011 H; Department of Health 2011 J). Fresh tissues can act as a physical barrier to virus-containing-droplets and should, therefore, be used on each occasion of sneezing or coughing. To avoid spread of the virus via contaminated tissues, they should be disposed of immediately after use.

Facemasks & respirators

2.7 Both infectious droplets and aerosols can be generated via coughing and sneezing, but also via certain procedures in the healthcare setting, such as tracheal intubation (Department of Health 2011 J; see Section 1). There is limited evidence that use of face masks and/or respirators in the *health care setting* can provide protection against infection with influenza when in close contact with infected patients (Department of Health 2011 G). Some data suggests that mask use is best undertaken as part of a package or 'bundle' of personal protection especially including hand hygiene in both the home and health care setting. However, in the vast majority of studies examined, mask/respirator use was not the only control measure in place or under evaluation. For example, several studies have included hand hygiene either alone or combined with respiratory protection (Department of Health 2011 G).

2.8 Evidence for the effectiveness of masks and respirators to prevent influenza transmission is less compelling for *non-healthcare settings*. All things being equal, masks and respirators would be expected to have similar benefits in protecting a susceptible individual when exposed to a patient with influenza in a setting such as a household (Department of Health 2011 G). However, there are a number of factors that influence the potential effectiveness of a mask/respirator in reducing influenza transmission and some of these would likely differ in healthcare and community settings.

2.9 Firstly, healthcare workers would be expected to receive formal training in the correct use of mask/respirators; although participants in these research studies were instructed in the proper use of a mask or respirator, it may not have been as extensive or re-occurring compared to a hospital setting (Department of Health 2011 G). Training outside of a research study would be even less predictable. Safe use of a mask/respirator is linked to access to hand hygiene facilities before donning and after removal of the device as well as to receptacles for disposal; access to these facilities may be more limited in a community setting.

2.10 Masks/respirators might also have to be worn for much longer periods of time in a household or similar setting where there is the potential for prolonged, regular contact with the infected patient (Department of Health 2011 G). In contrast, healthcare workers' use of masks/respirators is typically episodic; i.e. when they have close contact with a specific patient. Finally, as highlighted by the studies of healthcare workers during the SARS (Severe Acute Respiratory Syndrome) outbreak, compliance with recommended use is a key factor.

2.11 Compliance is difficult to achieve in a healthcare setting despite external prompts (e.g. posting of signs, positioning supplies of masks/respirators at the entrance to patient rooms); compliance in a community setting is all the harder. Even in the context of a clinical trial where one might expect optimal compliance, investigators encountered disappointing rates of adherence (Department of Health 2011 G). Nonetheless, improved compliance and early application of interventions are ways in which effectiveness could be improved.

2.12 Finally, suitable training, early initiation and regular wearing of masks/respirators may improve their effectiveness in healthcare, and household, settings. The effectiveness of masks and respirators is likely to be linked to consistent and correct usage. Thus, equipment cannot be

separated from the behaviours required to use the equipment effectively, and effective behavioural interventions are required to ensure this (Department of Health 2011 G).

Encouraging the uptake of pharmaceutical interventions

2.13 Evidence from many countries suggests that rates of vaccination against H1N1 influenza are sub-optimal amongst health professionals, clinical risk groups, pregnant women, general population and children (Department of Health 2011 F). For all groups rates of intentions to be vaccinated against H1N1 influenza tend to be higher than actual uptake of vaccination. Intentions to be vaccinated tended to change over time with studies carried out in the autumn of 2009 showing lower rates than earlier studies, more comparable to the subsequent uptake of vaccination (Department of Health 2011 F).

2.14 The evidence suggests the following likely explanations for the low intentions and uptake: a perceived lack of susceptibility to developing H1N1 influenza, low levels of concern and worry about the disease and concerns about the safety of the vaccine and its side effects (Department of Health 2011 F). This is in the context of the 2009 pandemic where there was a discrepancy between public perceptions of the predicted severity of the pandemic and its ultimate relatively "mild" manifestation, and considerable discussion in the media about the safety of the vaccine. There was evidence that having been vaccinated in the past against seasonal influenza may increase future uptake of vaccination against pandemic influenza. In addition, organisational factors may have played a role in the rates of coverage in some countries.

2.15 Evidence from studies of uptake of non-pandemic influenza vaccination indicate that interventions likely to be effective include those which communicate the risks posed by pandemic influenza, highlight the benefits of vaccination and address any safety concerns (Department of Health 2011 F). Strategies to do this include highlighting the risk posed by pandemic influenza whilst simultaneously offering tactics to ameliorate this risk (e.g. vaccination). The perceived costs of vaccination can be tackled by reducing the omission bias (a perception that harm caused by action is worse than harm caused by inaction) in order to help to ameliorate safety concerns. In addition, interventions to increase seasonal influenza vaccination in advance of a future pandemic may be an effective strategy to achieve high rates of vaccination against influenza during a pandemic.

2.16 As already mentioned, the evidence suggests that in some countries rates of vaccination against pandemic influenza will fall far short of targets and a review of this area has highlighted psychological factors which are associated with intentions and uptake of vaccination (Department of Health 2011 F). It should therefore be possible, in advance of a pandemic, to develop and implement interventions that are designed to increase vaccination rates. These could include targeting the uptake of seasonal influenza vaccination and also perceptions of risk and beliefs about the efficacy and safety of pandemic influenza vaccinations.

School closures

2.17 School closures can be “reactive”, where the intervention is used once pupils have fallen ill, or “proactive” when there is anticipation of an outbreak amongst children. Epidemiological evidence suggests that school closures can influence transmission of pandemic influenza but that their impact is highly dependent upon their timing (Department of Health 2011 K). Some studies show increases in influenza incidence after schools reopened, suggesting that school closures can reduce transmission under certain circumstances.

2.18 School closures are likely to be more effective if implemented early in the epidemic. However, there is limited evidence available regarding the optimal timing and duration of closure from either epidemiological or modelling studies. A limit at which it is “too late” to close schools has not been demonstrated in the few studies that have, to date, been reported (Department of Health 2011 K).

2.19 Whilst there is evidence that school closures are able to reduce transmission amongst children, no studies from the evidence base investigated transmission specifically amongst adults. However, other evidence suggests that vaccination of schoolchildren against seasonal influenza can reduce mortality in the general population and so a similar effect may be expected from reducing transmission through school closure (Department of Health 2011 K).

2.20 Both epidemiological and modelling studies have found that the peak and cumulative attack rates can be reduced by school closures (Department of Health 2011 K). The extent of these reductions is, however, unclear and likely to depend on many factors including population behaviour, viral transmissibility and age-specific attack rates. Some modelling studies indicate that the pandemic peak could be reduced by as much as 50% by school closures (Ferguson *et al.*

2006; Cauchemez *et al.* 2008; Halloran *et* al. 2008). Modelling studies also suggest that school closures are likely to achieve the greatest reductions in peak incidence and cumulative attack rates if the transmissibility of the causative virus is relatively low and if attack rates are higher in children than in other age groups.

2.21 There is currently insufficient evidence to recommend one particular type of school closure policy over another, for example “proactive" versus “reactive”. There is evidence indicating that both reactive local closures and proactive national closures have had an effect on transmission. However, further research is required to assess the relative benefits of different school closure strategies (Department of Health 2011 K).

2.22 Despite this and the high economic costs associated with this intervention, evidence supports school closure being considered as one component of a suite of potential mitigation measures during pandemic influenza (Department of Health 2011 K). The scientific evidence also indicates that policy should be responsive to the features of a new pandemic virus. For example, where transmission occurs mainly in schools, as it did during the 2009 pandemic, and where the illness is severe, there is stronger justification for school closure than in the situation where significant transmission occurs in adults or where the disease itself shows only limited severity (Cauchemaz *et al.* 2009; Department of Health 2011 K).

Restrictions on mass gatherings, including travel

2.23 There is limited data indicating that mass gatherings are associated with influenza transmission. Some evidence suggests that restricting mass gatherings together with other behavioural interventions may help to reduce transmission, but this would be insufficient to consider restrictions by default in a pandemic (Department of Health 2011 I).

2.24 Most studies of mass gatherings have been limited at a large number of US cities during the 1918 pandemic and have highlighted the difficulty of interpreting what was meant by a “mass gathering” and, for example, whether to include schools, cinemas, theatres and other public places in the term. In general, evidence suggests that these measures had a beneficial effect, especially where implemented early in the course of the outbreak (Department of Health 2011 I). However, these benefits were not universal across all cities. In addition, it was not possible to distinguish the specific effects of mass gatherings restrictions from amongst the broad range of other public health

interventions that were applied.

2.25 Evidence supporting the role of mass gatherings in the transmission of influenza comes from events where there are crowds with high densities, and also where the participants are likely to live close together for prolonged periods, such as large musical festivals (Department of Health 2011 I). In these events, crowded accommodation is also likely to be relatively basic, such as communal camp style living. It seems apparent that events where close contact among participants extends beyond event venues and into accommodation areas are most associated with influenza. Event size *per se* does not seem to be a critical factor.

2.26 A number of studies have consistently demonstrated, over a number of years, that respiratory virus transmission occurs amongst pilgrims attending the annual Hajj in Saudi Arabia, and it is recognized as an issue of international public health significance that could be particularly important in a pandemic situation (Department of Health 2011 I). A significant proportion of pilgrims are affected by symptoms of either an influenza-like illness or an acute respiratory illness with the proportion affected reaching about 40% in some studies. The Hajj is however a unique event with almost three million people converging on a relatively small geographic area for over five days. Crowd density is very high and over-crowding in the living accommodation is common. Given the unique nature of this event the applicability of these findings to other mass gatherings is therefore limited.

2.27 In contrast, there is no convincing evidence that major organised sporting events are associated with significantly increased influenza transmission in those attending the event (Department of Health 2011 I).

2.28 Mathematical modelling suggests that modern international travel would allow a pandemic to spread much more rapidly than even in the 20th century (SPI-M 2010). With the high degree of interconnectivity of the UK with the rest of the world, a pandemic originating in Southeast Asia can be expected spread to the UK within two to four weeks, with a peak of infection occurring 50 days later (SPI-M 2010). Imposition of a 90% restriction on all air travel in such an event would only delay its arrival by one to two weeks, whereas a 99.9% restriction might delay an outbreak in the UK by some two months (SPI-M 2010). However, such restriction of air travel would have substantial social and economic effects, including on food security. Even if it were possible to screen passengers for clinical symptoms before or after travelling, or to even prevent those

infected from travelling, modelling indicates that an outbreak is only likely to be delayed by one to two weeks (SPI-M 2010). In addition, such measures would do nothing to prevent the spread of virus via those individuals with asymptomatic infections.

Work attendance of healthcare professionals during a pandemic

2.29 In order for the health service to run effectively during a pandemic, it is essential that health care professionals are both willing and able to work (Department of Health 2011 E). Paradoxically, whilst they are a central component of the frontline response to a pandemic, they are also likely to be at increased risk of exposure to influenza infection, particularly those subject to aerosol-generating procedures on influenza patients (see Section 1).

2.30 Behavioural evidence suggests that, during a relatively “mild” pandemic such as 2009, most health care professionals will work, though as many as a third may be absent from duty (Department of Health 2011 E). However, there is also evidence that, in a more severe pandemic, only a minority of such staff are likely to be willing to work.

2.31 Demographic and job based factors are associated with health care professional willingness to work. Men, older people, those without dependents, doctors and full time employees are less likely to absent themselves from duties (Department of Health 2011 E). Research also suggests that psychological factors play a part in willingness to work during a pandemic, with fears about safety for self or family being significant, as well as feelings of having a duty to work.

2.32 There is some evidence that absenteeism could be mitigated if effective measures are used to reassure health care professionals about their safety (Department of Health 2011 E). These would include the use of facemasks, respirators and other personal protective equipment in the workplace and the provision of antiviral medication and vaccination for health care professionals and their families.

3. Pharmaceutical Interventions

Antivirals

3.1 The antiviral drugs amantadine, oseltamivir and zanamivir act to block the proliferation of new viral particles from infected host cells and thus limit the spread of the virus (Haaheim 2010; Department of Health 2011 B; Van-Tam 2010; Van-Tam & Gupta 2010). Specifically, amantadine acts by blocking the M2 channel (see Annex B), but circulating strains of influenza virus are commonly resistant to this drug and its widespread use is, therefore, very limited. By contrast, both oseltamivir and zanamivir are a different class of antiviral that act by inhibiting the neuraminidase enzyme (see Annex B). To date, significant levels of resistance to neuraminidase inhibitors amongst circulating influenza viral strains have not been consistently detected, favouring their use in outbreaks of both seasonal or pandemic influenza.

3.2 For healthy adults there is strong, statistically significant, evidence from clinical trials involving seasonal influenza that zanamivir and oseltamivir, given within 48 hours of symptom onset for clinically-diagnosed “Influenza-Like Illness” reduces the time to symptom alleviation by roughly half of one day. In cases where Influenza has been confirmed by laboratory tests, the magnitude of benefit rises to roughly one day. (Falagas *et al* 2010; Department of Health 2011 B). In addition, the likelihood of requiring antibiotics is reduced by 60% if antivirals are given within 48 hours on the appearance of symptoms (Department of Health 2011 B).

3.3 Both neuraminidase inhibitors also appear to be safe and are generally well-tolerated, with the exception of nausea and vomiting associated with treatment and prophylaxis using oseltamivir.

3.4 Whilst the primary purpose of treating those infected is to reduce the severity of an individual’s illness, modelling indicates that treatment of all clinical cases of infection with antiviral drugs may concomitantly decrease the overall clinical attack rate, provided treatment is sufficiently rapid (SPI-M 2010; see Annex F).

3.5 Alternatively, antiviral drugs can be used *prophylactically* to either (i) prevent infections before individuals have been exposed to an infected contact (“pre-exposure prophylaxis”) or (ii) prevent infections after an individual has been exposed to an infected contact (“post-exposure

prophylaxis") (Van-Tam & Gupta 2010). In healthy adults, the effectiveness of zanamivir in preventing laboratory confirmed influenza was in the range of 50-70% across two studies, whereas for oseltamivir the estimated effectiveness was highly consistent at 75%, again across two studies. There is also strong evidence from clinical trials that both oseltamivir and zanamivir are more than 80% effective in preventing laboratory-confirmed influenza in household contacts when prophylaxis is initiated within 48 hours of initial contact (Department of Health 2011 B).

3.6 For a pandemic with similar characteristics to 1918, modelling suggests that the use of post-exposure prophylaxis of household contacts, combined with school closures and the use of antibiotics, could reduce the clinical attack rate by 50% and case fatality ratio by 80% (SPI-M 2010). Further observational data are available from outbreak settings in elderly residential homes and hospitals (Department of Health 2011 B). These estimates of effectiveness are not as consistently high and may reflect 'real life' practical and logistic difficulties associated with outbreak identification and the early application of control measures.

3.7 Little new data from the 2009 H1N1 outbreak on the use antivirals for either treatment or prophylaxis has been published thus far. A small number of observational studies of post-exposure prophylaxis, without control groups and constituting only weak data, have noted secondary attack rates in households or household-type settings that would appear to be lower than historical, seasonal influenza norms (Department of Health 2011 B).

Antibiotics

3.8 Viral influenza infection can result in severe complications, commonly secondary bacterial pneumonia, which can be treated in most cases with antibiotics (Department of Health 2011 A). Both clinical experience and modelling studies indicate that the number of cases of infection, hospitalisations and deaths can be significantly reduced by treating patients with antibiotics during a pandemic (SPI-M 2010).

3.9 Depending on the nature and severity of a pandemic strain of influenza A virus, an increased demand for orally-administered antibiotics in primary care services may occur. However, a more severe pandemic would inevitably cause a higher demand for antibiotics, even if the incidence of influenza-related bacterial pneumonia were low (Payne and MacDonald 1958).

3.10 In secondary care, there is more likely to be an increased demand for antibiotics to be used by the intravenous (or intramuscular) route (Department of Health 2011 A). Co-amoxyclav, macrolides and broader-spectrum antibiotics such as levofloxacin and cefalosporins would be the likely requirement. In a severe pandemic, outpatient injectable antibiotics, such as daily ceftriaxone, may occasionally be used as one-off dosage to assist patients who are moderately to severely ill but not likely to gain admission to hospital.

3.11 The number of patients cared for in critical care services will be limited by availability of facilities. These patients are more likely to require treatment for ventilator-associated pneumonias, with antibiotics such as ceftazidime, meropenem or ertapenem, as well as vancomycin or teicoplanin for MRSA and enterococcal infections (Department of Health 2011 A).

3.12 In the majority of cases, alternatives may be used but for healthcare-acquired infections with highly resistant pathogens, especially if outbreaks were seen, supply problems could occur.

Vaccines

3.13 Vaccines also can potentially affect the course of pandemic influenza (Department of Health 2011 L). Vaccines against pandemic influenza could be used (i) during the inter-pandemic period in anticipation of an influenza pandemic at some point in the future, (ii) in the pre-pandemic period when there is evidence that an influenza pandemic may be arising and/or (iii) during an influenza pandemic.

3.14 Whilst candidate pre-pandemic vaccines can be produced against one (or possibly more) particular strain of influenza virus with pandemic potential, a future pandemic may arise from a very different strain of influenza virus.

3.15 Data suggest that influenza A H5N1 pre-pandemic (and pandemic) vaccines may need to be given in two doses to provide adequate protection in healthy adults (Department of Health 2011 L). Data from clinical trials on the response to vaccination of young children and elderly adults is more limited and very few data are available of the immune response to vaccination of clinical risk groups (Department of Health 2011 L).

3.16 It is not possible to know or predict in advance, the level of cross-protection offered by a pre-pandemic vaccine against a future pandemic virus. However, evidence of cross-reactivity against a wide breadth of virus variants will increase the chances of cross-protection against related strains (e.g. Kash *et al.* 2010; Wei *et al*. 2010a; Wei *et al*. 2010l).

3.17 There is some evidence to suggest that the immune response induced by priming doses of pre-pandemic vaccine may be boosted by vaccination with pandemic specific vaccine potentially years following priming (Stephenson *et al.*, 2008). A single dose of vaccine (especially if formulated with adjuvant) may therefore be enough to boost immunity to protective levels, especially in those with some previous exposure to antigenically-similar strains of influenza (Department of Health 2011 L).

3.18 Vaccination can also have a population-based effect called “herd immunity.” When a sufficient proportion of the population, or “herd”, is immune to infection (either through having experienced infection or through vaccination), protection from infection is conferred on individuals who are not themselves immune to that infection (e.g. Miller *et al.* 2010).

3.19 Herd immunity occurs when the number of susceptibles within the population is so low that the virus can no longer be transmitted effectively, so that *R*, the reproduction number, becomes less than one (i.e. the average infected person transmits to less than one other person before they cease to be infectious, so the prevalence of infection does not increase).

3.20 Vaccination is, therefore, central to the control of influenza in public health programmes because modelling indicates that levels of immunity of 50%, or perhaps even less, across the population would be sufficient to prevent an outbreak of influenza via herd immunity.

3.21 The rapid availability of a vaccine against a novel influenza strain might prevent a national epidemic of the pandemic virus. However, under current manufacturing methods and capacities, a pandemic-specific vaccine is unlikely to be available in sufficient amounts until after the first pandemic wave.

3.22 Experience with influenza A H5N1 vaccines in clinical trials and from the very wide use of pandemic 2009 H1N1 vaccines suggests that the risk of an unfavourable safety profile for a pandemic vaccine seems low, although it cannot be ruled out (Department of Health 2011 L).

3.23 The rate of vaccination uptake amongst the public is crucial to ensuring that appropriate levels of immunisation are achieved (see Section 2 for further discussion).

Combining Interventions

3.24 Modelling studies provide evidence to suggest that it *might* be possible to stop a global influenza pandemic by 'containment' at source (Ferguson *et al.* 2005; Longini *et al.* 2005), if all of the following combination of criteria are met: (i) the initial epidemiological outbreak is rapidly detected, (ii) it is localised to an isolated region of the globe so that rapid dissemination by trade and travel does not occur, (iii) accurate diagnoses can be made quickly and (iv) widespread antiviral treatment can be rapidly deployed (Ferguson *et al.* 2005). In practice this is only likely to occur if the strain in question has high severity such that it causes a cluster of severe illness or death that is big enough to be detected before the virus has spread very far. In the case of H1N1 from 2009, an example of a relatively "mild" pandemic, there were many thousands of infections in Mexico before the virus had even been detected.

3.25 As is more likely to be the case, a pandemic in the UK will occur as a result of multiple, parallel cases of importation of the novel viral strain. In strategies for mitigating the effects of a pandemic, any one intervention, by itself, may be not fully achieve the anticipated outcome for a range of reasons. For example, antivirals may be less than optimally effective should a pandemic viral strain emerge that is resistant to neuraminidase inhibitors. The behaviour of individuals may also change over the course of a pandemic, reflecting the perceived risk (or lack-of-it) from infection by the pandemic virus. This could impact a range of behavioural interventions, from the adoption and maintenance appropriate levels of respiratory and hand hygiene, to acceptance of antiviral medication or uptake of pandemic-specific vaccine. Moreover, the primary purpose of certain interventions may be to target different aspects of the pandemic; the alleviation of clinical symptoms in an individual patient with secondary bacterial infections, for example, via the use of antibiotics versus protection at a population level via mass vaccination with a pandemic-specific vaccine.

3.26 Given the infrequency of real pandemic events, modelling can be used to examine the impact of combining a number of interventions against a future pandemic, as this clearly cannot be tested empirically (Ferguson *et al*. 2006; Germann *et al.* 2006). Overall, such modelling suggests that, depending on the nature and development of the pandemic in question, the most successful

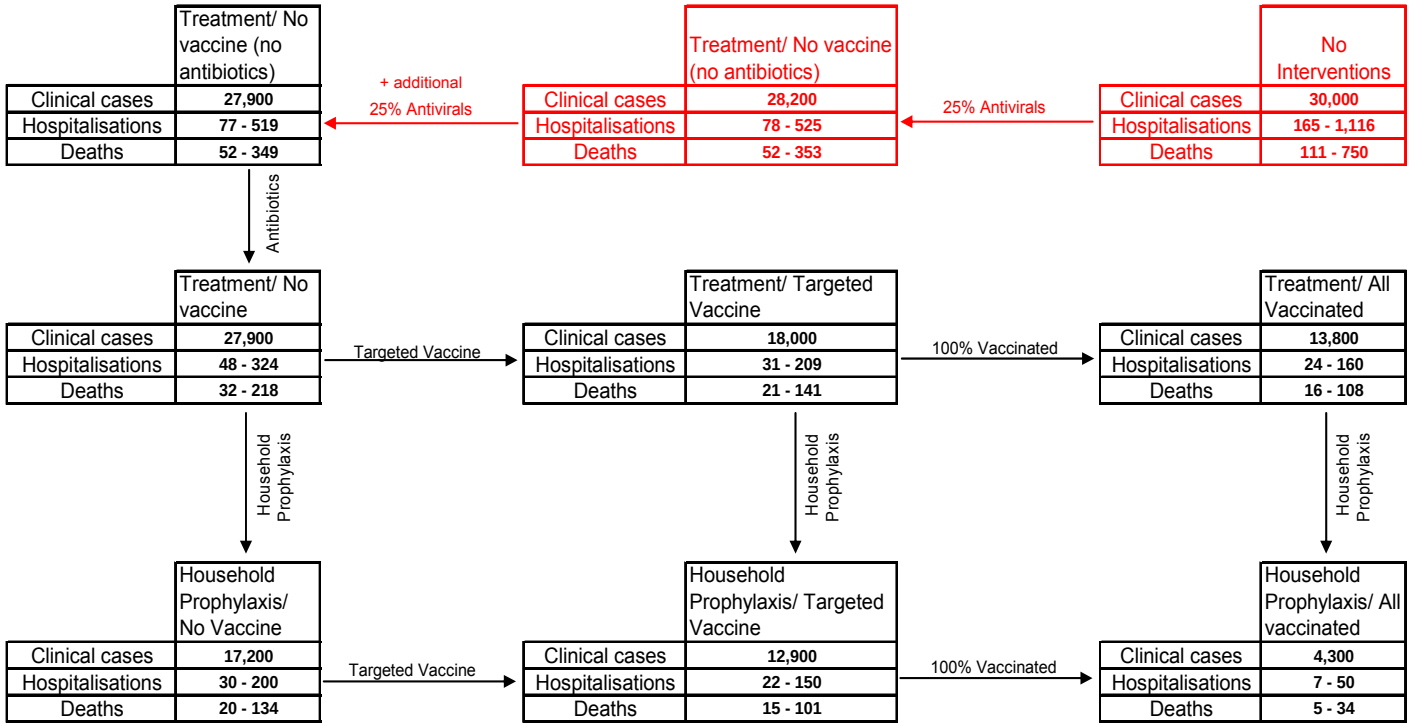
mitigation strategies are likely to involve the combined use of antiviral drugs, antibiotics, vaccines and school closures, all in a background of stringent respiratory and hand hygiene [see Box (ii); SPI-M 2010].

3.27 Thus, there is a range of measures that, when combined, help to target as many different aspects of the pandemic are likely to have the most significant impact on the pandemic. Such a strategy is known as “defense-in-depth”.

BOX (ii): Combining interventions against a pandemic of influenza

Based on a population of 60 million. All figures in thousands. Reactive School Closure is also assumed in the 'Household Prophylaxis' entries.

Number of clinical, hospitalisations and deaths for various countermeasure options with a raw clinical attack rate of 50%



* targeted vaccine at 45% of population

(SPI-M 2010)

Annex A:

Influenza pandemics & related events through history

A1 Pandemics, or pandemic-like events, of influenza appear to have occurred consistently, albeit rarely and randomly, throughout human history, with the timing, severity and duration of each event being extremely variable and unpredictable (Van-Tam 2010). Taubenberger and Morens (2009), for example, have estimated that there were 13 true influenza pandemics in the last 500 years [see Box A1]. Pandemics of the last 100 years are described below. Also included here are brief descriptions of outbreaks that are "sub-pandemic"; that is, events which did in themselves result in a true pandemic but which, nonetheless, may prove to be informative to understanding the development of pandemics of the future.

1918

A2 The first pandemic of the 21st century began in 1918, just as the First World War was drawing to a close (Potter 2001; Hsieh *et al.* 2006; Kilbourne 2006; Taubenberger and Morens 2006, 2009; Sellwood 2010 B). The event is estimated to have been responsible for over 50-100 million deaths, several times more than for the war itself. It remains unknown from where the pandemic originated. Although often referred to as "Spanish flu", the pandemic appears to have occurred in three simultaneous outbreaks in North America, Asia and Europe (Taubenberger and Morens 2009; Sellwood 2010 B). First reported in North America in March 1918, the pandemic was propagated by US troops mobilised to the Western Front in Europe, reaching epidemic levels there within a month. By the end of 1918, the pandemic had spread to North Africa, India, China and Australia. Most countries experienced multiple waves of infection, with later waves being more severe than the first. In the UK, there were three distinct waves (see Box A1); Kilbourne 2006). The first began in spring 1918 and featured high rates of illness but relatively modest death rates.

Box A1: Historical Episodes & Potential Threats of Pandemic Influenza

Year of Outbreak	Scope of Outbreak	Geographical Spread[17]	Viral Subtype[18]	Viral Origin	Epidemiological Features[19]	References (see Notes)
1580	Pandemic	Asia→ROW	Unknown	Unknown	High rates of infection; multiple waves of infection	***1, 2, 3, 4***
1729-33	Pandemic	Russia→ROW	Unknown	Unknown	High rates of mortality; two waves of infection, the second more severe	***1, 3, 4***
1781-82	Pandemic	China→ROW	Unknown	Unknown	High rates of infection, with low rates of mortality	***1, 3, 4***
1830-33	Pandemic	China→ROW	Unknown	Unknown	Two waves of infection; outbreak as severe as 1918	***1, 3, 4***
1889-92	Pandemic	Russia→ROW	H3[20]	Unknown	High rates of infection, with low rates of mortality. Three waves of infection. CAR: 60%; CFR: 0.28%.	***3, 4, 5***
1898-1900	Pandemic	Origin unknown[21]	H3	Unknown	Multiple epidemics in Europe, Pacific and North America.	***3, 4***
1918	Pandemic	Unknown[22]	H1N1	Avian with additional unexplained features[23]	High rates of infection and mortality, particularly in young adults. Estimated global deaths: 50 million. Secondary bacterial infections of the lung common. Three waves of infection in UK, the second most severe. CAR: 25%; CFR: 2.5%.	***1, 2, 3, 4, 6, 8, 9***
1947[24]	Pandemic Threat	Japan/Korea→USA	H1N1	Unknown	Moderate rates of infection, with low rates of mortality	***6, 7***
1957	Pandemic	China→ROW	H2N2	Reassorted avian and human	Lower rates of infection in elderly, higher rates of mortality in elderly, pregnant and patients with chronic heart or lung conditions. Two waves of infection, the second more severe. CAR: 30%; CFR: 0.4%.	***1, 2, 3, 4, 6, 9***
1968	Pandemic	China→ROW	H3N2	Reassorted avian and human	Moderate rates of infection, with low rates of mortality. Two waves of infection, the second more severe in Europe, the first more severe in North America. CAR: 35%; CFR: 0.4%.	***2, 4, 6, 9***
1976[25]	Pandemic Threat	USA	H1N1	Swine	Abortive pandemic restricted to single location.	***4, 6***
1977[26]	Debatably a Pandemic	China→ROW	H1N1	Unknown[27]	Most infections restricted to those under 20 years old.	***2, 3, 4, 6***
1997[28]	Pandemic Threat	Hong Kong→South East Asia, Middle East, Africa and Southern Europe[29]	H5N1	Avian	In 1997, the slaughter of 1.5 million poultry in Hong Kong following 18 human cases, including six fatalities, may have prevented a pandemic. As of July 2010, the WHO reported 500 human cases, 296 of which have been fatal.	***2, 3, 10***
1998[28]	Pandemic Threat	China	H9N2	Avian	Nine cases of human infection in Southern China and two subsequent cases in Hong Kong.	***2, 11***
2003[28]	Pandemic Threat	Holland	H7N7	Avian	Precautionary mass slaughter of poultry following infection of 89 poultry workers, with one fatality.	***10, 12***
2004[28]	Pandemic Threat	Canada	H7N3	Avian	Following two initial cases of mild human infection, more than 16 million poultry were slaughtered as a precaution.	***10, 13***
2009	Pandemic	Mexico/USA→ROW	H1N1	Swine	Low rates of infection and mortality in general population; higher rates in children, pregnant women, those immunosuppressed or with neurological conditions. CAR: 7%; CFR: 0.05%.	***14, 15, 16***

Notes to accompany Box A1

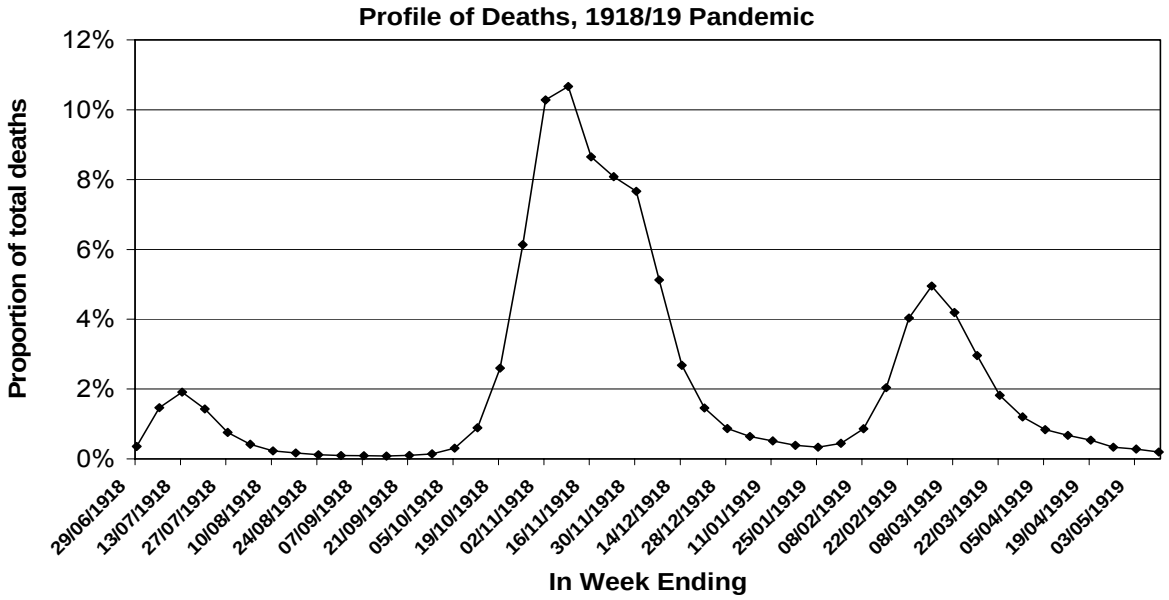
1 Potter (2001)
2 Wilschut, McElhanye and Palache (2006)
3 Taubenberger and Morens (2009)
4 Sellwood (2010b)
5 Valleron *et al.* (2010)
6 Kilbourne (2006)
7 Kilbourne *et al.* (2002)
8 Taubenberger and Morens (2006)
9 Hsieh *et al.* (2006)
10 Sellwood (2010 A)
11 Lin *et al*. (2000)
12 Koopmans *et al.* (2004)
13 Skowronski *et al.* (2007)
14 Fraser *et al* (2009)
15 Yang *et al.* (2009)
16 Writing Committee of WHO Consultation on Clinical Aspects of (H1N1) 2009 Influenza (2010)
17 ROW: Rest Of World.
18 Pandemics of influenza have typically been associated with the type A viruses.
19 Rates of infection and mortality are relative to the second wave of the 1918 UK pandemic. Multiple waves may be caused by more than one viral subtype.
20 Conflicting reports on whether the virus responsible was of the H2 or H3 subtype. Neuraminidase subtype is undocumented.
21 Substantial epidemics occurred in Europe, Pacific and North America during this period that may or may not have been independent events.
22 Both China and North America have been implicated as origins. Multiple simultaneous epidemics occurred in Europe, North America and Asia.
23 There is still uncertainty regarding the genetic origin of the 1918 virus; although avian it developed an ability to infect swine and humans.
24 Kilbourne (2006) classified as a 'pseudopandemic', rather than a true pandemic; the outbreak spread only from US military bases in Asia to North America.
25 This outbreak was considered to be an aborted potential pandemic that was restricted in its entirety to the US military base of Fort Dix, New Jersey.
26 Because the outbreak was highly age-restricted, it has been argued by some that such an event could not be considered to constitute a true pandemic
27 Some have argued that the genetic similarity of this virus to the 1957 subtype suggest that the outbreak may have been the result of a laboratory escape.
28 Sustained human-to-human transmission has not occurred with this subtype; therefore it only constitutes a pandemic threat.
29 Geographical spread refers to both enzootic presence in avian stocks and cases of human infection.

A3 However, cases of infection subsequently increased again in the autumn and early winter of that year, with far more people being infected than in the first wave (see Box A1).Those that were infected were more severely affected than those in the first wave. Clinical symptoms included rapid onset, pneumonia, shortness of breath and, in the most severe cases, patients suffocated to death, probably due to pulmonary oedema (Hsieh *et al*. 2006). The clinical attack rate seems to have been around 25% across the national population (Kilbourne 2006, Taubenberger and Morens 2009, Sellwood 2010 B).

A4 Most strikingly, rates of infection, morbidity and mortality were high amongst young adults, in sharp contrast to typical influenza outbreaks where the very young and old are more severely affected (see Box A2; Hsieh *et al.* 2006; Kilbourne 2006). Indeed, the case fatality ratio was estimated at 4% in young adults, compared with 2.5% in the general population infected (Kilbourne 2006). In early 1919 in the UK, a third wave of infection appeared, although this time relatively mild and involving lower rates of infection. The “W”-shaped age distribution of mortality rates (see Box A2) implies a biological basis, rather than purely environmental influences (Hsieh *et al*. 2006; Kibourne 2006). It is, for example, possible that the elderly of the time will have had some pre-existing immunity, based on infections by sub-types of influenza circulating earlier in their lives. This could account for higher rates of mortality in young adults compared to the elderly, although not in young adults compared to children (Kilbourne 2006). There is also evidence that the 1918 virus may have caused the highly active immune systems of young adults to overreact, leading to situation known as a “cytokine storm,” whereby infected lung tissue of hosts would have been attacked and destroyed by the very defense systems evolved to protect against pathogens (Wilschut, McElhaney & Palache 2006; Hsieh *et al.* 2006).

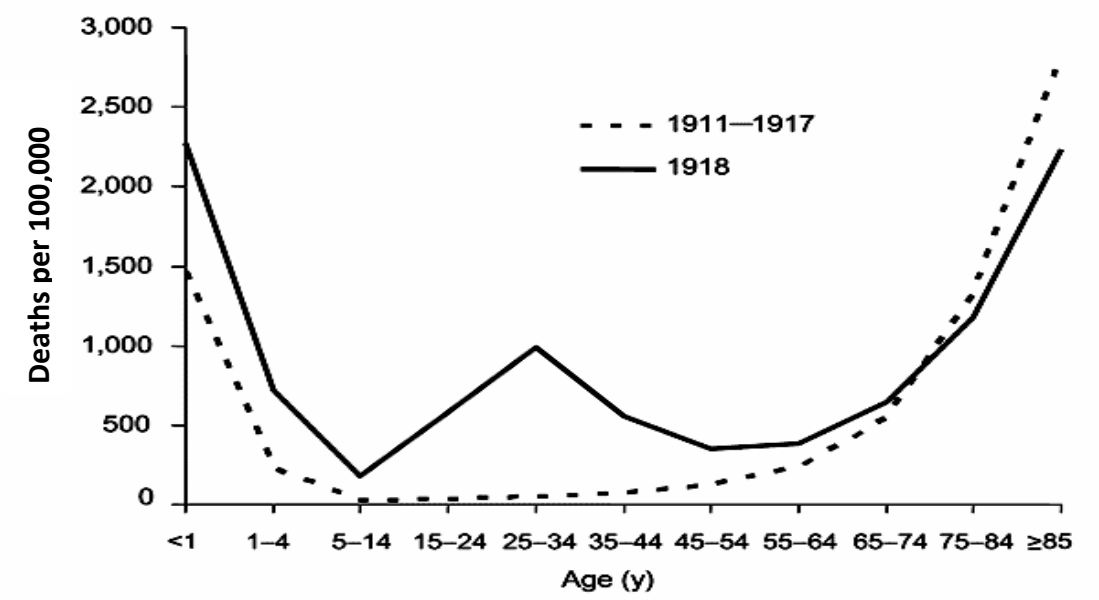
Box A2: Profile of 1918 Pandemic in the UK and USA

[a] Temporal profile of deaths in the UK



Generated from data held by the Department of Health

[b] Age distribution of deaths in the USA



Adapted from Figure 2 of Taubenberger and Morens (2006)
[http://www.cdc.gov/ncidod/EID/vol12no01/05-0979-G2.htm]

A5 The 1918 virus was established as a H1N1 subtype. The virus appears to have originated from an avian strain that adapted slowly to its human host over time (Taubenberger and Morens 2006, 2009). This is supported by reports of “herald” influenza epidemics observed in France from as early as 1916 (Taubenberger and Morens 2009; Sellwood 2010 B). Nonetheless, it is still unclear how such a potent, novelvirus could have emerged to cause such a dramatic illness by evolving slowly amongst humans without simultaneously generating at least some protective levels of immunity. The appearance of three waves of infection within months of each other may suggest that genetic adaptation of a milder virus to a more virulent form may have occurred between waves (Kilbourne 2006; Taubenberger, Morens & Fauci 2007). It is also possible that a yet unidentified animal reservoir was involved in the development of the 1918 pandemic virus. For instance, it is known that the 1918 virus developed the capacity of simultaneously infecting both humans and swine, despite having characteristics of an avian origin virus. Yet another possibility is that the pandemic involved the co-circulation of multiple viral subtypes.

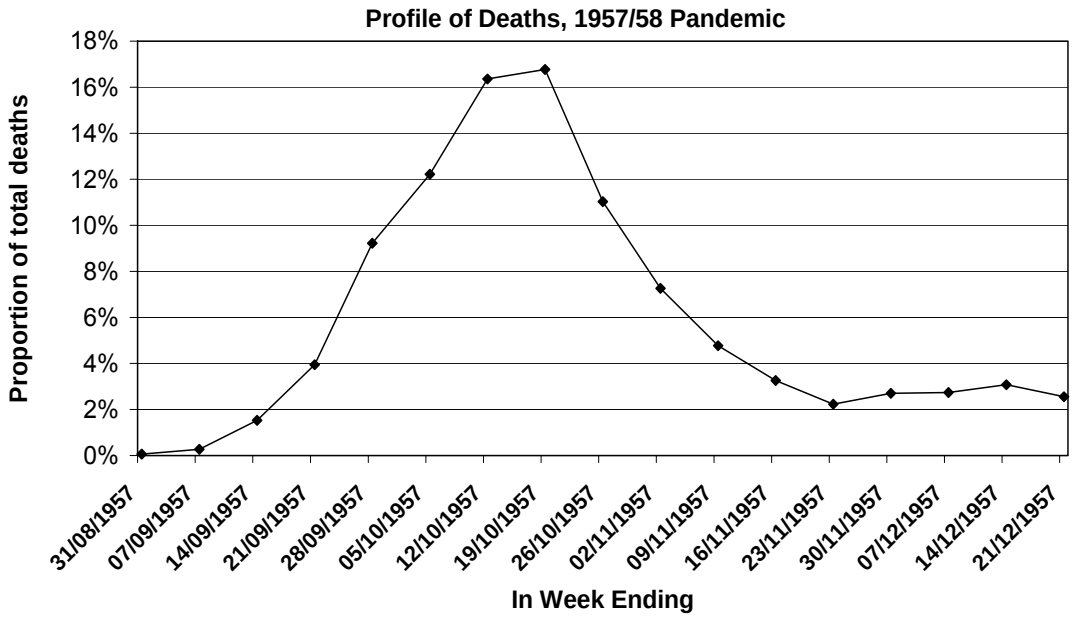
1957

A7 The viral subtype H2N2 was responsible for the “Asian Flu” pandemic and was thought to have arisen from a reassortment of avian and human strains in an unknown mammalian host (Wilschut, McElhaney & Palache 2006; Hsieh *et al.* 2006). The pandemic began in China in February 1957 and travelled across the globe within six months. In the UK, outbreaks began in September and were first observed in children as the new school year commenced (see Box A3). Cases then spread to the infant and adult population, with a clinical attack rate of around 30%.

A8 In early 1958, a second wave of infection, in some countries as severe as the first, spread across Europe, North America and Russia. Unlike 1918, the pandemic was not associated with high mortality in the general population and had a case fatality ratio of about 0.2%. However, higher mortality rates were observed in the elderly, women in their third trimester of pregnancy and those with chronic heart or lung conditions. The pandemic was estimated to have been responsible for about one million deaths globally.

A9 The 1957 pandemic provided the first opportunity to study systematically the effects of pandemic influenza in the general population. Although secondary bacterial infections were commonly observed in 1918, primary viral pneumonia was shown to be the primary complication in 1957. With a population immunologically naïve to H2N2, it was shown that more vaccine against H2N2 was required in 1957 to induce immunity than in previous immunisations with vaccines directed against H1 subtypes already in existence. Circulating levels of antibody against H2 within the population steadily increased over 1958-60 and this was correlated with more readily observed immunological responses following vaccination. Thus, antibody levels were shown to be closely linked to immunity. Following the 1957 pandemic, H2N2 replaced 1918 H1N1 as the dominant circulating subtype of virus responsible for seasonal influenza.

Box A3: Profile of 1957 Pandemic in the UK



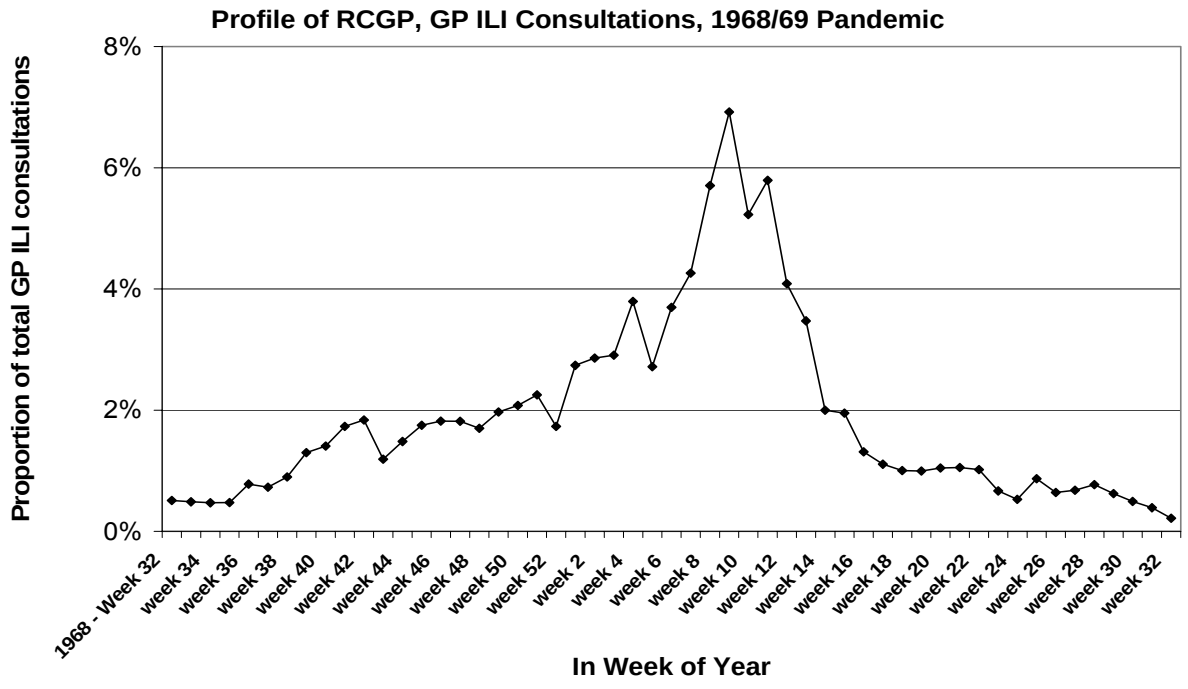
Generated from data held by the Department of Health

1968

A10 The “Hong Kong” influenza pandemic of 1968 originated in China and was characterised by its variable manifestations across the globe (Wilschut, McElhaney & Palache 2006; Sellwood

2010 B). In Japan, outbreaks remained small and sporadic until the end of 1968, whereas in North America infection and mortality rates were initially high. By contrast, in the UK infection rates were high (see Box A4), with a Clinical Attack Rate of over 35%, while mortality rates were low, with a Case Fatality Ratio of less than about 0.4%. Indeed, the pandemic was so mild in some regions that the incidence of influenza mortality was less than that observed in seasonal influenza. The pandemic typically consisted of two waves of infection; in North America the second wave was milder, while in the UK it was associated with a higher mortality rate than the first wave, most likely reflecting a change in the transmission characteristics of the virus over the course of the pandemic (Jackson, Vynnycky and Mangtani 2010). In total, the pandemic was estimated to have caused about one million deaths throughout the world.

Box A4: Profile of 1968 Pandemic in the UK



Generated from data held by the Department of Health

A11 The causative viral subtype was shown to be H3N2 during the first wave of the pandemic (Hsieh *et al.* 2006). Despite early identification of this subtype, insufficient availability of vaccine prevented widespread immunisation as a control measure. Subsequent to 1968, the 1957 H2N2 subtype was replaced by H3N2 as the dominant annual circulating subtype of virus responsible for seasonal influenza.

2009

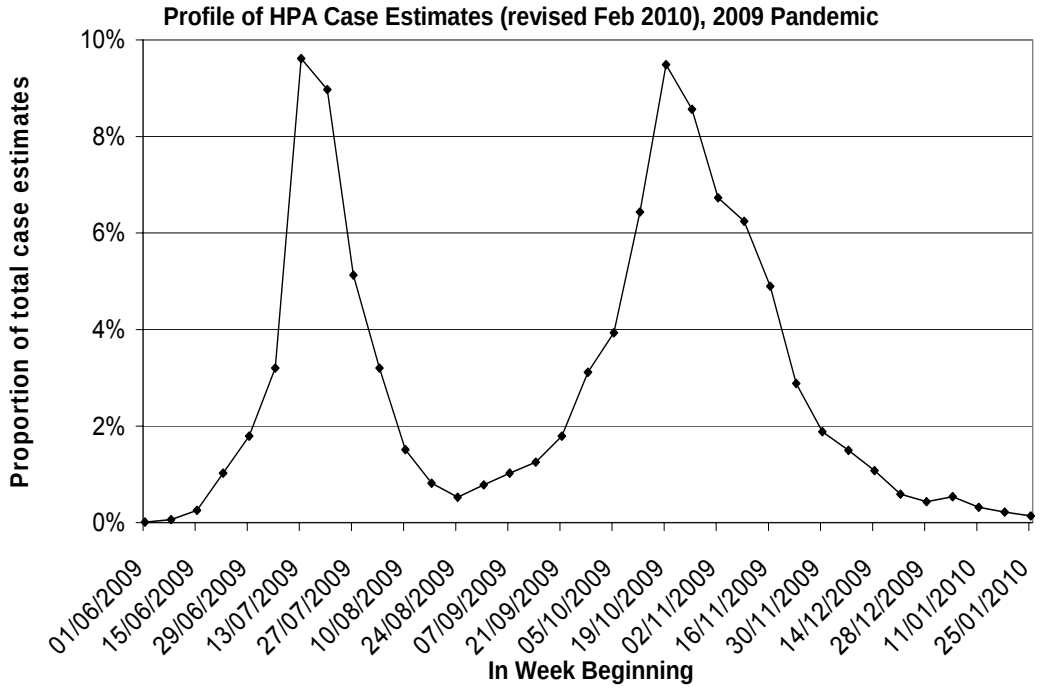
A12 Around March 2009, a novel subtype of H1N1 influenza was identified as the causative agent of an epidemic of respiratory illness in Mexico and California (Fraser *et al*. 2009; Yang *et al.* 2009). The viral subtype was soon established to have been a reassortment of viruses circulating in both Asian and North American swine. The disease spread through North America and to the rest of the world within eight weeks of the first reports of the H1N1 outbreak.

A13 Most illness was mild and self-limiting, with greater levels of infection observed in younger age groups (Writing Committee of WHO Consultation on Clinical Aspects of (H1N1) 2009 Influenza 2010). The overall clinical attack rate has been reported at around 7%, although half of all infections may have been asymptomatic, making the true figure difficult to estimate precisely. Those over 60 years of age were relatively spared from the illness, possibly due to background levels of pre-existing immunity from previous infections with seasonal H1N1 subtypes in circulation prior to 1957. It has been shown in mice that immunity to the 2009 H1N1 subtype confers resistance to 1918 H1N1 (Wei *et al*. 2010b).

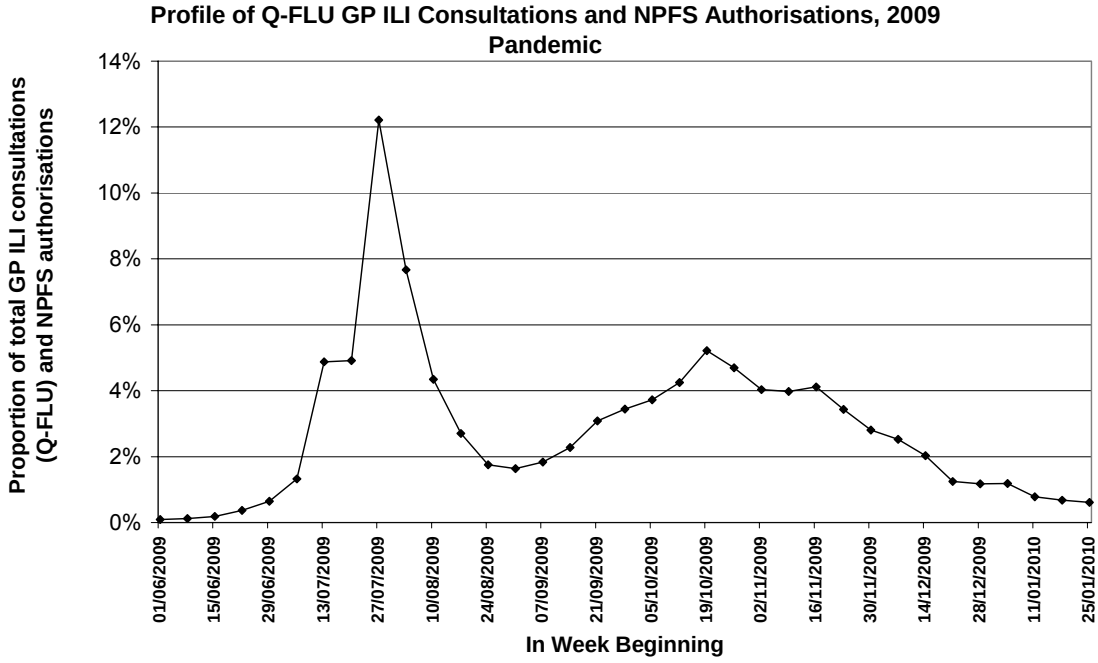
A14 Amongst those conditions linked to severe complications and death from H1N1 infection were cardiovascular disease; diabetes; pregnancy, especially during the third trimester or within two weeks post partum; obesity; immunosuppresssion, including HIV infection and neurological disorders (Writing Committee of WHO Consultation on Clinical Aspects of (H1N1) 2009 Influenza 2010). However, up to half of all infected patients who were hospitalised had no reported co-morbidities. Overall rates of mortality were variable but low, with reports of case fatality ratios of less than 0.05% (Donaldson *et al.* 2009). Mortality rates were highest amongst those over 50 years of age who were hospitalised.

A15 In the UK, the pandemic consisted of two waves (see Box A5) before the WHO announced that the virus had moved into a post-pandemic phase, adding that localised outbreaks of H1N1, varying in magnitude, would likely continue. Serological studies suggest that the second wave accounted for a greater number of infections, but resulted in a lower proportion of hospitalisations relative to infections. Antiviral drugs were provided to patients to reduce disease

Box A5: Profile of 2009 Pandemic in the UK



Generated from data held by the Department of Health



Generated from data held by the Department of Health

burden and hospitalisation rates. The 2009 virus was typically susceptible to both oseltamivir and zanamivir, but resistant to amantadine. Further analyses of the 2009 pandemic are ongoing.

Sub-pandemic events recorded in the 20th Century

1947

A16 An outbreak of influenza occurred in late 1946 amongst US troops in Japan and Korea, which had spread to military bases across America by 1947 (Kilbourne 2006). Not a true pandemic, the outbreak was considered to be mild, causing few deaths. The episode was, however, noteworthy in illustrating just how quickly an influenza subtype could mutate, so that a previously effective vaccine against H1N1 became completely ineffective within a period of less than two years (Kilbourne *et al.* 2002).

1976

A17 1976 saw an outbreak of H1N1 infection from swine in military personnel in Fort Dix, New Jersey, USA (Kilbourne 2006; Sellwood 2010 B). Over two hundred cases were identified, with one fatality. Although not a true pandemic, the outbreak raised anxieties at the time that another influenza pandemic was imminent. In addition to swine H1N1, the dominant influenza viral subtype of the time, H3N2, was co-circulating in the crowded military base, raising the possibility that a reassorted subtype of greater virulence could emerge (Kilbourne 2006).

A18 This led to a mass vaccination programme of 43 million people in the USA. However, the programme was terminated when the vaccine was linked to rare events of Guillain-Barré syndrome, a neurological condition. Despite this, the outbreak of H1N1 failed to spread outside of Fort Dix. It has not been established whether sufficient vaccination of the population prevented further spread of the virus, whether the virus was inherently incapable of transmission outside of the close living conditions of the military base or whether the co-circulating H3N2 subtype suppressed further transmission of the new H1N1 strain (Kilbourne 2006).

1977

A19 In the year after the Fort Dix episode, in late 1977, H1N1 reappeared in northern China, although the outbreak was popularly nicknamed “Russian Flu” (Kilbourne 2006; Wilschut,

McElhaney & Palache 2006, Taubenberger & Morens 2009; Sellwood 2010 B). The virus spread into the Soviet Union and across the globe, reaching the Americas, Europe and Australia within a year. Infections were predominantly amongst children and the disease was relatively mild. The age profile is believed to have been due to the then absence of circulating H1N1 virus, and consequent lack of background immunological protection, in human populations born post-1957 (Kilbourne 2006; Sellwood 2010 B). Thus, the very young were particularly susceptible to 1977 H1N1 infection. Despite the global spread of virus, the age distribution of cases means that the 1997 outbreak is not recognised as a true pandemic.

A20 Later, antigenic characterisation of the 1977 virus showed it to be highly similar to the H1N1 circulating in the 1950s. It is difficult to reconcile how a virus could exist in animal reservoirs over that period of time without adapting, raising the prospect that the outbreak had been caused by a laboratory escape (Kilbourne 2006; Taubenberger, Morens & Fauci 2007; Taubenberger & Morens 2009). Further indicating the unusual characteristics of this event, since 1977 ancestors of both the 1968 H3N2 and 1977 H1N1 subtypes have been co-circulating, along with reassorted H1N2 viruses (Taubenberger, Morens & Fauci 2007).

Examples of animal influenza outbreaks recorded in the 20th and 21st centuries

1997

A21 Prior to 1997, outbreaks of Highly Pathogenic Avian Influenza (HPAI) in poultry flocks were not considered a major public health threat (Wilschut, McElhaney & Palache 2006; Sellwood 2010 A; Sellwood 2010 B). However, at this time, the H5N1 subtype of influenza virus crossed the species barrier causing 18 cases of human infection, with six fatalities. This was the first documented example of an influenza outbreak in humans from an entirely avian viral subtype and resulting in death. Although no human-to-human transmission was observed, the incident provoked the mass slaughter of poultry flocks in Hong Kong (Wilschut, McElhaney & Palache 2006). Since then, outbreaks of H5N1 in poultry and wild birds have been observed in many parts of Asia, Africa and Europe (Taubenberger & Morens 2009; Sellwood 2010 A).

A22 As of July 2010, the World Health Organisation reported 500 human cases of H5N1 infection, normally from close contact with diseased poultry, 296 of which have been fatal (http://www.who.int/csr/disease/avian_influenza/en/index.html). None of these cases are believed to have been acquired due to human-to-human transmission of the virus. It remains unclear

whether such high levels of fatality would be sustained should H5N1 mutate to become transmissible from human to human, although it is worth reflecting on the fact that subtypes with low (2009) and high (1918) virulence have transmitted efficiently in humans (Taubenberger, Morens and Fauci 2007). Therefore, given a current case fatality ratio of over 50%, H5N1 must be still seen as one of the most serious pandemic threats (Hsieh *et al.* 2006).

1998

A23 In 1998, nine cases of H9N2 infection in humans were reported in southern China (Lin *et al.* 2000; Wilschut, McElhaney & Palache 2006). The following year, an additional two human infections from Hong Kong were reported. In all of these human cases, no evidence for human-to-human transmission was detected. H9N2 has also been detected in swine, allowing for potential reassortment with other circulating viruses such as H1N1 or H3N2. There were two further cases of human infection with H9N2 (both in Hong Kong but unrelated) in 2008 and 2009.

2003

A24 In 2003, a number of agricultural workers became infected with the H7N7 subtype of the influenza virus following an outbreak of HPAI in poultry in the Netherlands (Koopmans *et al*. 2004; Sellwood 2010 A). The majority of human infections resulted in mild symptoms such as conjunctivitis, about one in ten developing influenza-like illness and one case was fatal. A mass slaughtering of infected poultry took place. Workers received antiviral treatment, as well as vaccination against circulating influenza subtypes to limit the possibility of genetic reassortment.

2004

A25 Between February and May 2004, an outbreak of HPAI of the H7N3 subtype took place in British Columbia, Canada (Skowronski *et al.* 2007; Sellwood 2010 A). The source of the virus was never established but 42 commercial poultry farms consisting of 1.3 million birds were thought to have been infected. In an effort to contain the circulation of this subtype, more than 16 million birds were destroyed in more than 410 commercial poultry operations. Only two human cases of mild infection amongst poultry workers were associated with the outbreak.

Annex B:

The influenza virus

B1 Influenza viruses are sub-classified into three broad types, referred to as A, B & C (Wilschut, McElhanye and Palache 2006; Haaheim 2010). Influenza C belongs to a group of several hundred viruses that cause variations of the “common cold” and is therefore not considered relevant to pandemic influenza. Influenza B is linked with seasonal influenza, but tends to be associated with less severe illness, smaller outbreaks and higher rates of infection in children. By contrast, Influenza A viruses are responsible for all virologically-characterised influenza pandemics, and most seasonal influenza.

B2 Under high-powered electron microscopy, the three-dimensional structure of the influenza virus can be seen as an enveloped structure, made up of proteins and lipid (see Box B1). Spikes are seen on the viral surface, consisting of two proteins known as Haemagglutinin (H) and Neuraminidase (N). Influenza A viruses are themselves divided into further subtypes depending on the characteristics of the H and N proteins on their surface. To date, there are 16 H and nine N recognised subtypes. For example, an influenza viral strain possessing the Haemagglutinin three and Neuraminidase seven subtypes is referred to as H3N7. In addition, the ‘M2 Channel’ can been seen under electron microscopy; this is a viral envelop protein which allows the RNP to dissociate from the rest of viral particle during infection of the host cell and is the target of the antiviral drug, amantadine.

B3 The genetic material of the influenza virus, or its genome, is packaged inside the outer envelop and consists of eight independent segments of RNA, encoding a total of eleven proteins, eight of which are structural and three are thought to be regulatory (Wilschut, McElhanye and Palache 2006; Haaheim 2010). The segmented nature of the influenza RNA genome is an important feature, as it allows genetic reassortment to occur; during co-infection of a host with two different viral subtypes, entire segments from one genome can be replaced with the equivalent from another subtype, creating a novel virus. The viral RNAs are complexed with viral proteins, referred to as the Ribonucleoprotein (RNP), which are transferred to the host nucleus during viral replication.

BOX B1: The Influenza Virus

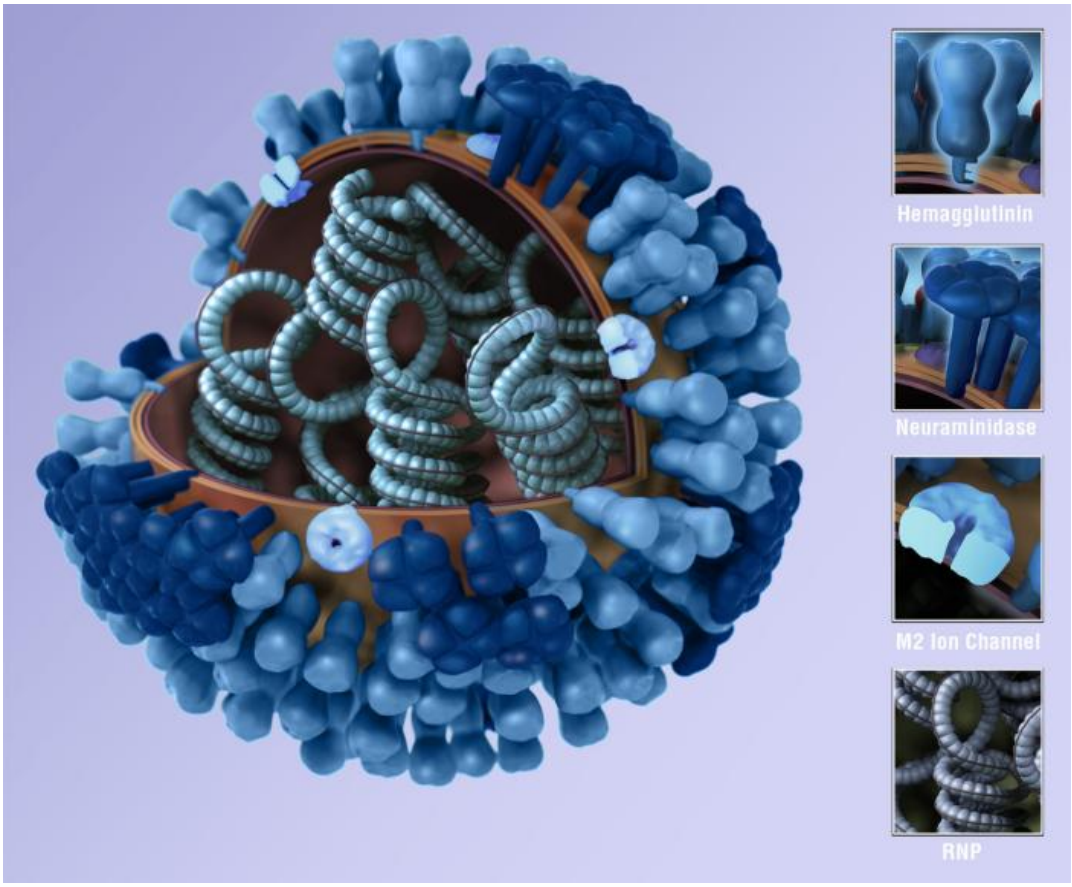


Image Courtesy of CDC/ Doug Jordan, M.A.

B4 The viral RNA genome is replicated by the virus's polymerase enzymes. These are considerably error prone when compared with the accuracy polymerases of animal and human host cells. This another important feature of viral replication as it means that individual viruses can and do arise with smaller, more subtle changes, or mutations, which over time can accumulate within the viral population (in a process known as "antigenic drift"). The development of antiviral resistance amongst a subtype, for example, usually occurs through this mechanism. Drift is also central to the seasonal aspect of influenza, where the ability of the immune system to recognise the altered subtype is slightly diminished by relatively minor viral mutations, thus increasing the overall possibility of infection and illness when conditions favour the spread of virus during the winter months (Wilschut, McElhanye and Palache 2006; Haaheim 2010).

B5 Typically, in otherwise healthy individuals, significant replication of the virus begins with, or just before, the onset of symptoms and gradually diminished over about six days (Wilschut, McElhaney & Palache 2006; Lee *et al.* 2009; Enstone 2010). During the initial 48 hours of this period, high levels of newly replicated, infectious viral particles are usually excreted, or "shed," from the respiratory system of the infected individual. There is also evidence indicating that those who are infected, but who do not show symptoms, also shed virus.

B6 In the case of the young, those hospitalised because of secondary complications or the immunosuppressed, viral shedding may be more active and continue for a greater duration than in other groups. In case reports, prolonged shedding has been observed 48 days after symptom onset in otherwise healthy individuals who have also been treated with antiviral drugs (Fleury *et al*. 2009).

Annex C:

Animal reservoirs of influenza virus

C1 Influenza A viruses can infect a range of animals, including birds and mammals such as primates, horses, swine, whales, seals, mink ferrets and companion animals including cats and dogs. In the case of birds, the principal reservoir is wild migratory waterfowl, such as ducks and geese. Most avian influenza strains do not appear to cause disease and are referred to as Low Pathogenicity Avian Influenza (LPAI). On rare occasions there have been limited infections in humans with such LPAI viruses ie H7N7, H7N3, H9N2.

C2 In contrast to LPAI, there are two subtypes, H5 and H7, which can also occur in a highly virulent form for avian species (principally gallinaceous poultry such as chickens and turkeys), which is extremely contagious in, and fatal to, birds; termed Highly Pathogenic Avian Influenza (HPAI). Epizootics[1] of both HPAI H5N1 and HPAI H7N7 have also been associated with deaths in humans (Sellwood 2010 A). Indeed, before 1997 and the first recorded appearance of H5N1, outbreaks of HPAI were extremely rare. However, since then, epizootics of HPAI H5N1 have been commonly observed in Southeast Asia, Africa, the Middle East and Southern Europe (Taubenberger & Morens 2009). Indeed, in many parts of Asia, and Egypt, HPAI H5N1 is thought to be enzootic in avian populations.

C3 Of non-human mammalian hosts, the influenza viral reservoir in pigs has particular relevance to public health. This is because, as discussed in Annex A, airways of the pig possess the two types of receptors facilitating infection by both avian and human influenza viruses. The species therefore represents an ideal “mixing vessel” for the generation of reassorted subtypes of both mammalian and avian influenza. Swine influenza is enzootic in all regions of the globe where pigs are bred (Sellwood 2010 B). Indeed, the two subtypes associated with the last three major pandemics; H1N1 in 1918, H3N2 in 1968 and H1N1 in 2009; have been the most frequent ones identified in swine.

C4 However, periodically other virus subtypes are detected but most are characterised by a transient appearance without truly establishing in swine populations. Generally, H1N2 is found

[1] When referring to animal populations, the corresponding terms for “epidemic”, “pandemic”, and “endemic” are “epizootic”, “panzootic” and “enzootic”, respectively.

globally, but others include H2N3, H3N1, H4N6 and H9N2.

C5 Thus, the circulation of influenza viruses is sustained via stable maintainence in a readily accessible pool of animal hosts. Moreover, the sheer numbers of animals susceptible to infection, as well as the capacity of some to be infected simultaneously with multiple subtypes of virus, provides a mechanism enabling novel, viral subtypes of pandemic potential to emerge on a regular basis.

Annex D:

The human immune system

D1 Viral infection of humans typically causes activation of an individual's immune system, which can be divided into the "innate" and "adaptive" responses (Wilschut, McElhanye and Palache 2006; Haaheim 2010). The innate response can react with immediate effect to viral infections. Small signalling proteins (interferons, chemokines and cytokines) are secreted at the site of infection, alerting neighbouring cells to infection, recruiting cells to the site of infection and triggering the adaptive responses. These signalling proteins activate a variety of white blood cells, such as natural killer cells, macrophages and dendritic cells, to migrate, attack and digest any foreign pathogens.

D2 The dendritic cells have elaborate projections (dendrites) that continuously scan their environment for foreign proteins, such as those found on the surface of invading influenza viruses. As well as absorbing and digesting the foreign material, the dendritic cells, belonging to a larger class of cells called Antigen Presenting Cells. They are potent activators of the adaptive immune response.

D3 The adaptive immune response is considerably slower than the innate response, taking of the order of 3-4 days (Wilschut, McElhanye and Palache 2006; Haaheim 2010). However, it is far more specific in its effects, recognising individual viral antigens; portions of viral proteins with signature peptide sequences or three-dimensional structures that can, thereafter, be used by the immune system to uniquely identify the strain of virus to which they belong. This adaptive response is itself further subdivided into "humoral" and "cellular" responses. In the case of the humoral response, a key feature involves the binding of viral antigens to antibody, either in secreted form or as receptors on the surface of circulating cells known as B-lymphocytes. These B-lymphocytes (or B-cells) are then stimulated to proliferate into Plasma Cells which produce and secrete antibodies against those viral antigens. Such antibodies can specifically bind viral surface HA and NA antigens, neutralising viral particles and preventing their entry into host epithelial cells.

D4 In the cellular response, viral antigens are presented on the surface of Antigen Presenting Cells to T-lymphocytes (or T-cells), which mature in the thymus. Such T-lymphocytes help in the proliferation and conversion of B-lymphocytes into Plasma Cells and in the proliferation and

activation of cells known as cytotoxic T-lymphocytes (CTLs). Such virus-specific CTLs can then activate the programmed cell death of host cells that have already become infected with virus, halting further spread of the virus.

D5 A crucial aspect both of the humoral and cellular adaptive responses is that they can maintain a “memory” of previously encountered viral strains (Wilschut, McElhanye and Palache 2006; Haaheim 2010). Upon subsequent encounters with the virus, or novel viral strains sharing the same antigens as that virus, virus-specific B cells and T cells become activated and proliferate, inducing a far more rapid adaptive response than would otherwise occur. Indeed, vaccination exploits immunological memory. Here either inactivated virus or virus-specific antigens that have been designed to mimic the antigens of a particular strain of influenza virus are presented to the immune system in order to generate an immune response to strains of influenza virus that are predicted to be circulating in the community. Depending of the efficiency of the vaccine, once exposed to the virus, the immune system can attenuate or neutralise influenza viruses because of this vaccine-induced adaptive response. Moreover, despite its specificity, an adaptive response to one strain of virus can be sufficient to allow the immune system to respond partially to other strains with similar antigenic profiles. Such a broadening of the immune response to a wider range of viruses is known as “cross-protection” (Wilschut, McElhanye and Palache 2006; Haaheim 2010). Finally, whilst it appears that robust antibody responses can be reactivated throughout life, the effectiveness of cellular responses appear to diminish over time and may be one reason why the elderly are particularly susceptible to seasonal influenza (Haaheim 2010).

Annex E:

Seasonal influenza *versus* pandemic influenza

E1 As explained in Section 1, seasonal and pandemic influenza are quite different types of event; however, they do have certain features in common. As a disease, in the case of both seasonal and pandemic outbreaks, influenza is an acute respiratory illness characterised by much more severe symptoms than the "common cold," including cough, headache, fever, malaise and fatigue. Individual infections can also vary considerably in severity, ranging from asymptomatic to fatal. Typically, the illness is self-limiting and clinical symptoms diminish after about six days, but convalescence may last several weeks and continue to be associated with fatigue and lethargy (Van-Tam 2010). In addition, infection can result in severe complications, commonly secondary bacterial pneumonia, which can be treated in most cases with antibiotics. However, other significant complications can occur and include damage to the heart muscle and neurological defects. Moreover, influenza infection can exacerbate underlying conditions, such as chronic lung and heart disease.

E2 It is difficult to determine the actual number of cases, or deaths, attributable to either seasonal, or pandemic, influenza (Van-Tam 2010). Most patients self-medicate, do not seek formal healthcare assistance and, therefore, such infections go unrecorded via currently-used surveillance mechanisms. It is also worth noting that, of those identified with influenza infection using serological measurements, half, perhaps even more, show no clinical symptoms at all. Moreover, in cases where patients are hospitalised due to secondary complications, the original influenza infections may well have abated before admission to secondary care and testing can take place, masking the contribution of the virus to the case histories.

E3 Death rates from seasonal or pandemic influenza can be described via estimates of "excess mortality", figures that reflect the additional fatalities that occur over and above those anticipated during the same time of the year in the absence of the influenza outbreak (Wilschut, McElhanye and Palache 2006; Van-Tam 2010). There is inevitably significant uncertainty in these estimates, and these data are inappropriate for detecting relatively small numbers of deaths, where 'noise' in the data is likely to be as great as the 'signal' generated by the number of deaths. Indeed, the 2009 pandemic in the UK caused too few deaths to be detected by excess mortality.

E4 Seasonal influenza occurs in temperate regions annually over the winter months and is caused when circulating subtypes of virus alter in only minor ways, usually in their HA and NA proteins. Because these alterations are minor, immune systems are at least partially capable of recognising the circulating viral subtype, limiting the potential of new strains to cause disease. Winter months in locations such as the UK allow individuals to become exposed for prolonged periods to low temperatures, increasing their susceptibility to infection. Such conditions also allow viruses to survive better in the environment because of higher humidity, lower temperatures and reduced UV light, compared with summer months. In addition, the population generally spends more time indoors, living in closer quarters and with poorer ventilation than the summer, favouring human-to-human transmission of viral agents.

E5 The clinical pattern in seasonal influenza tends to be more predictable than in pandemics (Wilschut, McElhanye and Palache 2006; Van-Tam 2010). In seasonal influenza, Clinical Attack Rates are highest in children and teenagers, while greater levels of medical complications and higher Case Fatality Ratios are reported in the elderly. Seasonal influenza also tends to be associated with more severe disease in those over 75 years of age; children under two years of age; pregnant women; and those with chronic heart, lung or metabolic diseases, where influenza infection can exacerbate the underlying condition. The most significant effects of seasonal influenza are caused by secondary complications. Whilst the most common complication is acute bronchitis, by far the most serious is secondary bacterial pneumonia, which can be treated in modern times with antibiotics (Van-Tam 2010). However, other significant complications can occur and include damage to the heart muscle and neurological defects. Typically, in seasonal influenza excess mortality is concentrated in the elderly and can range in the UK from “none”, as in the 2005/6 season, to over 27,000, in 1989/90 (Health Protection Agency, unpublished data).

Annex F:

Mathematical modelling of pandemic influenza

F1 Previous influenza pandemics have varied widely in their characteristics and impact (see Annex A) and show considerable variation in their local patterns of activity (Van-Tam 2010). The nature and development of influenza pandemics can be affected by multiple factors, including the environment, population dynamics, contact patterns, time of year, behavioural responses of the population, immune system responses and viral subtype. Of the small sample of pandemics recorded through history (see Annex A), most have been incompletely described or occurred before the development of modern clinical interventions, such as antiviral drugs or antibiotics. With such limited empirical evidence, it is difficult to draw directly from history on how a future pandemic might develop.

F2 In mathematical modelling, information from previous pandemics and seasonal influenza can be placed in a conceptual framework based on our knowledge of infectious diseases and the range of possible pandemics investigated (Grove 2010). Typically, the population is divided into four categories with regard to their infection status: those *Susceptible (S)*, who have not been infected and so are not currently infectious; Latently infected individuals (*E*), who are infected but have not yet become infectious; those who are *Infectious (I)*; and those who have *Recovered (R)* and are no longer infectious and are now immune. Those who have died of infection are removed from the model population.

F3 Such models allow a spectrum of “virtual” pandemics to be simulated, so that the extent of possible pandemic scenarios and their associated risks can be defined; notably how rapidly a pandemic might spread through the population. In addition, modelling can help identify interventions that are likely to be effective over a broad range of such scenarios. When a particular model is developed, a number of assumptions and judgements on the nature and development of the simulated pandemics must be made. This means that confidence can only be highest in any assessment of the risks of or interventions on particular pandemic scenarios when multiple, independently-created mathematical models reach a consensus view (Grove 2010).

F4 There are a number of key values that define a pandemic which modelling can help us to establish and can be used to plan for future pandemics. The clinical attack rate is the proportion of

the population who develop symptoms. It depends both on the proportion of the population infected by the virus and the proportion of those infected who show clinical symptoms (Grove 2010). The proportion of the population that becomes infected is called the "infection attack rate" and is broadly determined by the initial Reproduction Number, or *R*. As the epidemic progresses and the susceptible population is depleted by individuals becoming infected and developing immunity, the Reproduction Number falls.

F5 The initial *R* of the 1918 pandemic has been estimated from the rate of build up of cases in the second wave to be in the range 1.8 to 2.0 (SPI-M 2010). For the 1957 pandemic, a range of 1.4 to 1.7 has been estimated both from the rate of build up of cases and from the infection attack rate observed in serological studies. In planning for a future pandemic, modelling leads us to expect an *R* somewhere in the range of 1.4 to 2.2. Depending on the specific mathematical model used, this could lead to a national infection attack rate of up to around 80%.

F6 A pandemic would be associated with illness ranging in severity from asymptomatic to fatal. Serological studies suggest that less than half of those infected have obvious clinical symptoms. Other surveys indicate that up to 67% of those infected show symptoms of sufficient clinical severity to seek treatment. Therefore, based on the 80% infection attack rate and the upper limit of 67% of the population showing clinical symptoms, this implies an upper limit for a national clinical attack rate of about 50% (that is, 67% of 80%). This 50% national clinical attack rate is currently planned for in the UK as the worst case that might plausibly be expected from an influenza outbreak (SPI-M 2010). However, even at a lower and more historically representative national clinical attack rate, local variations in both attack rate and the temporal profile of the outbreak are possible and indeed likely. In addition, it should be emphasised that this value is proposed for planning purposes only; it is not a prediction of the impact of a future pandemic.

F7 Case Fatality Ratios from seasonal or pandemic influenza are also difficult to establish directly. The influenza infection in patients who go on to suffer from severe complications may already have disappeared by the time they are hospitalised and the cause of death in infected patients may be masked by their underlying conditions. Death may even be caused by influenza-induced exacerbation of co-morbidities. Because of this, case fatality ratios are typically established via estimates of "excess mortality", figures that reflect the additional fatalities that occur over and above those anticipated during the same time of the year in the absence of the influenza outbreak.. The case fatality ratio for 1918 was around 2% for the general population

infected, although this figure was as high as 4% in young adults. The case fatality ratios of the general population infected in 1889, 1957, 1968 and 2009 events, have been estimated at around 0.28, 0.2, 0.4 and 0.05, respectively (SPI-M 2010). However, it should be noted that, as of July 2010, in the 500 or so cases where humans have been infected with H5N1 from animals since 1997, over 50% have died.

F8 As well as being a vital tool for planning, modelling is required during an epidemic to provide real-time synthesis of data from disparate sources. Real-time data are always incomplete – due to many infections not being recorded because many people do not seek care; deaths being in 'suspected' but or 'confirmed' cases; and due to variable reporting delays from case-finding and surveillance systems – and modelling is required to account for these sources of uncertainty to provide situational awareness. Delays in data-streams and incompleteness of data mean that it is necessary to project forward from the most recent data to the present moment ("nowcasting"), as well as the course that the pandemic is likely to chart over subsequent days ("forecasting") (Grove 2010). This would be necessary when policy decisions, such as how antiviral stockpiles are used or whether or not to close schools, need to be taken based on the features, especially severity, of the particular pandemic of the moment.

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