Cabinet Office

OVERARCHING GOVERNMENT STRATEGY TO RESPOND TO PANDEMIC INFLUENZA

ANALYSIS OF THE SCIENTIFIC EVIDENCE BASE

Issued by:

Civil Contingencies Secretariat

Cabinet Office

Making government work better

Foreword

The possibility of a worldwide influenza pandemic presents a real and daunting challenge to the economic and social wellbeing of any country and a serious risk to the health of its population. The Civil Contingencies Secretariat and the Department for Health have therefore placed a significant emphasis on planning and preparing for a pandemic now to ensure that the UK is well prepared to deal with a pandemic when it emerges.

We understand that public confidence in the Government's pandemic strategy depends on it being based on a credible and wide-ranging evidence base, which has been objectively analysed. This enables informed decisions and ensures that all options are explored to their full potential. With this in mind, the Cabinet Office has led a group of experts from across government in analysing the evidence available on possible measures to reduce the impact of an influenza pandemic.

This paper summarises this work. It aims to provide a 'snap-shot' of the available scientific evidence underpinning the spectrum of possible strategies to respond to pandemic influenza. It covers both the medical and social countermeasures available, including those proposed by the UK and defined in *The National Framework for Responding to an Influenza Pandemic* (available at www.dh.gov.uk). We hope that it will provide scientists and the public with more detailed evidence to underpin the UK strategy and information on why certain decisions have been taken.

Our understanding of the science surrounding possible medical and social countermeasures are likely to change and progress over time. As a result, the science covered in this paper will need to be reviewed as more evidence becomes available. In turn assumptions, presumptions and response options will also need to be modified. We would expect to develop the evidence base in parallel with the development and refinement of the UK strategy.

This advice was produced by the Cabinet Office in consultation with the Health Departments and with other Government Departments. The Cabinet Office has issued it as part of our role in supporting the Department of Health, as Lead Department, in preparing and planning for a possible influenza pandemic.

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1. Introduction

1.1 This paper has been produced by the Civil Contingencies Secretariat in consultation with the Department for Health (DH), Health Protection Agency (HPA), the Government Office for Science, HM-Treasury and the Devolved Administrations and draws on:

- available science papers produced by DH (or on its behalf by HPA), as approved by their Pandemic Influenza Scientific Advisory Group (SAG), reviewed by international experts and the Science Colloquium on the scientific evidence base for pandemic flu response chaired by the Secretary of State for Health in April 2007, all of which are publicly available;

- summary of the results from the SAG modelling subgroup published on the DH website;

- other relevant sources of evidence, including economic assessments, real events, social sciences and international comparisons; and

- points raised at, and conclusions of, the Science Colloquium on the scientific evidence base for pandemic flu response options chaired by the Secretary of State for Health in April 2007.

1.2 In working through the available evidence for each of the response options, as well as on the risk of emergence of a pandemic virus, the CCS-led review has sought to capture and draw conclusions on:

- what we know;

- what we do not know and cannot expect to know in advance of the emergence of a pandemic virus;

- what we do not know but could learn through further research before the pandemic virus emerges, i.e. where the gaps in research are;

- what we may know in the near future from work/research in progress; and,

- views across the science community, including differences of views.

1.3 This paper is divided into 3 main sections:

- Section A – provides the evidence base underpinning the assumptions upon which pandemic influenza plans are based;

- Section B – provides the evidence underpinning the clinical countermeasures, divided into those measures aimed at risk reduction, mitigation and suppression.

- Section C – outlines evidence underpinning the proposed social measures.

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2. Response strategy

2.1 Cross-departmental work on pandemic influenza preparedness over the past two years suggests a response strategy comprising three major components which provide the overall structure for the paper:

- **Risk reduction** – reducing the conditions which might encourage the spread of virus, and rapid control of outbreaks involving the H5N1 virus by using some pharmaceutical countermeasures such as World Health Organization (WHO) antiviral stockpiles. (However, N.B. Sections 4.7, 4.9 and 4.11, there can be no safe assumption that H5N1 will produce the next pandemic)

- **Mitigation/treatment** - reducing the severity of cases and the number of deaths in the UK through a range of pharmaceutical measures aimed at treating the pandemic. Although this strategy is expected to reduce the number of severe cases and deaths (and to a limited extent amount of illness generally) the UK pandemic would still be significantly worse than the usual seasonal influenza. This has been the main focus of the UK's response strategy and cross sector planning work to date.

- **Suppression/prevention** – reducing the number of cases and deaths in the UK through a range of pharmaceutical and social measures aimed at interrupting transmission of the virus in the community.

2.2 Although the distinction between mitigation and suppression is in some respects arbitrary as the level of control is a spectrum, suppression can be thought of in terms of reducing the number of people one infected person goes on to infect to close to (or below) one. In such a case a large scale epidemic would be largely averted and its impact reduced (i.e. those cases that do occur have access to adequate care, partly because sufficient treatment is available for each case, and partly because the cases will be spread over a longer period of time so that the pressures on the health service are eased).

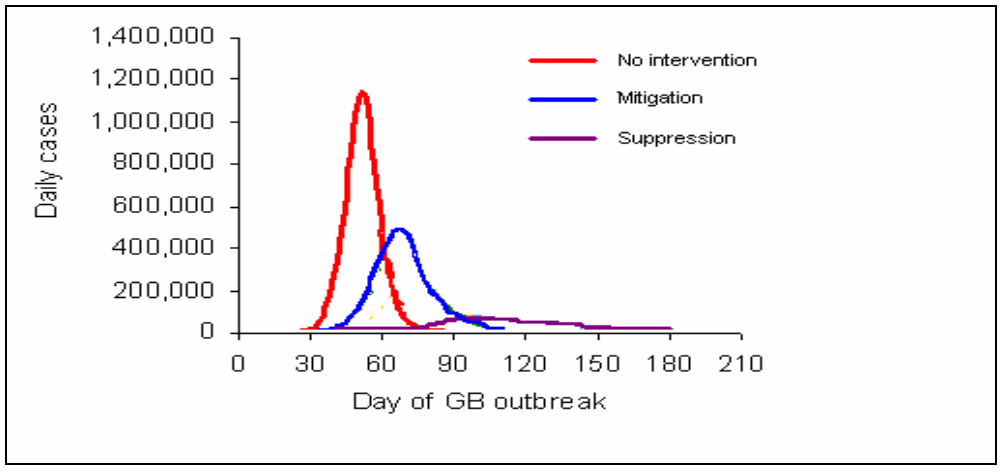

Figure 1: showing the indicative impacts in terms of reducing cases from mitigation and from suppression.

Section A – Evidence underpinning the Planning Assumptions

3. Background

Influenza

3.1 Influenza is an illness caused by influenza viruses. In humans it is characterised by rapid onset of cough and fever, chills, together with a range of other respiratory and generalised symptoms including sore throat, headache, whole body aching, loss of appetite, prostration and lethargy. In otherwise healthy persons, it typically manifests as a relatively unpleasant respiratory infection, significantly worse than a common cold and lasting typically 7 days, albeit full recovery might take longer, occasionally up to several weeks.

3.2 There are three broad types of influenza viruses – A, B and C.

- Influenza A viruses cause most winter epidemics (and all pandemics) and affect a wide range of animal species as well as humans. Indeed the natural reservoir for influenza A viruses is in wild aquatic shorebirds. Influenza A viruses have a marked propensity towards adaptation and change – this is one factor that enables them to remain in circulation year on year in slightly different forms; the resulting viruses can have widely differing impacts.

- Influenza B viruses only infect humans. They circulate most winters but generally cause less severe illness and smaller outbreaks; their effect is most often seen in children.

- Influenza C viruses are amongst the many causes of the common cold.

3.3 The range of possible symptoms associated with infection with an influenza A type virus, range from none at all (asymptomatic infection) through to a severe life-threatening or even fatal illness. About half of those who become infected have no symptoms and are therefore not even aware of the infection. For the majority of the other half, ‘seasonal’ influenza is an unpleasant but self-limiting and not life-endangering illness.

3.4 The very young, elderly people and those with underlying diseases such as heart disease, diabetes and chronic bronchitis are particularly at risk of serious illness, such as pneumonia, which may result in hospitalisation. Without interventions, those in high-risk groups can suffer significant ill health, and a small percentage of those affected die. An estimated 12,000 – mainly elderly – people die each year from seasonal influenza in England and Wales. The cornerstone of reducing the impact of seasonal influenza is selective annual vaccination, with an appropriately formulated vaccine, of those groups most at risk of serious illness, complications and death.

3.5 Influenza occurs to a greater or lesser extent each winter, and from time to time produces winter epidemics lasting 8-10 weeks, some of which are severe. For example in 1989/90, an influenza epidemic in Great Britain caused an estimated 26,000 excess deaths (deaths in excess of what would normally be expected for the time of year), mainly in the elderly, over a period of 56 days.

Pandemic Influenza

3.6 Influenza pandemics are natural phenomena that have occurred from time to time for centuries – including three times during the last century. They are associated only with influenza A viruses.

3.7 An influenza pandemic is not the same as a winter influenza epidemic. A pandemic occurs as the result of the emergence of a variant of influenza which is either entirely novel to humans or at least has not been seen for several decades, i.e. very different from recent winter influenza strains. When this happens, the population at large have either little immunity to the virus or none at all, so the effect on the human population is larger and more widespread (more people are susceptible, therefore more become infected), and also more intense than during a 'normal' winter epidemic (the virus is novel and can produce severe illness). One possible route by which a pandemic may arise would be as a result of an avian influenza virus making small mutations over a period of time so that the virus gradually genetically adapted to humans. The conditions continue to exist for new pandemic influenza viruses to emerge and spread and are discussed in section 4.

Pandemic Influenza virus characteristics

Symptoms

3.8 Symptoms of avian influenza in humans have ranged from typical human influenza-like symptoms (fever, cough, sore throat, and muscle aches) to eye infections (conjunctivitis), vomiting and diarrhoea, pneumonia, severe respiratory diseases (such as acute respiratory distress syndrome), multi-organ failure and other severe and life-threatening complications. The symptoms of avian influenza appear to depend on the specific virus subtype and strain. For example, influenza A/H5N1 typically produces a severe life-threatening pneumonia, whereas influenza A/H7N7 produces mainly conjunctivitis and mild respiratory illness.

3.9 The symptoms of avian influenza described above do not necessarily represent the likely human symptoms of a future pandemic virus. The latter is simply unknown. Influenza pandemics of the last century produced relatively severe respiratory disease in 1918, but symptoms far more typical of 'normal' winter influenza in 1957 and 1968. We will not know the symptoms of the next pandemic virus until after it has emerged. Severe disease can neither be assumed nor can it be ruled out.

Transmission

3.10 The virus is likely to become ubiquitous across all areas of UK society within weeks of its introduction to the UK. The risks of exposure to symptomatic persons will be present in all areas of society (not least of which are the family home or workplace) and will certainly not be limited to healthcare or occupational settings.

3.11 For planning purposes, it is assumed that a future pandemic influenza virus will have similar transmission parameters (modes, incubation period, period of communicability) to normal seasonal influenza. However, although this is very likely to be a valid assumption, this is an area where uncertainty remains and will continue to remain until epidemiological data on the pandemic virus begin to emerge.

3.12 Influenza is well established to be transmitted from person-to-person through close contact with an infected coughing or sneezing person. Transmission almost certainly occurs through multiple routes[1] [2] including droplets and direct and indirect contact. Aerosol transmission may also occur in certain situations. There is no evidence which establishes a clear hierarchy for modes of transmission. However, the patterns of transmission observed during outbreaks frequently point to droplet and contact transmission as the most important and the most likely routes.

i. Droplets: particles propelled by coughing, sneezing and during the performance of certain medical procedures such as suctioning and bronchoscopy. They are generally regarded to be larger than 5 to >10μm in diameter, although there is no consensus on an absolute size. Droplets can be deposited on the conjunctiva or mucous membranes of the nose, mouth or respiratory tract and the environment. However, because of their relatively large size, generally droplets travel only short distances (typically less than one metre) before falling to the ground.
ii. Direct contact: occurs when the influenza virus is transferred from an infected person to a susceptible person without involvement of a contaminated intermediate object or person.
iii. Indirect contact: occurs when the influenza virus is transferred from an infected person to a susceptible person via a contaminated intermediate object (e.g. tissue) or person (e.g. contaminated hands).
iv. Aerosols: very small particles (typically thought to be <5μm in diameter although there is no consensus on absolute size) that can remain suspended in the air, due to their small size, and travel over long distances. Aerosols can be generated by certain medical

[1] Department of Health and Health Protection Agency. Pandemic Influenza: Guidance for infection control in hospitals and primary care settings (in press)
[2] Brankston G, Giterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. Lancet Infect Dis 2007; 7: 257-65.

procedures such as intubation, manual ventilation and suctioning, cardiopulmonary resuscitation, bronchoscopy, surgery and post-mortem.

3.13 The evidence base on influenza transmission is acknowledged to be relatively sparse and new research is urgently needed in this area. Unsurprisingly, there is a lack of international consensus over how this limited evidence base should be interpreted and translated into guidance and policy.

3.14 A literature review performed to inform the Pandemic Infection Control Guidance for healthcare settings in October 2006 concluded that the patterns of transmission observed during seasonal human influenza outbreaks most often point to short-range transmission suggesting that droplet and contact transmission are the most important and likely routes. However it has also been hypothesised by some researchers that "*in cases in which the source produces a low concentration of infectious particles, the aerosol becomes so dilute as it travels away from the source that most secondary infections occur in the immediate vicinity of the index patient. Therefore, the epidemiologic pattern associated with a dilute aerosol mimics that expected with large-droplet sprays or surface contact (i.e. face-to-face contact)"*[3]. This is an alternative explanation, but one which is currently hotly debated by scientists.

3.15 Since the time when the literature review was performed, no real new evidence has been presented in the scientific literature. A review by Tellier, which aimed to answer the question of whether aerosol transmission took place at all, concluded that aerosol transmission of influenza is significant[4]. Another recent review attempts to determine the relative importance of the different modes. Reviewing basically the same evidence, it arrives at the conclusion that the data are limited, but what data there are gives greater significance to transmission at close range rather than over long distances. They therefore conclude that aerosol transmission is unlikely to be of significance in most clinical settings[5]. Indeed, many of the publications reviewed in the article have been previously cited by other reviewers (including HPA) as supporting the case for predominantly droplet transmission. The EC European Centre for Disease prevention and Control (ECDC) also recommend concentrating countermeasures on the droplet and direct contact modes.

3.16 While the fundamental role of droplet transmission for symptomatic patients is accepted it is generally acknowledged that there may also be some transmission from pre-symptomatic and asymptomatic patients, although the observational evidence for this is limited. Experimental and observational studies have found that influenza viruses may be recovered at low levels from

[3] Roy CJ, Milton DK. Airborne transmission of communicable infection--the elusive pathway. N Engl J Med 2004;350(17):1710-2.
[4] Tellier R. Review of aerosol transmission of influenza A virus. Emerg Infect Dis;12(11):1657-62
[5] Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. Lancet Infect Dis 2007;7(4):257-65.

the respiratory tract of infected people a short while (typically up to 12 hours, occasionally up to 24 hours) before they develop symptoms. Reports of asymptomatic or pre-symptomatic patients excreting high levels of virus are rare and it is possible that any infections resulting from such transmission are mild or asymptomatic, although they could be of importance in maintaining chains of transmission. Other surveys suggest that many more people have been infected during annual epidemics than can be explained by the number of symptomatic cases observed. However, there are very few reports of new infections actually having arisen from contact with asymptomatic or pre-symptomatic persons. Certainly any infections which might arise as a result of transmission from pre-symptomatic or asymptomatic persons during a pandemic will most likely represent only a small minority of the total.

Virus survival

3.17 The evidence about human influenza virus survival on communal surfaces is effectively limited to one experimental study[6] in which human influenza A viruses were cultured from swabs of hard non-porous surfaces for up to 72 hours after inoculation and from soft porous items (e.g. tissues) for up to 24 hours. When the transferability of influenza A virus from contaminated surfaces onto hands was evaluated, measurable virus could be transferred to hands from hard stainless steel surfaces for up to 24 hours after the surface had been contaminated and from soft materials (pyjamas, magazines, tissues) for up to two hours after, although in very low quantities after 15 minutes. Therefore careful and frequent hand hygiene and sensible (manageable) environmental cleaning are important to help control direct and indirect contact spread.

3.18 One further experimental study[7] (Tiwari et al, 2006) recently noted far longer survival of low pathogenicity avian influenza virus A/H13N7 on a variety of surfaces (steel, latex, cardboard, fabric and plastic). However it is difficult to extrapolate the findings from a low pathogenicity H13N7 virus (which has never caused documented human infection) to a human adapted pandemic influenza virus and therefore could be misleading. The most recent experimental study (Thomas et al, 2007)[8] demonstrated that human influenza viruses mixed with respiratory secretions could survive on banknotes for up to 17 days (based on MDCK virus culture) depending on the concentration of virus applied to the note, but not necessarily in concentrations capable of infecting others; however other surfaces and materials were not tested.

3.19 Thus the current evidence base on virus survival is extremely limited and very difficult to translate confidently into national and international guidance. Further research is urgently needed in this area.

[6] Bean B, Moore BM, Sterner B, Petersen LR, Gerding DN, Balfour HH Jr. Survival of influenza viruses on environmental surfaces. J Infect Dis 1982;146:47-51.
[7] Tiwari, A, Patnayak D P, Chander Y, Parsad M, and Goyal SM. Survival of two avian respiratory viruses on porous and nonporous surfaces. Avian Dis. 2006 Jun; 50(2):284-7.
[8] Thomas Y, Vogel G, Wunderli W, Tapparel C and Kaiser L. Survival of influenza on banknotes. Poster P1531, Options for the Control of Influenza VI, Toronto, July 2007

Predicting the health and wider impacts of a pandemic

3.20 Past pandemics have varied in scale, severity and consequence, although in general their impact has been much greater than that of even the most severe winter 'epidemic'. Although little information is available on earlier pandemics, the three that occurred in the 20th century are well documented. The worst (often referred to as 'Spanish flu') occurred in 1918/19. It caused serious illness, an estimated 20–40 million deaths worldwide (with peak mortality rates in people aged 20–45) and major disruption. Whilst the pandemics in 1957 and 1968 (often referred to as Asian and Hong Kong flu respectively) were much less severe, they also caused significant illness levels and an estimated 1–4 million deaths between them.

3.21 It is impossible to predict the exact nature, timing or impact of any future pandemic, because the causal event will be the circulation of a new strain of influenza virus and such viruses differ in their attributes and effects. For planning purposes, impact assessments are derived from a combination of current virological and clinical knowledge, expert analysis, extrapolations from previous pandemics and mathematical modelling.

3.22 When influenza pandemics happen, many millions of people around the world become infected, up to around 50% become ill with symptoms, and a variable proportion die from the disease itself or from complications such as pneumonia. Depending upon the virulence of the influenza virus, the susceptibility of the population and the effectiveness of countermeasures, up to one half of the population may become infected and between 20,000 and 750,000 additional deaths (that is deaths that would not have happened over the same period of time had a pandemic not taken place) may have occurred by the end of a pandemic in the UK.

3.23 In the absence of early or effective interventions, society is also likely to face much wider social and economic disruption, significant threats to the continuity of essential services, lower production levels, shortages and distribution difficulties. Individual organisations may also suffer from the pandemic's impact on business and services. Difficulties in maintaining business and service continuity will be exacerbated if the virus affects those of working age more than other groups, and fear of infection, illness, care-providing responsibilities, stress, bereavement and potential travel disruption are all likely to lead to higher levels of staff absence. Staffing is therefore the critical element in business and service continuity plans.

3.24 High levels of public and political concern, general scrutiny and demands for advice and information are also inevitable at all stages of an influenza pandemic. An effective communications strategy that provides timely advice and information on the situation in the UK and in other countries must form a key part of the management strategy.

3.25 Given the lack of relevant information, assessments of impact on the overall economy are necessarily simplistic and can only be illustrative. One such

illustrative assessment suggests that illness-related absence from work of 25% of employees over the course of the pandemic (only half of what may be expected in a widespread pandemic) could reduce the year's gross domestic product (GDP) by between £3 billion and £7 billion. Additional premature deaths could cause a further reduction of between £1 billion and £7 billion depending on whether case fatality rates are low or high and whether earnings or gross output are used in the calculation. It is also possible that workers not affected by influenza directly may choose not to work for fear of contamination or because of the need to care for unwell relatives.

3.26 Against this, there may be scope for unaffected workers to make up some of the lost output. In addition, other losses may be made up later in the year as workers recover and resume normal working patterns. Overall, therefore, an influenza pandemic might be expected to reduce current year GDP growth by some 0.75%, which is relatively modest in the context of some of the macroeconomic fluctuations seen in the 1970s, 1980s and 1990s. In the longer term, the impact of premature death could reduce future lifetime earnings by between £21 billion and £26 billion at a low case fatality rate and by between £145 billion and £172 billion at a high case fatality rate; estimating this impact depends critically on assumptions about the age ranges affected and about future economic trends.

4. Emergence of an influenza virus with pandemic potential

4.1 This section addresses the three key questions about the risk of a pandemic:

- the likelihood of a new pandemic virus emerging;
- the likelihood that the next pandemic virus will emerge from the currently circulating H5N1 virus or from other influenza viruses; and,
- how serious the next pandemic is likely to be.

Historical evidence to support the emergence of a pandemic

4.2 It is generally agreed that a new pandemic virus will emerge at some stage, but no quantitative estimate of the probability of a pandemic can be made based on virological theory due to the lack of knowledge about the steps, processes and timescales involved in the evolution of the influenza virus' into those with pandemic potential. Analysis of historical records indicate that over the last few hundred years, major epidemics (possibly pandemics) have occurred at a frequency of around three per century, an empirical chance of around 3% per year[9]. However, the emergence of a pandemic virus remains random and as such cannot be predicted beyond the empirical assessment.

4.3 A number of authors have investigated the frequency of influenza epidemics and pandemics. For instance, Symes Thompson[10] describes 28 epidemics from 1510 to 1890, but not all of these were likely to be pandemics. Potter[11] provides an overview of the literature on influenza epidemics and classifies them into possible and definite pandemics (based on whether two or more authors reviewing the source material determined that they were pandemics). He lists three such "pandemics" in the 18th century (1729-33, 1781-82, 1799-1802), and three in the 19th century (1830-33, 1847-48, 1889-91), along with five (for which we have serological analysis) in the 20th century (1900, 1918, 1957, 1968-69, 1977-78). However, most experts classify 1900 and 1977-78 as epidemics only (in 1900 excess mortality was recorded in only a very restricted number of countries, and it is thought that the 1977 virus originated from a laboratory and had been circulating previously, resulting in a significant proportion of the population already having immunity).

4.4 To summarise, it is generally accepted that there were three pandemics in the 20th century (all of which also currently fall into the last hundred years; 1918-H1N1; 1957- H2N2; 1969- H3N2) with evidence of a similar frequency of pandemics in the 18th and 19th centuries. However, it remains impossible to predict the timing of the next pandemic as the event remains random.

[9] Nguyen-Van-Tam JS, Hampson AW. The epidemiology and clinical impact of pandemic influenza. *Vaccine* 2003;21(16): 1762-8

[10] Symes Thompson, E. Influenza or epidemic catarrhal fever: An historical survey of past epidemics in Great Britain from 1510 to 1890. Percival & Co. London. 1890.

[11] Potter CW Chronicle of Influenza Pandemics. In: Textbook of Influenza, Eds Nicholson KG, Webster RG & Hay AJ Blackwell Science, Oxford 1998.

Emergence of a pandemic influenza virus

4.5 Influenza viruses constantly evolve through a series of small consecutive but random mutations. They may also evolve in larger more abrupt steps, through a process known as genetic reassortment – genetic material is exchanged between influenza viruses which are markedly different from each other, sometimes originating from different species (e.g. material exchanged between a human influenza virus and an avian influenza virus).

4.6 An influenza pandemic occurs when an influenza virus evolves which is:

- markedly different from recently circulating (human) strains;
- able to infect people;
- readily transmissible from person to person;
- capable of causing illness in a high proportion of those infected; and
- able to spread widely because few – if any – people have natural or acquired immunity to it.

4.7 There is evidence that the human pandemics of the 20th century probably emerged via different means. In 1918 there is some evidence that the pandemic virus emerged as the result of an avian influenza virus making small mutations over a period of time so that the virus gradually genetically adapted to humans. However, in 1957 and 1968 it is more likely that these viruses emerged through genetic reassortment (genetic exchange between human and avian influenza viruses). This abrupt exchange of genetic material may have occurred in a third party species such as the pig, in whom there is evidence that simultaneous infection with human and avian influenza can occur. The possible origins of the 1918 pandemic virus (directly from an avian virus) help to explain the concerns now being raised about H5N1, although it is far from certain that H5N1 will produce the next pandemic.

4.8 Whilst a pandemic virus could first emerge anywhere in the world – including the UK – two of the three pandemics of the last century emerged in China (1957 and 1968). The most likely geographic origin of the earlier pandemics since the 18th century were China and central (Asian) Russia. The origin pandemic of 1918 is unknown[12]. Thus, this region of the world represents the most likely potential sources of the next pandemic. A pandemic virus is likely to initially spread to cause outbreaks and epidemics within the country of origin and its immediate neighbours before spreading globally to cause a pandemic. The conditions that allow a new virus to develop and spread continue to exist, and some features of modern society, such as air travel, could accelerate the rate of spread.

[12] Hampson, A. Surveillance for pandemic influenza. J Infect Dis. 1997;176(Suppl 1):S8-13

4.9 One such influenza A virus with pandemic potential is the avian influenza virus A/H5N1, which thus far has caused severe human illness in a few hundred cases worldwide (of whom approximately 60% have died), but which has not yet shown any ability to transmit efficiently from person to person. Whilst H5N1 is a possible progenitor for the next human pandemic, it is by no means certain that H5N1 will produce a human pandemic ever, and even if it were to do so, there is no clear indication as to when this might be.

Likelihood of emergence from an avian influenza virus

4.10 The relative probability of a pandemic originating from the current highly pathogenic avian H5N1 viruses rather than from any other influenza virus cannot be quantified because no comprehensive comparative data are available and there is poor understanding of viral evolution processes and risk factors.

4.11 The impossibility of quantifying either the absolute or relative risk from H5N1 is a key conclusion from a 2007 review paper by the Department of Health on 'Risk of a human influenza pandemic emerging from avian H5N1 viruses'[13]. The paper reflected available published scientific literature on this issue and was agreed by a number of government and independent scientific groups including DH's Pandemic Influenza Scientific Advisory Group (SAG), national and international peer review, independent scientific experts at the Secretary of State's High Level Scientific Colloquium on pandemic influenza and received final endorsement as the scientific evidence base by the Scientific Advisory Group. As that paper makes clear, H5N1 is of particular concern not because of any higher likelihood but because of the potential severity of its impact.

4.12 Avian influenza viruses are not the only possible source of a pandemic. Pigs, for example, have been widely reported to be theoretical mixing vessels for the origin of pandemic influenza, although definitive evidence supporting their role in the generation of a pandemic virus prior to its emergence in humans has not been proven. Nevertheless, they are receptive to infection with both human and avian viruses and the role of pigs in the generation of reassorted viruses has been shown with a number of virus subtypes.

4.13 There is endemic infection in pigs in the UK with H1N1 and H1N2 subtypes of influenza and it is well-established that humans with occupational exposure to pigs carry an increased risk of infection with influenza strains from pigs.

4.14 It should be noted that the extensive circulation of H5 viruses in regions where there are extensive pig populations that are also endemically infected with other influenza viruses indicates that these viruses are not efficient at a) infecting pigs and/or b) reassorting with other influenza viruses.

[13] Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_077276

4.15 It may be sensible not to distinguish between animal populations until there is a clear understanding of their potential role. However, should H5 or H7 infection become established in pigs, this might indicate that the virus has acquired the necessary characteristics to infect and spread within mammalian species.

4.16 Several avian viruses have in recent years infected humans. The following table summarises the number of confirmed human infections with avian influenza world-wide since 1997 to 1 June 2007.

Avian virus	H5N1	H7N2	H7N3	H7N7	H9N2	H10N7
Human cases (deaths)	329 (194)	7	2	89 (1)	3	2

Table 1. Summary of the number of human cases of Avian Influenza (as of June 1st 2007)

4.17 Whilst these have primarily been due to direct exposure to infected poultry there have been a few cases of suspected human-to-human transmission, including one cluster of H5N1 cases in Indonesia, which occurred in May 2006 (however, WHO have confirmed that efficient human-to-human transmission was not suspected).

Progress of H5N1 towards pandemic potential

4.18 All influenza A viruses can potentially cause a pandemic. The following section examines the factors considered by scientists to be important to this process with respect to H5N1.

Ability to mutate

4.19 Even though the probability of a pandemic arising from H5N1 cannot be quantified, the ease with which viruses mutate would appear to be a risk factor in assessing a virus' pandemic potential. Since their emergence in 1996, the current avian H5N1 viruses have shown an (ongoing) ability to change in a number of ways including:

- Considerable genetic variation in circulating viruses as a result of high rates of genetic drift (i.e. change in the virus due to accumulating mutations in individual genes) leading to the formation of distinct genetic families (or clades) of the H5N1 virus[14]. Within each of the H5N1 families or clades, there are separate sub-types (or genotypes) of the virus (Chen et al 2006[15]).

[14] The Writing Committee of the World Health Organisation (WHO) Consultation on Human Influenza A/H5. Avian Influenza A (H5N1) Infection in Humans. N Engl J Med 2005; 353 (13): 1374-85

[15] Chen H, Li Y, Li Z, et al. Properties and dissemination of H5N1 viruses isolated during an influenza outbreak in migratory waterfowl in western China. J Virol. 2006;80(12):5976-83.

- Expanded host range. Not only chickens, but also domestic ducks, other poultry[16], a broad range of non-domesticated avian species[17] and some mammals[18][19], including cats[20] dogs[21], civets[22], humans[23], mink and stone marten[24].

Transmissibility

4.20 To become a human pandemic strain, the current H5N1 avian virus will need to develop greater affinity for humans and efficient human transmission behaviour.

4.21 The ability of an influenza virus to establish in a new host population such as humans is thought to require at least two key properties. First, an ability to attach to target cells in the upper respiratory tract (this facilitates initial infection) and second, once inside the cell, a capability to direct the host cells to manufacture virus (to promulgate infection). Current transmissibility of H5N1 viruses in humans is relatively inefficient as these viruses lack the necessary genetic make up for efficient binding to predominant target cells in the upper airway of humans. In addition, virus replication will be influenced by key interactions between all viral genes and the replication machinery of the host and this is currently limited in H5N1 viruses with respect to human infection.

4.22 However, there continues to be a significant knowledge gap over the precise genetic characteristics required for efficient infection and transmission within humans. It is also possible that there are many different combinations of changes that could lead to the same end result and hence great uncertainty regarding the number of mutations required to convert a virus (including H5N1) into a pandemic strain.

4.23 Further discussion on developing a greater affinity for humans and efficient human transmission behaviour is given in Annex A.

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[16] Shortridge KF. Poultry and the influenza H5N1 outbreak in Hong Kong, 1997: abridged chronology and virus isolation. Vaccine. 1999;17 Suppl 1:S26-9
[17] Ellis TM, Bousfield RB, Bissett LA, et al.. Investigation of outbreaks of highly pathogenic H5N1 avian influenza in waterfowl and wild birds in Hong Kong in late 2002. Avian Pathol. 2004;33(5):492-505
[18] Thiry E, Zicola A, Addie D, Egberink H, et al. Highly pathogenic avian influenza H5N1 virus in cats and other carnivores. Vet Microbiol. 2007; 122(1-2):25-31.
[19] Vahlenkamp TW, Harder TC. Influenza virus infections in mammals. Berl Munch Tierarztl Wochenschr. 2006;119(3-4): 123-31
[20] Thiry E, Zicola A, Addie D, Egberink H, et al.. Highly pathogenic avian influenza H5N1 virus in cats and other carnivores. Vet Microbiol. 2007; 122(1-2):25-31.
[21] Songserm T, Amonsin A, Jam-on R, et al. Fatal avian influenza A H5N1 in a dog. Emerg Infect Dis. 2006;12(11): 1744-7
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[23] Alexander DJ. Avian influenza viruses and human health. Dev Biol (Basel). 2006;124:77-84
[24] WHO. Strengthening pandemic-influenza preparedness and response, including application of the International Health Regulations (2005) - Report by the Secretariat. 24 April 2006. At:www.who.int/gb/ebwha/pdf_files/WHA59/A59_4-en.pdf

4.24 Although H5N1 has clearly demonstrated its ability to infect humans, the ease with which transmission occurs from birds to humans is currently low. Retrospective serological analyses performed in a Cambodian village where a confirmed human case of H5N1 had occurred and where there had been numerous poultry fatalities (in 67% of all households), confirmed that, other than the index case, none of the 351 participants from almost 100 households in which frequent, direct contact with poultry had occurred had been infected[25]. In addition from recent data obtained on more than 1000 workers in Indonesia involved in the culling of H5N1 infected poultry, only two showed serological evidence of H5N1 infection (personal communication)[26]. New data released orally in Toronto in June 2007 reveal that among Nigerian poultry workers in an area affected by H5N1 die-offs, no seroconversions had occurred[27].

Virulence

4.25 The impact of a pandemic will also depend on its virulence (the ability to cause disease and severity of the disease) of the pathogenic virus as well as its transmissibility. As detailed in table 1, the case fatality ratio of around 50 - 60% for the reported human cases of avian H5N1[28] confirms that this virus is highly virulent for humans. A case fatality rate of 2.5% is used as the upper boundary for planning purposes. This is based on estimates of the case fatality rate for 1918/1919 (the most severe of the three 20th century pandemics) which generally fall between 2.0 and 2.5% for the UK. It also reflects the uncertainty surrounding the relationship between virulence and transmissibility i.e. to successful pass from human to human some scientists predicts that the case fatality rate would be reduced.

4.26 This case fatality ratio is based only on cases that have come to medical attention, and medical intervention has often been late. Theoretically, there might be cases of infection without serious symptoms that therefore go undetected. This would reduce the case fatality rate. However, as more countries institute monitoring of people in the vicinity of an avian outbreak of H5N1 and fail to detect asymptomatic infections and as more population surveys from H5N1 endemic areas fail to reveal asymptomatic infections, this seems so far unlikely.

[25] Vong S, Coghlan B, Mardy S, Holl D, Seng H, Ly S, Miller MJ, Buchy P, Froehlich Y, Dufourcq JB, Uyeki TM, Lim W, and Sok T. Low frequency of poultry-to-human H5NI virus transmission, southern Cambodia, 2005. Emerg Infect Dis. 2006; 12(10):1542-7.
[26] Promed posting by Prajitno TY, archive number 20070605.1821, available on http://www.promedmail.org/pls/promed/f?p=2400:1000
[27] Katz MA, Ortiz JR, Mahmoud M, Ahmed S, Bawa S, Farnon EC, Sarki MB, Nasidi A, Ado MS, Yahaya AH, Joannis TM, Achenbach J, Breiman RF, Vertefeuille JF, Katz JM, Uyeki TM, Wali S. Risk of Occupational Transmission of Avian Influenza A (H5N1) Virus, Northern Nigeria, March 2006. Oral O20. Options for the Control of Influenza VI, Toronto, July 2007
[28] WHO. Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO. Available at: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2007_03_12/en/index.html

4.27 Key areas of uncertainty are whether an avian H5N1-derived pandemic virus would retain its very high fatality rate as it adapts, or whether the changes required to make it transmissible between humans would impact on this. The precise relationship between transmissibility and virulence has not been established for influenza viruses in general. Experts agree that understanding of this relationship is a significant gap in our knowledge and further studies are needed. However, the majority of experts consider that there is no direct link between transmissibility and virulence. It cannot, therefore, be assumed that the virus would lose its virulence as it became more transmissible

Host susceptibility and host-pathogen interactions

4.28 There is little evidence available on which characteristics make a host more susceptible to infection from influenza viruses in general and H5N1 in particular. Recent family clusters of H5N1 in Indonesia may suggest evidence for an as yet unspecified shared susceptibility factor, although the clustering could also be due to shared exposure factors[29]. Experts agree that this is another key area for future research.

4.29 With regard to seasonal influenza, an outbreak of influenza A/H3N2 in the Fianarantsoa province of Madagascar in 2002, which caused unusually high mortality, was attributed in part to underlying malnutrition in the population.[30]

Summary

4.30 There are many uncertainties surrounding the question of whether the next pandemic virus will emerge from the currently circulating H5N1 virus, and the simple answer is that we do not know. Most experts, including the World Health Organization (WHO) and the European Centre for Disease prevention and Control (ECDC), advise that pandemic flu planning should be prepared for an H5N1-origin pandemic virus, but not at the cost of disregarding other potential sources. For example, H2 viruses have a track record of causing human illness and have not been in human circulation for many years therefore increasing the susceptibility of the population. Other avian viruses are also in circulation in birds and some of these have demonstrated clearly that they can cause clinically apparent illness in humans (e.g. H7, H9 viruses) as per table 1.

How serious will the next pandemic be?

4.31 The potential impact of a pandemic virus will be determined by its:

- Clinical Attack Rate (CAR; the proportion of the population who develop symptoms severe enough to be readily identified as influenza[31]); and

[29] http://www.cdc.gov/eid/content/13/7/1074.htm?s_cid=eid1074_e
[30] MMWR 2002; 51(45):1016-18
[31] The measured clinical attack rate is not always the number who actually develop symptoms, but the number remembering symptoms (retrospectively), or the number seeking healthcare. This may be the most important reason for variation between different estimates.

- Case Fatality Rate (CFR).

4.32 These key parameters will only become known once the virus has emerged and been circulating in the community. Previous pandemics, modelling and published papers have suggested a range of possible assumptions for these parameters to assist national and local planning. Advice from DH's Scientific Advisory Group (SAG) and its modelling subgroup has been the basis for the planning assumptions used in the UK.

Clinical Attack Rate

4.33 The clinical attack rate depends on:

i) the infection attack rate: the proportion of the population infected by the virus. This is determined broadly by the parameter R_0, the basic reproduction number, which measures the number of people infected by one infected individual early in an epidemic; and

ii) the proportion of those who show characteristic clinical symptoms[32].

4.34 Determining the clinical attack rates of previous pandemics is problematical as most of those with mild clinical symptoms will not have come into contact with the health care system. Therefore evidence that does exist comes from various local studies. For the 1918/19 pandemic, attack rates in the UK (over multiple waves) seem to have varied from a little over 20% to 30% suggesting a national clinical attack rate of around 25%. 1957 reported clinical attack rates seem to have been higher, at around 30%, but with a similar local variation. The attack rate in 1968/69 may have been over 35%[33]. Taken together this suggests an historical range of attack rates between 25% and 35% in the UK with significant (~5% points) local variation and generally higher rates in closed communities.

4.35 The value of the basic reproduction number R_0 currently being used by other countries planning for a pandemic ranges from 1.4 – 3.5, although the scientific basis for the value selected is not always clear. Pandemic modelling has tended to work on the basis of R_0 1.8 to 2.5[34]. Based on expert views in SAG, the UK's assumption for R_0 has been close to 2. The general consensus is that a future pandemic would be expected to have an R_0 in the range 1.4 - 2.2. Depending on the detailed model used, this could lead to a national infection attack rate of the order of 80%.

4.36 The combination of an 80% infection attack rate and a figure of 67% for the proportion of these showing clinical symptoms (based on the higher estimates from surveys of those in previous pandemics and outbreaks of seasonal influenza) suggest an upper limit for the national clinical attack rate of the

[32] Assuming that in a pandemic situation initial immunity in the population is negligible.
[33] Based on comparisons with the epidemic in the United States.
[34] Because models are fitted to actual historical data, the variation in different model results for different estimates of Ro is less than might be assumed given the spread in the numerical estimates of Ro. The range of Ro-s used *within* a particular model is, however, significant.

order of 50%[35]. While such a figure would be extreme for the national epidemic, planning to this figure also allows for variation in local infection transmission rates which may generate local attack rates in excess of the national average in some areas.

Case Fatality Rate

4.37 The Case Fatality Rate (CFR) for seasonal influenza and for the 1957 and 1969 pandemics was approximately 0.4% (though this overall figure masks considerable variation by age, with most deaths occurring in the elderly in these pandemics), whereas the 1918 pandemic estimated CFR was around 2%, with less variation by age group. Based on historical pandemics the draft UK National Framework suggested that it would be prudent to plan for up to 2.5% CFR as a reasonable worst case.

4.38 In advising that pandemic preparedness activities should be prepared for an H5N1-origin pandemic virus, but not at the cost of ignoring other potential sources, a key element of experts' risk assessment has been the highly pathogenic nature of the current H5N1 strain and whether that would be retained following further virus evolution, in particular the high case fatality rate. Experts express diverse views on this, with some proposing that the virus could in the worst possible case retain a very high case fatality rate should it become pandemic. There is general agreement that an H5N1 epidemic would, in general, be expected to be a severe disease. However, experts also agree that the question whether there is a relationship between transmissibility between humans and virulence is important and needs further research.

How long will the next pandemic be?

4.39 The duration of the UK epidemic will also be a key factor in determining the impact of the pandemic (for a similar CAR, the shorter the duration of the epidemic, then the higher the peak, and therefore the greater the stress on services). A pandemic profile (i.e. the proportion of cases, deaths etc expected each week) has been constructed to guide planning. The profile is similar to that of the second wave of the 1918/19 pandemic in London and suggests a pandemic wave might last around 15 weeks. There might be a number of such waves weeks or months apart. This profile represents the fastest build up that might be expected for a *national* epidemic. About 22% of new cases occur in each of the peak weeks.

4.40 Local epidemics in Primary Care Trust (PCT) sized areas would be expected to be both more highly peaked and of a shorter duration than the national epidemic. Empirical evidence from 1918 suggests that there would also be a large variation in profile from PCT to PCT.

[35] In special circumstances however, for example enclosed communities, a much higher figure closer to 90% has been observed in previous pandemics.

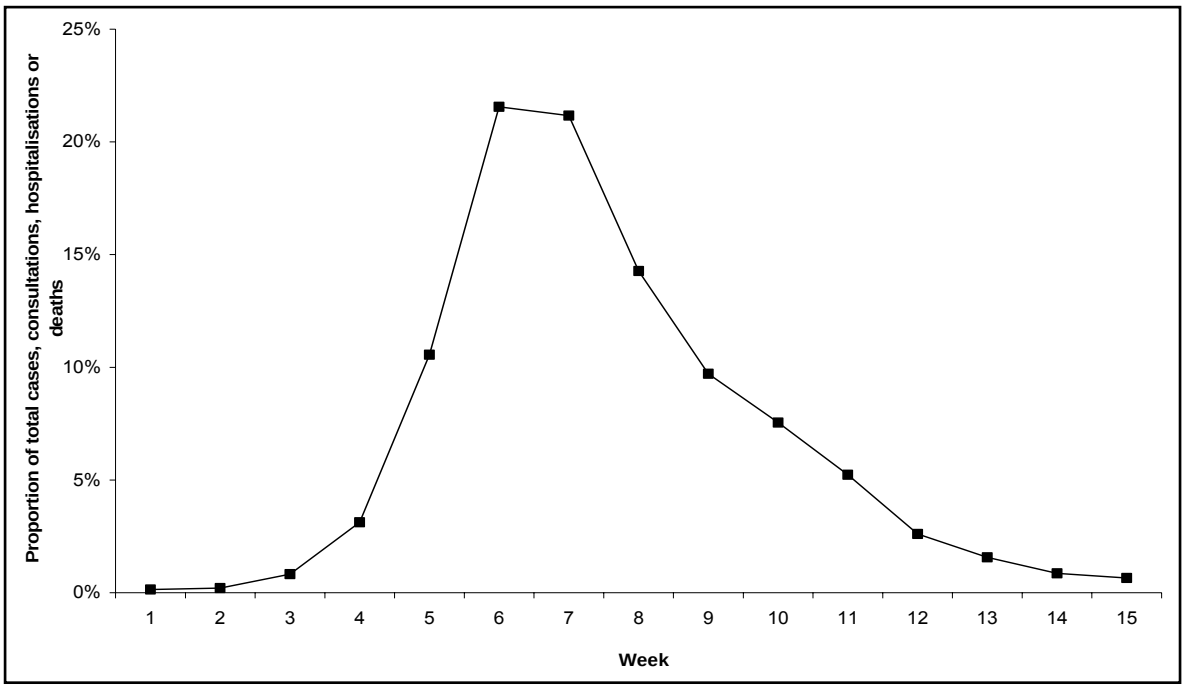

Figure 2: UK national planning profile of weekly numbers of cases, hospitalisations, deaths etc. as proportion of total numbers, over single wave pandemic. The profile shows what proportion of the total over the entire pandemic wave could be expected in a given week.

Section B – Evidence underpinning the Clinical Countermeasures

5. Risk Reduction

5.1 This section considers the evidence base for measures to delay the spread of the disease and focuses on the use of antiviral drugs for prophylaxis of early clusters both in the UK and in other countries.

What are antiviral drugs?

5.2 Antiviral drugs can be used to treat a viral infection or to prevent infection from a virus (prophylaxis).

5.3 Antiviral drugs work by inhibiting viral proteins (e.g., M2, or neuraminidases) on the surface of the influenza virus and preventing the ability of the virus to replicate effectively within the body, hence lessening symptoms and the likelihood of complications. The evidence base for these characteristics is established through the regulatory process for the three antivirals licensed in the UK for the treatment and prophylaxis of (seasonal) influenza:

- oseltamivir (Tamiflu®) and zanamivir (Relenza®) which target the neuraminidases on the surface of the virus and are known as neuraminidase inhibitors; and

- amantadine (Symmetrel®) which targets the M2 proteins on the surface of the virus.

5.4 Unlike vaccines, which must be based on a strain closely related to the pandemic strain to provide protection, these antivirals have 'generic' activity against the surface proteins of influenza A and/or B strains (though with some degree of variation depending on the specific virus encountered).

5.5 Further information on the factors affecting antiviral choice, including effectiveness, side effects and resistance is discussed in section 6.

Use of antivirals for prophylaxis of early clusters

5.6 The primary purpose of antivirals is to reduce the severity and duration of illness in individual patients. In addition to their use in the treatment of cases, antiviral drugs can be used to prevent infection (i.e., prophylaxis) in two ways:

I. Post-exposure prophylaxis: in which a short course of antiviral drugs (10 days duration) is given to those who have been in contact with an infected person with the intention that this will act as a form of 'early treatment' that will stop the virus beginning to multiply in the body. Such treatment may still allow the development of a natural antibody

response to influenza, providing longer term protection. In addition to the individual effect of post-exposure prophylaxis (prevents the recipient getting influenza) there is an additional population effect brought about by the recipients being less likely to become infectious cases themselves.

II. Pre-exposure prophylaxis: when antiviral drugs are given for a long period, beginning in advance of any exposure to influenza and continuing for the duration of the likely risk of exposure. It seems most likely that once pre-exposure prophylaxis ceases, the recipients' underlying susceptibility to influenza is unaltered, i.e. it is far less likely that the recipient will have developed protective antibodies. Pre-exposure prophylaxis thus requires very large stocks of antivirals and, unless it can be sustained until individuals are vaccinated, will merely delay a pandemic until the supply of drug is exhausted.

5.7 The effectiveness of antivirals against a new pandemic influenza strain cannot be known until that virus has emerged. However, neuraminidase inhibitors demonstrate activity against all influenza strains (although susceptibility may vary) and it is a reasonable assumption that in broad brush terms, a pandemic virus should be sensitive to some extent.

5.8 The UK's current response strategy includes limited post-exposure prophylactic use of our current stockpiles of antivirals (oseltamivir) in the very early stages of a pandemic when the UK is responding to the possible first introductions of the pandemic virus. This strategy of attempting to 'stamp out' the first sparks of a pandemic, would be undertaken in order to buy a little extra time for the UK, but would be unsustainable, and would ultimately fail to prevent the virus being introduced into the UK. It is intended that no more than 0.1% of the UK's existing stockpile will be used in this way; however, the logistics of delivering post-exposure to large numbers of people may mean that even this amount is not used before the strategy is abandoned.

5.9 Although the use of antivirals for limited post-exposure prophylaxis in the very early stages of a pandemic is unlikely to delay the pandemic's arrival in the UK by more than 1-2 weeks (and possibly for much less than this). Nevertheless, by adopting such an approach, valuable epidemiological data will be obtained about the effect of antivirals on household transmission, which may influence the way in which the UK deploys its antiviral stockpile in subsequent Alert Levels of the UK response.

5.10 Post-exposure prophylaxis is more practicable than pre-exposure. Modelling has suggested that a combination of targeted post-exposure prophylaxis and social distancing measures could in theory contain an emerging pandemic in the first affected country (assuming a rural rather than an urban population) and that a stockpile of 3 million courses would be sufficient for a reasonable chance of success. Whilst this modelling is well established and respected internationally, the practical application of such an approach (as outlined in the *WHO interim protocol: Rapid operations to contain the initial emergence*

of pandemic influenza[36]) including timely receipt and distribution of antivirals in a containment zone would pose considerable challenges in many countries and remains untested.

5.11 Considerable evidence indicates that both the neuraminidase inhibitors (i.e., oseltamivir and zanamivir) and the M2 inhibitors (e.g., amantadine) work well in prophylaxis against susceptible seasonal influenza viruses and that prophylaxis does not increase resistance. In fact, amantadine prophylaxis has been tested in a pandemic situation and showed efficacy against influenza illness of 70%–80%[37], although as with most amantadine trials this evidence is of an age to predate current regulatory standards for conduct and assessment. No direct comparisons have been carried out, but oseltamivir and zanamivir appear at least as efficacious as amantadine[38]. However, due to issues with the propensity for resistance and its side-effect profile, amantadine is not regarded as a good choice for prophylaxis by most authorities (see Sections 6.13 and 6.18).

5.12 In summary, the evidence base is largely supportive of post-exposure prophylaxis of contacts in the early stages of the pandemic, subject to adequate logistical arrangements being in place to ensure rapid delivery of the drugs (i.e. within 12 to 24 hours of the first symptoms).

[36] *WHO interim protocol: Rapid operations to contain the initial emergence of pandemic influenza.* Geneva, World Health Organization 2007 (http://www.who.int/csr/disease/avian_influenza/guidelines/draftprotocol/en/index.html, accessed August 2007)

[37] Monto AS, Gunn RA, Bandyk MG, King CL. Prevention of Russian influenza with amantidine. JAMA. 1979; 241:1003-7

[38] Monto AS, Robinson DP, Herlocher ML, Hinson JM Jr, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomised control trial. JAMA. 1999; 282:31-5; Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med. 1999; 341:1336-43;
Cheer et al. (2002) 'Zanamivir: an update of its use in influenza' *Drugs* 62(1): 71-106;
Langley et al. (2004) 'Prevention of influenza in the general population' *CMAJ* 171(10): 1213-22; Welliver et al. (2001) 'Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial' JAMA 285(6): 748-54

6. Mitigation/treatment

6.1 This section considers the evidence base for clinical countermeasures aimed at reducing the severity and number of deaths in the UK, other than essential medicines and healthcare supplies for other illnesses.

Antiviral drugs for treating those who become ill

6.2 This part of the paper considers the evidence base on the use of antiviral drugs for treatment. Section 5 of this paper, on suppression, considered the evidence base on the use of antivirals for prophylaxis of early clusters.

6.3 Decisions on which antivirals to stockpile for their use in treatment against a pandemic virus are likely to be based on consideration of the following scientific and technical factors:

i. Their effectiveness in the treatment of seasonal influenza viruses (particularly influenza A type viruses) in reducing morbidity and mortality, preferably using the results of head-to-head studies;
ii. The risk that the pandemic virus could develop resistance to the antiviral drug;
iii. The risk of adverse events from their use;
iv. Their ability to reduce the risk of complications;
v. Their systemic bio-availability (ability to get into various tissues/organs of the body) in the event that the pandemic virus also infects other parts of the body as well as the respiratory tract;
vi. Their ease of use or administration;
vii. Whether they are licensed for all age groups; and
viii. Their cost.

6.4 Factors i. to iv. are considered in the discussions below and are generally supportive of the neuraminidase inhibitors (zanamivir and oseltamivir), compared with amantadine for stockpiling in the event of an influenza pandemic. The remaining scientific and technical factors (v. to vii.) add further weight to the case in support of oseltamivir compared with zanamivir.

Effectiveness

6.5 The evidence has been reviewed by the National Institute for Clinical Excellence (NICE) in developing their guidance on the use of antivirals for the treatment and prevention of seasonal flu[39]. These reviews reported data which demonstrated the effectiveness of oseltamivir and zanamivir in alleviating and reducing the duration of symptoms. The reviews also highlighted the limited clinical data available for amantadine which did not allow firm estimates of its effectiveness. One study did suggest that

[39] NICE technology appraisal No. 58 (2003) Guidance on the use of zanamivir, oseltamivir, and amantidine for the treatment of influenza. Available at: http://www.nice.org.uk/pdf/58_Flu_fullguidance.pdf

amantadine might reduce fever and symptoms more rapidly than aspirin[40]. Oseltamivir and zanamivir are recommended for treatment of seasonal influenza in children or adults who fall into one or more of several specifically defined 'at risk' groups. However, NICE guidelines are aimed at seasonal influenza and explicitly do not apply to pandemic influenza, for which seasonal influenza may or may not be a good model.

6.6 The NICE reviews also considered data on the effectiveness of antivirals in reducing complications which suggested that oseltamivir and zanamivir were effective, although this was based on very limited evidence and only reached statistical significance for oseltamivir. The suggested levels of benefit for oseltamivir are a 40-50% reduction in both hospitalisations and complications requiring antibiotics (note that data are from meta-analyses). There are no published estimates of the effectiveness of oseltamivir or zanamivir on reducing deaths from influenza. There are no clinical data on amantadine on reducing complications.

6.7 The evidence base has also been reviewed by a range of authors, including a systematic review and meta-analysis of the efficacy, effectiveness and safety of antivirals used for the treatment and prophylaxis of seasonal influenza in healthy adults which considered evidence from 52 randomised control trials[41] [42] [43]. The meta-analysis (Jefferson et al 2006) presented a mixed picture of the effectiveness of antivirals for seasonal influenza in healthy adults and concluded that the use of amantadine (and rimantidine) should be discouraged. Even though it also recommended neuraminidase inhibitors should not be used in seasonal influenza control because of their low effectiveness, it did recommend these for use in a pandemic alongside other public health measures.

6.8 Antiviral drugs, whether for treatment or for post-exposure prophylaxis, work by reducing or eliminating virus replication. In order to do this effectively they need to be administered relatively quickly after the onset of symptoms (in the case of treatment) or after exposure to the virus (in the case of post-exposure prophylaxis). In the case of both neuraminidase inhibitors, the licence specifies that treatment should commence within 48 hours of the onset of symptoms. However data exist which indicate that for treatment, the effects are significantly improved when the delay between starting drug and symptoms or exposure is of the order of 12-24 hours. Logistically, this is a serious challenge, but one where the potential benefits of success are high.

6.9 Clinical data reveal that the earlier treatment is commenced after the onset of symptoms, the less virus will be excreted by that individual. Modelling data

[40] Younkin SW, Betts RF, Roth FK, Douglas RG Jr. Reduction in fever and symptoms in young adults with influenza A/Brazil/78 H1N1 infection after treatment with aspirin or amantidine. Antimicrob Agents Chemother. 1983; 23:577-82

[41] Monto AS (2003) The role of antivirals in the control of influenza. Vaccine. vol. 21(16), 1796-1800.

[42] Monto AS (2006) Vaccines and antiviral drugs in pandemic. Emerging Infectious Diseases. Vol.12, No.1, January 2006

[43] Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367(9507):303-13.

suggest it is possible that, if treatment was started early enough, antivirals may also reduce both the length of time people are infectious to others, and their infectivity during this period and hence reduce spread of the virus.

6.10 Knowledge of the effectiveness of antiviral drugs is based on treatment and prevention of seasonal influenza epidemics. Their effectiveness against pandemic influenza cannot be known until a pandemic virus has emerged.

6.11 It may be possible to extrapolate potential efficacy against a pandemic strain from experience of using antivirals to treat human infections with avian influenza (i.e. because the population is as immunologically naive to such viruses as it would be in a pandemic). Data recently presented from the human cases of H5N1 in Turkey suggest that the use of oseltamivir within 5 days of symptom onset was associated with survival (3 of 3 cases) whereas later treatment than this (6-10 days after symptoms) carried a poorer prognosis (4 of 5 died)[44]. Nevertheless, extreme care is needed in trying to extrapolate this experience to pandemic efficacy[45].

Ability to develop resistance

6.12 The potential for a pandemic virus to be, or to become, resistant to an antiviral cannot be predicted, although the evidence below gives an indication of potential resistance levels of currently available antivirals.

6.13 Some strains of the influenza A virus rapidly become resistant to amantadine. Most notably resistance had occurred in approximately 30% of those given the drug for treatment of H3N2 strain of seasonal influenza. In that case, the resulting resistant viruses were fully pathogenic and transmissible[46]. When outbreak control with amantadine has failed in closed communities, amantadine resistant virus has been isolated. However, when amantadine has been widely used for treatment, as in Japan, there is evidence to show that there is limited circulation of resistance virus[47]. Notwithstanding, recent data from the US revealed that in 2005-06, over 90% of influenza A/H3N2 viruses isolated from patients, contained a mutation on the M2 gene which confers resistance to amantadine (and rimantadine)[48]. Adamantane resistance has reached 100% among A/H3N2 isolates from some Asian

[44] Oner AF, Bay A, Arslan S, et al. Avian influenza A (H5N1) infection in eastern Turkey in 2006. N Engl J Med. 2006 23;355(21):2179-85.
[45] European Medicines Agency (EMEA) *Review on influenza antiviral medicinal products for potential use during a pandemic* (2005); WHO Rapid Advice Guidelines (2006) and Roche fact sheet on oseltamivir www.roche.com/med_mboseltamivir05e.pdf.
[46] Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantidine and rimantidine. Curr Top Microbiol Immunol. 1992; 176:119-30
[47] NICE technology appraisal No. 58 (2003) Guidance on the use of zanamivir, oseltamivir, and amantidine for the treatment of influenza. Available at: http://www.nice.org.uk/pdf/58_Flu_fullguidance.pdf
[48] Bright RA, Shay DK, Shu B, Cox NJ, Klimox AI. Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. JAMA, 2006;295(8):891-4

countries.[49]. Due to its propensity for resistance, the Neuraminidase Inhibitor Susceptibility Network (NISN) advises that amantadine cannot be relied upon for clinical management of influenza and it is currently not recommended for treatment or prophylaxis of seasonal flu in many countries (including the UK, US and Canada). Strains resistant to amantadine are able to transmit disease and its safety profile is unfavourable relative to the neuraminidases. For these reasons, amantadine is not currently regarded as the preferred drug for pandemic stockpiling.

6.14 However, because of its significantly lower cost[50] and the fact that amantadine inhibits a different part of the replication process than the neuraminidases, it has been cited[51] as a potentially useful addition to the antiviral anti-pandemic arsenal. This is in case the new virus should prove insensitive to neuraminidase inhibitors, and also to allow treatment with a combination of antivirals in serious cases, or for prophylactic use only (where there is less chance of inducing resistance). Notwithstanding the above argument, it should be noted that two of the four major variants of H5N1 are already resistant to the drug[52].

6.15 While resistance does occur when oseltamivir is used for treatment, it is far less frequent than with amantadine, and the resistant viruses have appeared to be less infectious and transmissible than the original (wild) virus. However, it is possible that with high volume use of oseltamivir, for example during a pandemic, resistant viruses could begin to circulate.[53] No influenza virus resistant to zanamivir has yet been identified, possibly because zanamivir has been used less, but possibly because it binds extremely tightly to the neuraminidase site. There is likely to be the same potential for future resistant strains as for oseltamivir. Whilst no clinical data on the susceptibility to zanamivir of oseltamivir resistant strains is available, laboratory data indicate that such strains isolated thus far would still be sensitive to zanamivir[54].

[49] Deyde VM, Xu X, Bright RA, Shaw M, Smith CB, Zhang Y, Shu Y, Gubareva LV, Cox NJ, Klimov AI. Surveillance of reitance to adamantanes among influenza A(H3N2 and A(H1N1) viruses isolated worldwide. J Infect DIs, 2007;196(2): 249-57

[50] BNF March 2007: cost of course of oseltamivir (Tamiflu®) £16.36, zanamivir (Relenza®) £24.55 and amantadine (Lysovir®) £2.40.

[51] Sotirios Tsiodras, John D Mooney, and Angelos Hatzakis. Role of combination antiviral therapy in pandemic influenza and stockpiling implications BMJ 2007 334: 293-294

[52] Hay A. Overcoming Antiviral Resistance – prospects for new NA and HA inhibitors. Oral TS2. Options for the Control of Influenza VI, Toronto, July 2007

[53] Monto AS. Vaccines and antiviral drugs in pandemic preparedness. Emerging Infectious Diseases. 2006; Vol 12, No.1: 55: 60 and Lipsitch M, Cohen T, Murray M, and Levin BR. Antiviral Resistance and the Control of Pandemic Influenza. PLoS Med. 2007 Jan 23; 4(1):e15.
Notes: G:PI\science\antivirals

[54] Hayden, F. G. and Pavia, A. T. Antiviral management of seasonal and pandemic influenza. J Infect Dis. 2006;1;194(Suppl 2):S119-26.

6.16 The latest view from the NISN, taking account of all the information on potential resistance, is that oseltamivir and zanamivir would be suitable to stockpile for pandemic purposes.[55]

6.17 The possible emergence of resistance of the virus to antivirals is a key consideration in deciding on the make-up of a stockpile. Stockpiling an alternative antiviral(s) in the UK, as advised by the Royal Society and the Academy of Medical Sciences, may allow an alternative strategy should resistance to oseltamivir develop and produce clinical failures. As recommended by the Science Colloquium, having more than one antiviral drug in a stockpile may be prudent and thus represents good business continuity management. The DH science paper concludes that based on current knowledge, neuraminidase inhibitors are the preferred choice for stockpiling.

Side-effects

6.18 Oseltamivir and zanamivir are generally well-tolerated products and experience so far is that serious side-effects are very rare. On the other hand nausea and vomiting are common (meaning occurring in 1-10% of patients) with oseltamivir but not with zanamivir. Special precautions apply to use of oseltamivir in patients with severe renal disease because the drug is excreted via the kidneys. Very rarely zanamivir (an inhaled drug) is associated with acute bronchospasm which may be severe and serious. Special precautions apply to use of the drug in patients with asthma and chronic bronchitis. Amantadine is associated with a wide variety of adverse events affecting the central nervous system (loss of concentration, dizziness, agitation, nervousness, depression, insomnia, fatigue, weakness) and myalgia (pain in muscles), cardiovascular and gastrointestinal systems, and the skin, eye and urinary tract. A recent review[56] concluded that the balance of efficacy versus trivial adverse effects was considered unfavourable for healthy adults aged 14-60 for all three antivirals but the validity of these conclusions for pandemic flu is not known.

6.19 Recently, the Japanese regulatory authorities have recommended that oseltamivir should not be used in teenagers, following reports of two teenage boys taking the drug who both broke legs whilst attempting suicide by jumping from windows, and 64 other reports of abnormal behaviour whilst on the drug. The European and US regulatory bodies have not replicated this advice, and in these territories the drug merely carries a precautionary statement about possible neuro-psychiatric effects. The European Medicines Agency has stated that it cannot draw a causal link between oseltamivir and suicide. New data (not yet published) drawn from a large US insurance cohort based on 226,000 patients with influenza-like illness of whom 101,000 received

[55] Information taken from Hayden et al (2005) 'Neuraminidase Inhibitor Susceptibility Network (NISN) position statement: antiviral resistance in influenza A/H5N1 viruses' *Antiviral Therapy* 10:873-877

[56] Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367(9507):303-13.

oseltamivir, demonstrate that the incidence of neuro-psychiatric events was no higher in those treated with oseltamivir compared with those not treated.

Ease of use

6.20 Zanamivir and oseltamivir differ in the way they are administered, by oral inhalation and by capsule or solution respectively, which means that zanamivir has a different distribution profile (lower systematic availability but higher availability in lung tissue) than oseltamivir. The enhanced systemic bio-availability of oseltamivir could be a significant advantage should the pandemic virus also involve infection of the brain and the gastrointestinal tract, as well as its more usual target, the respiratory tract. This wider spread of infection has already been observed in some human cases of H5N1 and has also been demonstrated in laboratory animals such as ferrets and cats exposed to H5N1[57].

6.21 Data exist which suggest that a large proportion of elderly people will have difficulty in operating the device used to administer zanamivir[58]. By inference, the same is likely to apply to younger children.

6.22 Oseltamivir is licensed for use for treatment (and prophylaxis) of adults and children over one year. In contrast, zanamivir is indicated for treatment (and prophylaxis) in adults and children aged 5 years and over.

6.23 In summary, the scientific case indicates that zanamivir and oseltamivir are supported by reasonable clinical data on effectiveness: they are better tolerated than amantadine; antiviral resistance has not emerged as a significant problem; and limited evidence suggests they may reduce the frequency of influenza complications. Oseltamivir may have additional benefits to zanamivir by being more systemically available against a wider spread of infection in the body; it is easier to use and can be given to younger children (one year and over). However, zanamivir has fewer side-effects, a higher bio-availability in the lungs and theoretically less potential for viruses to develop resistance to it than oseltamivir[59]. In contrast to zanamivir and oseltamivir, amantadine and other M2 inhibitors have downsides including side-effects of a more serious nature, and with amantadine, the emergence of

[57] Govorkova EA, Rehg JE, Krauss S, Yen H-L, Guan Y, Peiris M, et al. Lethality to ferrets of H5N1 influenza viruses isolated from humans and poultry in 2004. J. Virol. 2005; 79:2191-8 and Rimmelzwaan GF, van Riel D, Baars M, Bestebroer TM, van Amerongen G, Fouchier RA, Osterhaus AD, and Kuiken T. Influenza A virus (H5N1) infection in cats causes systemic disease with potential novel routes of virus spread within and between hosts. Am J Pathol. 2006 Jan; 168(1):176-83;

[58] Diggory P, Fernandez C, Humphrey A, Jones V, and Murphy M. Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial BMJ, 2001; 322: 577-9.

[59] Varghese JN, et al. Drug design against a shifting target: a structural basis for resistance to inhibitors in a variant of influenza virus neuraminidase. Structure 1998;6:735-46 and Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med, 2005;353:1363-73.

antiviral resistance and the lack of demonstrated prevention of complications[60].

6.24 In the absence of any certainty about the effectiveness of antivirals, the size of the stockpile of antivirals that countries should secure depends on the antiviral policy adopted, the level of risk accepted and the assumed effectiveness of the drugs against a virus which does not currently exist.

Antibiotics for treating secondary infections

6.25 The main complication of seasonal influenza is secondary bacterial infection, particularly pneumonia, due to a range of bacteria with staphylococcal pneumonia being the most serious. Secondary bacterial infections can be serious, particularly in the very young, the elderly and those with clinical risk factors such as pre-existing chronic respiratory and cardiac conditions. Patients with secondary bacterial infections are treated with antibiotics which would mitigate the effects of the secondary bacterial infection but would not impact on transmission of the influenza virus. It is possible that some complications associated with a pandemic virus will be caused by other viruses against which antibiotics will not be effective.

6.26 The incidence of pneumonia associated with seasonal influenza ranges from 2 to 38% of cases. Mortality associated with cases of secondary bacterial pneumonia ranges from 7% to 24% although some studies report higher mortality rates. Depending on the nature of the virus, pandemic influenza could potentially be associated with higher or lower rates of secondary infection. It is possible that secondary bacterial infection may be the main cause of death during a pandemic. In addition, a proportion of patients with pandemic influenza can be expected to develop bacterial complications even with effective antiviral treatment. Hence antibiotics will have a key role in a pandemic in treating secondary infections and reducing deaths, and the WHO has recommended that countries buy increased supplies of antibiotics for use in a pandemic. If effective vaccines were available, this would reduce the proportion of secondary bacterial infections arising during the pandemic and hence the need for additional antibiotics.

6.27 Even though the pandemic virus will be new, the bacterial infections will not. The use of antibiotics for treating secondary bacterial infections is a well-understood area with a well-developed evidence base which is considered in the provisional clinical guidelines prepared for the Department of Health by the British Thoracic Society, British Infection Society and Health Protection Agency[61]. There is limited if any scope for alternative scientific views. A

[60] Monto AS (2003) The role of antivirals in the control of influenza. Vaccine vol 21(16) 1769-1800

[61] *Clinical Guidelines for patients with an influenza like illness during an influenza pandemic* Department of Health; British Thoracic Society; British Infection Society; and Health Protection Agency. Published October 2005, revised March 2006. Available at:

possible downside of increased and widespread use of antibiotics during a pandemic could be additional further emergence of multiple drug resistant bacteria for which the treatment options are limited.

6.28 Modelling indicates that having sufficient stocks of antibiotics could reduce hospitalisations and save lives (between 8,000 and 75,000). This is detailed in the table below, based on a scenario of a 35% clinical attack rate and providing antivirals for treatment[62].

	Without Antibiotics	**With Antibiotics**
Clinical Cases	17,700,000	17,700,000
Hospitalisations	43,000 to 322,000	31,000 to 209,000
Deaths	29,000 to 216,000	21,000 to 141,000

Table 2: showing number of clinical cases, hospitalisations and deaths with and without antibiotics (based on a 35% clinical attack rate)

6.29 In the absence of information on either the nature of any bacterial complications of influenza in a future influenza pandemic, or the causative organisms and their antimicrobial susceptibilities, provisional recommendations for the use of antibiotics are given in the clinical guidelines. This is, and is likely to remain, the best advice available for Government to use as a basis for purchasing additional antibiotics in advance of a pandemic.

6.30 Routine arrangements for antibiotic supply to the National Health Service during a pandemic will not be adequate and relying on extra production capacity to deliver at the time is not a plausible option for the UK. Stockpiling should focus on setting up a strategic reserve that would be stored and routinely replenished, to respond to the demands of a pandemic.

6.31 One option for preventing secondary bacterial pneumonia would to be to offer pneumococcal polysaccharide vaccine to those identified to be at highest risk of acquiring pneumococcal pneumonia after influenza. However, pneumococcal vaccination is already recommended for all those 65 years and over, and those individuals with specific risk factors that are very similar to those for seasonal influenza vaccination. Therefore such a recommendation would bring little benefit over existing policy

<u>Additional clinical countermeasures</u>

6.32 Some virologists have also suggested that because the body's own immune response does part of the damage during influenza, anti-inflammatory drugs

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4121753

[62] Figure at lower end of range represents a mild disease such as 1957, that at the upper end of the range a severity similar to that of 1918/19. Assumptions: 50% of complications are bacterial, antibiotics are 75% effective in preventing hospitalisation or death in those with bacterial complications and treatment is successfully targeted at the 50% of complications that are bacterial.

should also be considered alongside antivirals during a pandemic [Menno de Jong, Oxford University]. Whilst anti-inflammatory drugs do not currently feature in the UK's mitigation strategy, clinicians treating pandemic influenza cases have access to these drugs should they chose to prescribe them. Certain anti-inflammatory drugs, such as aspirin (which should not be used in children) and ibuprofen, are available over the counter. Immunomodulatory statins have also been proposed by some health professionals for treatment in the absence of antivirals, although the debate on risks and benefits continues, and there is, as yet, insufficient evidence of clear benefit.

7. Suppression/prevention

7.1 Developments by the scientific modellers and the vaccine manufacturers over the last 1-2 years have presented governments with an (evolving) evidence base opening up the prospect of perhaps reducing the impact of pandemic influenza to that of a severe seasonal epidemic.

Personal hygiene and environmental measures to limit transmission

7.2 Multiple studies have documented both the major contribution played by contaminated hands in the transfer of infection and the effectiveness of hand hygiene in healthcare[63] and community settings[64] [65]. UK guidelines for preventing healthcare-associated infections indicate that effective hand decontamination results in significant reductions in the carriage of potential pathogens on the hands and logically decreases the incidence of preventable healthcare-associated infection (epic, 2006). At least one study has demonstrated that influenza virus is readily inactivated within 30 seconds by a commercially marketed alcohol hand disinfectant following experimental contamination of hands[66].

7.3 Logically, well adhered to respiratory hygiene such as covering coughs and sneezes will interrupt droplet transmission. A recent "cover your cough" campaign was found to prevent exposures of employees to pertussis, which is spread by droplet transmission[67].

7.4 There is little data demonstrating the effectiveness of environmental cleaning in reducing transmission of influenza. However experimental studies of influenza virus survival suggest that the influenza virus can survive for limited periods of time in the environment, depending on the surface contaminated and can be transferred from contaminated surfaces onto hands (see sections 3.17 -3.19). Influenza viruses are easily deactivated by washing with soap and water and household detergents and cleaners. Therefore sensible (manageable) environmental cleaning appropriate to the specific environment and, in healthcare settings, in line with national specifications[68], is important.

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[63] http://www.who.int/patientsafety/information_centre/ghhad_download_link/en/

[64] Luby SP, Agboatwalla M, Feikin DR, Painter J, Billhimer W, Altaf A, Hoekstra RM. Effect of handwashing on child health: a randomised controlled trial. Lancet 2005;366:225-33.

[65] Carabin H, Gyorkos TW, Soto JC, Joseph L, Payment P, Collet JP. Effectiveness of a training program in reducing infections in toddlers attending day care centers. Epidemiology 1999;10:219-27.

[66] Schurmann W, Eggers HJ. Antiviral activity of an alcoholic hand disinfectant: comparison of the in vitro suspension test with in vivo experiments on hands, and on individual fingertips. *Antiviral Res* 1983;3:25-41.

[67] Chatterjee A, Plummer S, Heybrock B, Bardon T, Eischen K, Hall M, Lazoritz S. A modified “cover your cough” campaign prevents exposures of employees to pertussis at a children’s hospital. AJIC 2007;35(7):489-91.

[68] National Patient Safety Agency. The national specifications for cleanliness in the NHS: a framework for setting and measuring performance outcomes. 2007. London: NHS/NPSA. http://www.npsa.nhs.uk/health/currentprojects/nutrition/cleaning

Antivirals for household prophylaxis

7.5 The evidence on the use of antivirals for post-exposure household prophylaxis is limited to two modelling papers[69] which are based on analysis of only four clinical trials[70] but are well respected within the science community. The modelling shows that antiviral prophylaxis of the household contacts of infected cases given within 24 hours of symptoms appearing in index cases, could have a much greater impact on a pandemic than a simple treatment policy, reducing cases and hence deaths. While such household prophylaxis could be more effective in mitigating and delaying the progress of the epidemic it would require an antiviral stockpile greater than the size currently available. As with the 'treatment only policy' well-planned access and logistical arrangements to ensure rapid delivery to affected households would be essential to the success of the intervention.

7.6 Stockpiling a greater number of antivirals would allow antiviral interventions to be augmented to one involving both treatment of all cases and post-exposure prophylaxis of their household contacts. Modelling endorsed through the Department of Health's Scientific Advisory Group's modelling subgroup indicates that combining this augmented antiviral intervention with other countermeasures[71], could be sufficient to reduce the pandemic in the UK to localised outbreaks of seasonal influenza proportions, for a 25% - 35% raw (i.e. without intervention) clinical attack rate. Even for higher attack rates, or if one component is ineffective, the combined intervention could significantly limit the impact of the pandemic.

7.7 The effectiveness of antiviral intervention is further enhanced by a policy of closing schools through at least the peak of an epidemic.

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[69] Longini IM, Halloran ME, Nizam A, Yang Y. Containing pandemic influenza with antiviral agents. Am J Epidemiol. 2004;159(7):623-33 and Ferguson et al. (2006) 'Strategies for Mitigating an Influenza Pandemic' *Nature* **442**: 448-452

[70] summarised in: Halloran ME; Hayden FG; Yang Y, Longini IM Jr, and Monto AS. Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. Am J Epidemiol. 2007 Jan 15; 165(2):212-21 and Yang Y, Longini, IM. Jr, and Halloran ME. Design and evaluation of prophylactic interventions using infectious disease incidence data from close contact groups. Journal of the Royal Statistical Society: Series C (Applied Statistics). 55(3):317–330.

[71] Modelling was conducted on the basis of a potential response scenario which included vaccination of 100% of the population with a pre-pandemic vaccine of 20% efficacy against infection, together with the use of antibiotic drugs for treating complications as well as the increased antiviral stockpile. Further detail is contained in the modelling summary prepared by the SAG modelling sub-group.

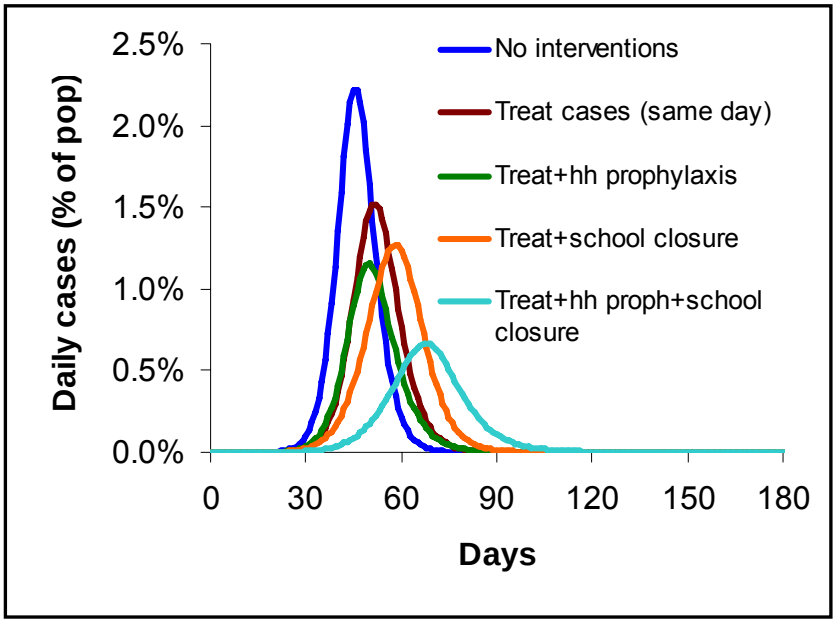

Figure 3: Indicative relative impacts of various antiviral policies for a 35% raw attack rate based on modelling carried out at Imperial College, University of London. The blue line represents the daily number of cases in a possible epidemic affecting 35% of the population. The other lines show the effect of various interventions on this possible epidemic. Options include treatment of all those with symptoms within 12 to 24 hours of their development, treatment of those with symptoms and prophylaxis of other members of their households, the same treatment and prophylaxis strategies combined with closing schools.

7.8 In summary, antiviral post-exposure prophylaxis of the household contacts of clinical cases with pandemic influenza could have a more marked impact on the pandemic than from treatment of the cases alone, and mitigate and delay the progress of the epidemic. This strategy would require an antiviral stockpile significantly greater than the size currently available.[72]

Pre-pandemic vaccines

7.9 Pre-pandemic vaccines are the only clinical countermeasure with the potential to develop population protection before a pandemic virus emerges. The current focus of the vaccine manufacturers is on the development of H5N1-based pre-pandemic vaccines. However there is a risk that the next pandemic may not be caused by an H5N1-derived virus or even by a virus from the H5 family. The H5N1-based vaccines currently in advanced phases of development are unlikely to be effective against other non-H5 influenza viruses.

7.10 Acknowledging the potential role that pre-pandemic vaccines could play in preparing for a pandemic, the European Medicines Agency (EMEA) has recently introduced a new licensing procedure for such vaccines. This would

[72] This conclusion has been endorsed by the DH Scientific Advisory Group as part of the modelling summary prepared by the SAG modelling sub-group.

allow for their licensed use before WHO Phase 6 is declared. Unlike the procedure for licensing pandemic-specific vaccines (see paragraph 7.37), such licence applications would follow the usual procedures for the authorisation of new vaccines.

7.11 Candidate pre-pandemic vaccines have been developed both with and without aduvants. There are a number of different adjuvants in trial, including well known ones like alum but also new proprietary adjuvants. There are adjuvanted seasonal influenza vaccines on the market (Novartis) which have been licensed for use in other EU countries, though not in the UK. These give a better immune response in the elderly compared to non-adjuvanted vaccines and have been in use for around 5 years with a good safety record.

7.12 At present, there are no standardised methods to compare the various types of vaccines, and no head to head comparisons have been made between the available pre-pandemic vaccines. This is a recognised research priority and efforts are underway by NIBSC in the UK to address this need.

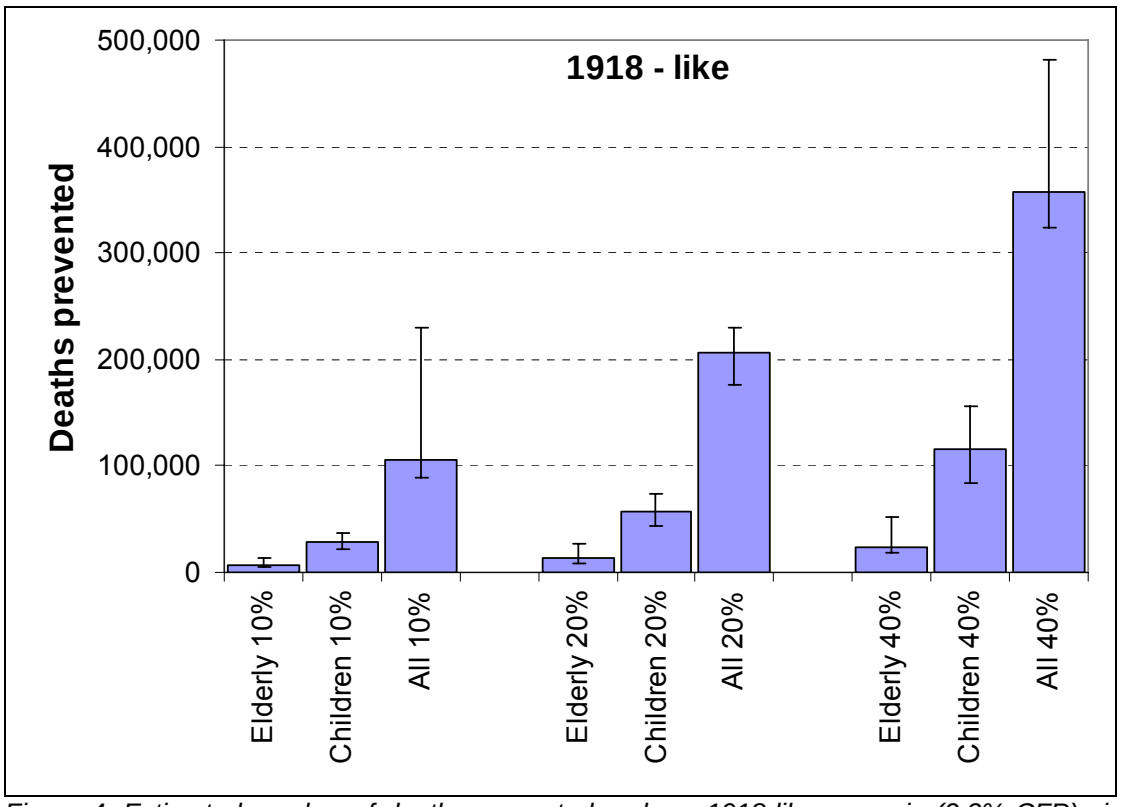

Figure 4: Estimated number of deaths prevented under a 1918-like scenario (2.3% CFR) via a pre-pandemic vaccine targeted at different age groups, by the level of effective coverage achieved.

7.13 The effectiveness of a pre-pandemic vaccine will be a function of:

(i) its ability to induce an adequate immune response to the viral strain used to produce the vaccine; and
(ii) the extent to which it can also protect against other strains ('cross-protection'). The scientific evidence on the potential effectiveness and cross-protection of pre-pandemic vaccines has evolved considerably over the last 12 months.

Ability to induce an immune response

7.14 During the pre-pandemic period, we can assess only the potential efficacy of pre-pandemic vaccines using immunological markers (i.e., levels of antibody response). As current markers are based on seasonal influenza vaccines, for which there is existing population immunity, and the need for cross-protection plays a smaller part, these markers may not necessarily apply to pre-pandemic (or pandemic-specific) vaccines. However, in the absence of other criteria, there is no other means of assessing the potential for protection so these must be used as the basis for licensing. Using these seasonal influenza criteria for assessing pandemic vaccines is one of the key risks in pursuing a pre-pandemic vaccination strategy that cannot be mitigated in advance since these criteria cannot be validated until vaccinated people are exposed in a pandemic. The main risk of a pre-pandemic vaccine strategy remains that the pandemic virus will not be sufficiently related to the virus on which the pre-pandemic vaccine is based.

7.15 Manufacturers have tested several vaccines with different types and quantities of antigen, and a range of adjuvants. The levels of antigen and adjuvant selected are based upon the need to induce the immune response required to meet the licensing requirements of the European Medicines Agency (EMEA). Further increasing the level of antigen may not necessarily increase the level of protection offered by the vaccine, and could negatively impact on available manufacturing capacity.

7.16 Antibody responses (immunogenicity data) from trials of 'mock-up' pandemic-specific vaccines which double as pre-pandemic vaccines have so far shown that, depending on the type and level of vaccine antigen and adjuvant system used, such vaccines can induce the antibody responses that are associated with protection against seasonal influenza.

7.17 The data also show that a single dose of vaccine can induce some antibodies. However, the antibody levels achieved do not consistently meet all the criteria required for EMEA licensure. The studies show that two doses, a minimum of three weeks apart, are generally required to induce the requisite antibody levels (see Annex B for more details).

7.18 The antibody levels induced after 2 doses (and meeting EMEA criteria) are assumed to protect, or at least prevent serious illness and death in infected persons. The requirement for two doses is in line with policy on seasonal influenza vaccine for those who have never previously developed immunity to influenza, i.e. very young children. Only one dose of seasonal influenza vaccine is required for non-naive individuals as they have existing levels of immunity.

Cross-protection

7.19 As per 7.13, a second critical property of a pre-pandemic vaccine is the ability to provide cross-protection against strains of influenza not perfectly matched to the vaccine viral strain. It will also be a useful, though less essential, property of pandemic-specific vaccine in order to protect against drift variants of the pandemic virus.

7.20 No measure for general cross-protectiveness exists. Cross-protection versus specific strains can be investigated to some extent. We can asses extrapolate potential cross-protection on the basis of induction of cross-neutralising antibody titres in human sera (cross-reactivity) and challenge studies in animals. These indications of potential cross-protection to specific strains cannot give any firm assurances on the likely protection offered. In addition, because the pandemic strain cannot be known in advance, it is not possible to even measure such potential cross-protection.

7.21 The potential for cross-protection has been demonstrated in several human and animal studies (summarised in Annex C). In brief, the results suggest that a vaccine containing a specific H5Nx surface protein could potentially provide some cross-protection against genetically drifted variants of that H5Nx strain and even H5 strains with different Ns (neuraminidases). There are some early indications that some vaccines, which are still in the experimental stages, may even provide limited cross protection against other Hs (haemaglutinins).

7.22 Whilst these challenge studies have provided good evidence of cross-protection from H5N1 vaccines against currently circulating different H5N1 virus clades, it is impossible to know to what extent such vaccines would protect against clades of H5N1 which might emerge in the future or future pandemic viruses (although further research may increase our confidence in the potential future efficacy of a vaccine).

7.23 An alternative could be to look towards producing a 4-valent pandemic vaccine offering protection against the main novel subtypes (H2, H5, H7, and H9) of the virus. It could take 4 to 5 years to produce the relevant clinical data for licensing this sort of product and a pandemic from other haemoglutinin types cannot be ruled out. Research aimed at developing a general influenza A vaccine is still further upstream. Most of the effort is currently focussed on H5 although some vaccine manufacturers are working on other H subtypes.

Safety

7.24 Based on a risk-benefit analysis of the available data, including the vaccines containing novel adjuvants, the reactogenicity of the pre-pandemic vaccines is generally considered to be acceptable by the Scientific Advisory Group and the scientific colloquium hosted by the Secretary of State for Health, particularly in the context of use during an emerging pandemic where the potential benefit is likely to outweigh the risk of adverse events.

7.25 The safety of FLUAD® (the Novartis Vaccines MF59-adjuvanted seasonal influenza vaccine licensed for use in Europe) has been shown to be comparable to the equivalent non-adjuvanted product (Agrippal®, Novartis Vaccines) in the elderly, although local reactions were more frequent when adjuvant was present (Podda, 2001)[73]. During 7 days post-vaccination, injection-site pain, malaise, and myalgia were more frequent in the MF59 vaccine group compared to the non-adjuvanted group, however, all local and systemic reactions were generally mild or moderate in severity, and of short duration (Baldo et al, 2007)[74].

7.26 The risk of serious side-effects or serious adverse events (most notably Guillain-Barré Syndrome – where the sufferer is paralysed, although usually only temporarily) from seasonal influenza vaccine is in the order of 1 in 1 million. Clinical trials would be unable to detect a risk of this order and hence adverse events can only be detected by post-marketing surveillance i.e., after the vaccine has been used on the population. Implementation of a pre-pandemic vaccine strategy would be based on the same consent principles normally used in immunisation. Acceptance and uptake of the vaccine would be very much dependent upon developments and the status of the threat at the time.

Immunisation strategies

7.27 A UK immunisation strategy using pre-pandemic vaccine would be based on two doses, three weeks apart. When a pandemic-specific vaccine becomes available, we expect to need two doses of that. In the unlikely case that the pre-pandemic vaccine strain closely matches the pandemic strain, investigations will need to show whether one further dose could be enough.

7.28 Some countries have been considering a strategy of giving only one dose of a pre-pandemic vaccine before a pandemic strikes, followed by one dose of the pandemic-specific vaccine once it becomes available. This may be considered a “prime-boost” strategy, so that only one dose of pandemic-specific vaccine is required for vaccination (instead of two). It might also be hoped to provide some degree of protection during the first wave of the pandemic while the pandemic-specific vaccine is being developed, although as outlined above, the available data consistently indicate that a single dose may not induce sufficient circulating antibodies.

7.29 The scientific basis of this prime-boost strategy is currently unclear. Although studies are ongoing to assess the response, there are currently no published data to support it. Expectations of effectiveness would decrease further with increasing difference between the viral strains used for the pre-pandemic and pandemic-specific vaccines. The time interval of several months between

[73] Podda A. The adjuvanted influenza vaccine with novel adjuvants: experience with MF59-adjuvanted vaccine. *Vaccine* 2001;**19**:2673-80

[74] Baldo V, Baldovin T, Angiolelli G, Trivello R, Longanella A, Fanelli A, Pellegrini M, Casula D, Ballini F, Podda A. Superior immunogenicity following MF59-adjuvanted influenza vaccination (FLUAD®) in at risk adults (18-60 Years Of Age) – a randomized, observer-blind study. Poster P733. Options for The Control of Influenza VI, Toronto, July 2007

primer and booster can also be expected to impact negatively on effectiveness.

7.30 Another factor to take into account is that it is unlikely that either the pre-pandemic or pandemic-specific vaccine will be licensed for single dose use. They are also unlikely to be licensed on the basis of a second dose that is different to the first. Thus, any strategy that depends on the combined use of a post-pandemic vaccine and a different pre-pandemic one is almost certainly going to be based on using vaccines in an unlicensed way (even if the vaccines are individually licensed).

7.31 Under most plausible conditions the use of a poorly-matched pre-pandemic vaccine (say 20% effective coverage) is likely to offer greater protection than a well-matched (say 65% effective coverage) pandemic-specific vaccine which is only available after the first wave. The most notable exception being the case where the first wave is relatively small, which may occur if the virus first arrives out of the normal influenza season.

Prioritisation of vaccine

7.32 In the case of a low efficacy vaccine, it is better to prioritise those who spread the disease most (generally children), rather than those who will benefit most at individual level. This is because the individual benefit of vaccination would be small but the effect on disease transmission large.

7.33 The exact balance depends on the efficacy of the vaccine in different groups, the transmission in different groups and the severity of the disease in each group. A prudent targeting policy for pre-pandemic vaccine would be to target both those in at risk groups and children. This accounts for some 40% of the UK population

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7.34 Some small quantities of pandemic-specific vaccine may be available in the late stages of a pandemic and will also need to be prioritised. Prioritisation of access to either pandemic-specific vaccine or pre-pandemic vaccine would need to be considered by Ministers, based on advice from the Joint Committee on Vaccination and Immunisation (JCVI) and the Committee on Ethical Aspects of Pandemic Influenza (CEAPI) on risks/benefits and ethics. Seasonal influenza vaccines are offered to health care workers, at-risk groups, older people and young children. Traditionally, the seasonal vaccine tends to induce a poorer immune response in the more vulnerable groups as compared to the response in healthy adults. However, the newer, adjuvanted vaccines have been specifically, and successfully, developed to overcome this issue. No data from these more vulnerable sub-groups to (pre-) pandemic vaccine is currently available. A prudent strategy might be to target health care workers if there is very limited supply of a pandemic-specific vaccine.

7.35 The modelling sub-group of the Scientific Advisory Group has recommended that surveys of immunity and surveillance information of the extent and severity of the disease following the first wave of the pandemic are used to target pandemic-specific vaccination.

Pandemic-specific vaccines

7.36 Pandemic-specific vaccine will be manufactured against the pandemic virus once it has emerged, and, using currently available processes, the first production lots will not be available until after the end of the first pandemic wave at the earliest. Although strictly speaking a suppression strategy because it would prevent transmission of infection and illness, due to the late availability a pandemic-specific vaccine will be more of a late stage mitigation or coping strategy.

7.37 Manufacturers are currently conducting studies with prototype pandemic vaccines for approval by the EMEA as 'mock up' vaccines in the pre-pandemic period. The purpose of these studies is to assess the immune responses and safety of vaccines containing strains to which the population is immunologically naïve. Most manufacturers are using H5N1 vaccines for these studies. The intention is that when licensed, the 'mock-up' strain would be rapidly replaced by the pandemic-specific strain without the need for further clinical studies so that the vaccines are quickly available for use. These same vaccines could potentially be used as pre-pandemic vaccines (but this would require a separate licence – see paragraph 7.10).

7.38 Due to the precise match with the virus strain, a pandemic-specific vaccine is expected to be the most effective vaccine against the pandemic virus (in comparison with a pre-pandemic vaccine which by definition would be produced before the emergence of a pandemic virus using a virus that differed from the pandemic strain). If the protection offered was comparable to that of seasonal influenza vaccines, pandemic-specific vaccine could potentially offer around 70-80% efficacy.[75]

7.39 Whereas seasonal influenza vaccines only require one dose, data from trials of 'mock up' vaccines indicate that two doses, three weeks apart, are generally required to induce a suitable response in healthy adults (because of the immunological naivety of the population).

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7.40 Traditionally, the seasonal vaccine tends to induce a poorer immune response in the more vulnerable groups as compared to the response in healthy adults..[76]. However, the newer, adjuvanted vaccines have been specifically, and successfully, developed to overcome this issue. To date no studies have been published on the response to the mock up vaccines in these 'at risk' groups

7.41 If it were possible to give a high efficacy vaccine (~80%) to a large proportion of the population (~75%) further pandemic waves could be eliminated, although it is not certain that further waves will definitely occur. It is difficult to see how (given such high coverage) 25% of the population could be selected *not* to be vaccinated, and therefore 100% coverage is a more practical target. In addition, for reasons of equity, our objective should be to vaccinate

[75] Fleming DM *et al*. (1995). *Epidemiology and Infection* 115: 581–9.
[76] Webster R, Vaccine 2000. 18(16): 1686-9, Groothuis J Vaccine 1994; 12: 139-41,

everyone and as quickly as possible. If we had to accept a lower figure for coverage, for example because of resource limitations or restrictions on access to supplier, then some prioritisation would be necessary. Also, because not all vaccine will be available at the same time, prioritisation in who to give it to first will be necessary.

7.42 In practice, in the suppression strategy, the main use of a pandemic-specific vaccine would be to make possible the cessation of measures such as household prophylaxis by reducing the susceptible population.

7.43 Other scientific and technical questions on pandemic vaccines focus on how to produce an immune response with the least amount of antigen, so that more doses can be available given the very limited global vaccine production capacity. The adjuvant aspect of that has been considered further in the section above on pre-pandemic vaccines.

Use of face masks during a pandemic

7.44 Policy decisions regarding the use of face masks in the UK need to be informed by:

- evidence about the modes of transmission of influenza viruses and the relative importance of each mode;
- evidence about the protection afforded by masks;
- practical considerations in specific settings;
- international context;
- procurement and logistics;
- the availability of antiviral drugs and vaccines within the UK;
- emerging morbidity and mortality data relating to the new virus.

7.45 There are few well designed experimental or observational studies to conclusively demonstrate that surgical masks protect healthcare workers from respiratory infections during routine ward work. However, the use of face masks to protect healthcare workers has a long history[77] [78] and has been incorporated into international[79] and national infection control guidance[80]. Two recent retrospective studies of the SARS epidemic suggested that surgical masks afforded health care professionals some measure of protection when in close contact with patients[81] [82]. Epidemiological evidence

[77] Weaver GH. Droplet infection and its prevention by the face mask. J Infect Dis 1919;24:218-30.
[78] Weaver GH. Value of the face mask and other measures. JAMA 1918;70:76.
[79] World Health Organization. Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care 2007 www.who.int/csr/resources/publications/WHO_CD_EPR_2007_6/en/index.html.
[80] Department of Health and Health Protection Agency (2007, in press) Pandemic influenza: guidance for infection control in hospitals and primary care settings, London: DH and HPA.
[81] Seto WH, Tsang D, Yung RW, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet 2003;361:1519-20.
[82] Loeb M, McGeer A, Henry B, et al. SARS among critical care nurses, Toronto. Emerg Infect Dis 2004;10:251-5.

has defined the area of risk around the patient as being a distance of less than one metre[83]. Recent CDC Isolation guidance suggests that this should be used as an approximation rather than an absolute distance[71]. Nonetheless using one metre as a basis for donning masks has been effective in preventing transmission of infectious agents via the droplet route. A surgical mask worn by healthcare workers for close patient contact (i.e., within one metre) will provide a physical barrier and minimise contamination of the nose and mouth by droplets.

7.46 The current Pandemic Infection Control Guidance for Healthcare Settings recommends the use of high-level respiratory protection (FFP3 standard) for healthcare workers engaged in aerosol generating procedures. Two recent studies compared surgical masks against respirators (N95 standard) for the protection afforded against small sub-micron sized particles. The data are conclusive that respirators offer vastly superior protection than masks against small particles, but even N95 standard filtration may not be sufficient.[84] This finding is unsurprising, but nevertheless supports the use of high-level respiratory protection when aerosols are likely to be generated during specific healthcare interventions.

7.47 With regard to use of face masks by the general public, three major studies contribute evidence. All are based on the SARS experience and all examined a range of other public health interventions in addition to masks[85] [86] [87]. In one study the effects of any single intervention were difficult to disentangle. All three major studies might have been open to significant recall bias. Only one study specifically examined the relationship between protective measures and other respiratory viruses including influenza. Nevertheless, protective effects against clinically diagnosed SARS were observed in two papers, and against the laboratory confirmed incidence of influenza in another.

7.48 The Health Protection Agency's views, shared by the Department of Health, as to how this evidence base would translate into practical advice from a purely scientific point of view, are outlined as follows:

- **Health care settings**
  HPA continues to support the use of infection control procedures, including personal protective equipment (PPE) such as surgical face masks, consistent with interrupting droplet and contact transmission, except under specific circumstances where aerosols are likely to be

[83] Feigin RD, Baker CJ, Herwaldt LA, Lampe RM et al. Epidemic meningococcal disease in an elementary school classroom. N Engl J Med 1982; 304:1255-7.
[84] Balazy A, Toivola M, Adhikari A, Sivasubramani SK, Reponen T, Grinshpun SA. Do N95 respirators provide 95% protection level against airborne viruses, and how adequate are surgical masks? Am J Infect Control 2006;34:51-7.; Lawrence RB, Duling MG, Calvert CA, Coffey CC. Comparison of performance of three different types of respiratory protection devices. J Occup Environ Hyg 2006;3(9):465-74.
[85] Lo JYC, Tsang THF, Leung Y-H, Yeung EYH, Wu T, Lim WWL. Respiratory infections during SARS outbreak, Hong Kong, 2003. EID 2005; 11(11):1738-41.
[86] Wu J, Xu F, Zhou W, Feikin DR, Lin CY, He X et al. Risk factors for SARS among persons without known contact with SARS patients, Beijing, China. Emerg Infect Dis 2004;10(2):210-6
[87] Lau JT, Tsui H, Lau M, Yang X. SARS transmission, risk factors, and prevention in Hong Kong. Emerg Infect Dis 2004;10(4):587-92

generated, e.g. certain healthcare procedures, where FFP3 respirators are recommended.

- **Surgical mask use by the general public**
  The specific evidence base regarding use of face masks by the general public is currently too uncertain and too limited to firmly support face masks for use by the public during an influenza pandemic. The evidence of harm from use by the general public is even more limited. The current evidence base is consistent with a permissive approach to voluntary mask use by the general public, but no recommendation or encouragement. As some members of the public are likely to choose to wear masks, it is important that guidelines on correct usage are provided to the general public.

- **Surgical mask use by symptomatic persons outside the home**
  Some data exist to support masking of persons with symptoms as a means of containing respiratory secretions and reducing contamination of the immediate environment around the patient. This policy is already applied within NHS pandemic guidance for patients in public waiting areas. Whilst it is clearly more desirable for persons with symptoms to be masked in public places than unmasked, the main message to promulgate is voluntary self-isolation (staying at home until symptoms resolved) together with a package of basic hygiene measures. Therefore, from an efficacy point of view, this measure could be considered, but it is noted there would be significant communication, logistic and training issues to overcome.

- **Surgical mask use by symptomatic persons inside the home**
  Some data exist to support masking of persons with symptoms as a means of containing respiratory secretions and reducing contamination of the immediate environment around the patient. However the main message to promulgate is voluntary self-isolation (living in another room or part of the house until symptoms resolved) together with a package of basic hygiene measures. Therefore, from an efficacy point of view, this measure could be considered, but it is noted there would be significant communication, logistic and training issues to overcome.

- **Surgical mask use by carers/lay attendants in home/household settings**
  This situation is the most analogous to close contact between healthcare workers and their patients. It could be supported scientifically but carries with it major issues about training, logistics and safe mask use.

8. Combined use of Clinical Countermeasures

8.1 This section considers the evidence base for an enhanced package of clinical countermeasures directed towards a strategy of suppression rather than mitigation.

8.2 Mathematical modelling has been used to indicate the possible impacts of various scenarios based on the proposed enhanced package of clinical countermeasures used in combination in a UK epidemic.

8.3 In the best case, a high population coverage with a pre-pandemic vaccine of only 20% effectiveness (against infection) combined with household prophylaxis, schools closure and use of antibiotics, could reduce the pandemic to, at worst, seasonal influenza proportions, if the attack rates were no worse than any of those experienced in the 20th century.

8.4 An additional advantage of the combined approach is that substantial mitigation would be achieved even if one or more of the countermeasures works less well than expected, a defence in depth strategy.

8.5 Table 3 indicates the impacts of various combinations of interventions (school closures are assumed in the household prophylaxis columns and antibiotic availability is assumed unless otherwise stated). The following tables and diagrams show how the full effect is built up from different levels and kinds of intervention.

Information on the assumptions used to construct the scenarios is provided in Annex D.

Table 3: Modelling results estimating the clinical cases, hospitalisation and deaths (thousands) for different scenarios and clinical attack rates

Clinical Attack rate	Outcome (thousands)	Scenario							
		Base Case (no intervention /no antibiotics)	**Treatment / No vaccine (no antibiotics)**	**Treatment / No vaccine**	**Household Prophylaxis/ No Vaccine**	**Treatment / Targeted Vaccine**	**Treatment / All Vaccinated**	**Household Prophylaxis/ Targeted Vaccine**	**Household Prophylaxis /All vaccinated**
25%	Clinical cases	15,000	11,700	11,700	7,200	7,200	4,100	Local outbreaks of seasonal flu proportions only.	Local outbreaks of seasonal flu proportions only.
	Hospitalisations	83 - 557	28 - 213	21 - 139	12 - 84	12 - 84	7 - 48		
	Deaths	56 - 375	19 - 143	14 - 94	8 – 56	8 - 56	5 - 32		
35%	Clinical cases	21,000	17,700	17,700	12,000	12,600	10,900	9,000	3,000
	Hospitalisations	116 - 780	43 - 322	31 - 209	21 - 139	22 - 146	19 - 127	15 - 105	5 - 35
	Deaths	78 - 525	29 - 216	21 - 141	14 -94	15 - 98	13 - 85	10 - 70	3 - 23
50%	Clinical cases	30,000	27,900	27,900	16,200	26,400	18,000	16,100	12,000
	Hospitalisations	165 - 1,115	67 - 507	48 - 327	28 - 188	45 - 307	31 - 209	28 - 187	21 - 139
	Deaths	111 - 750	45 - 341	33 - 220	19 - 127	31 - 206	21 - 141	19 - 126	14 - 94

Figure 5: Modelled number of clinical cases, hospitalisations and deaths with intermediate steps for an unmitigated clinical attack rate of 25%

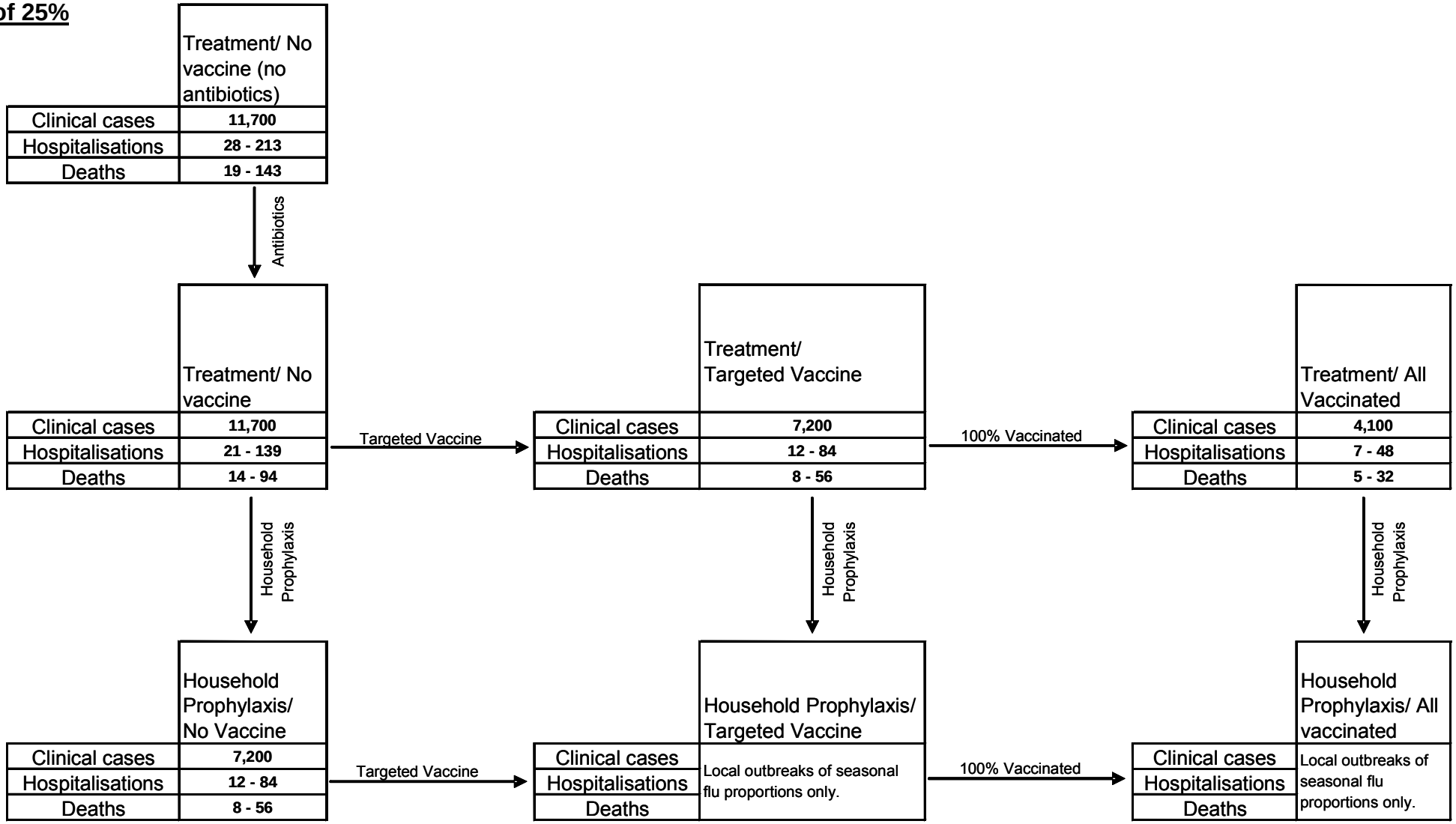


Figure 6: Modelled number of clinical cases, hospitalisations and deaths with intermediate steps for an unmitigated clinical attack rate of 35%

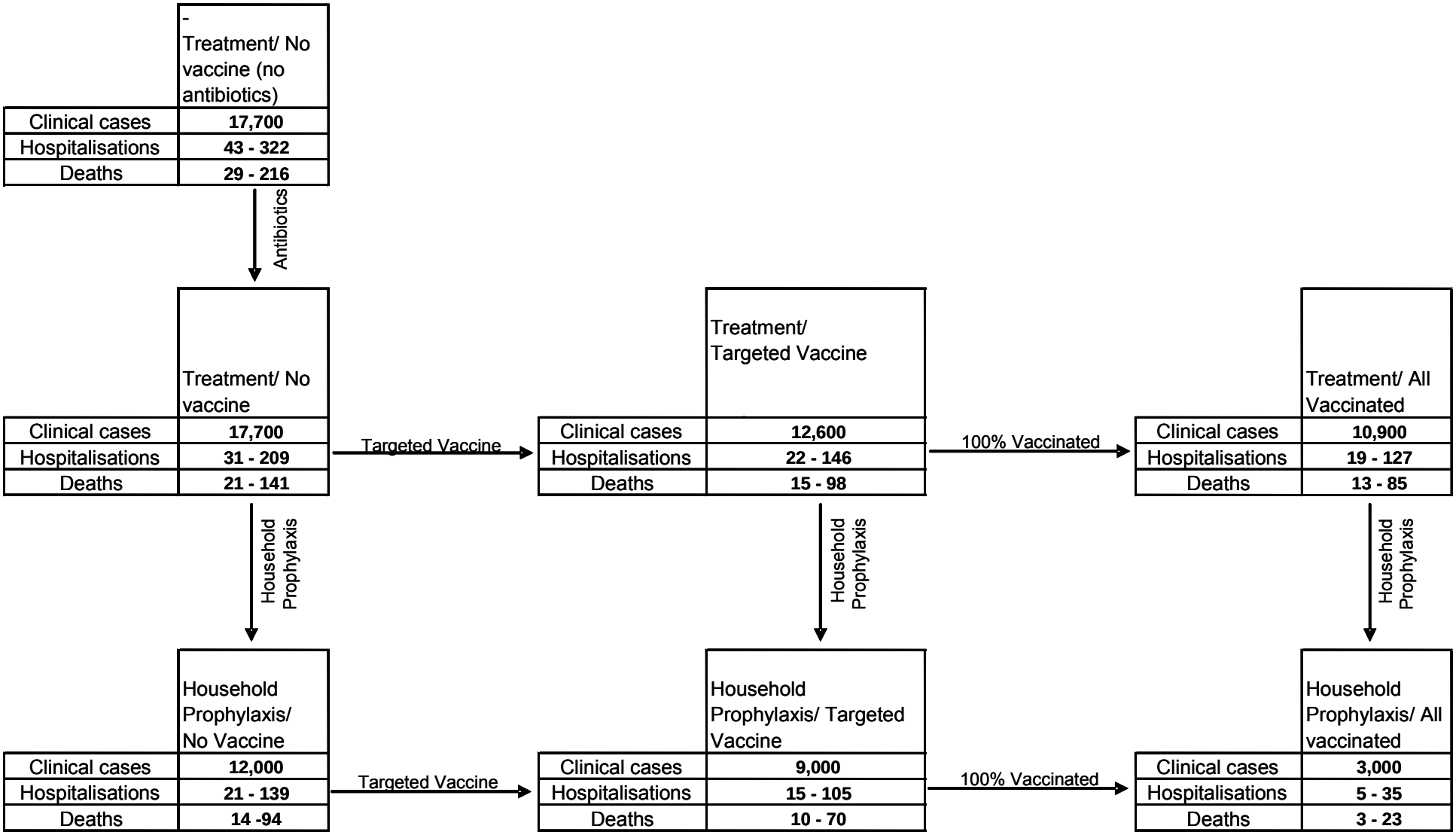
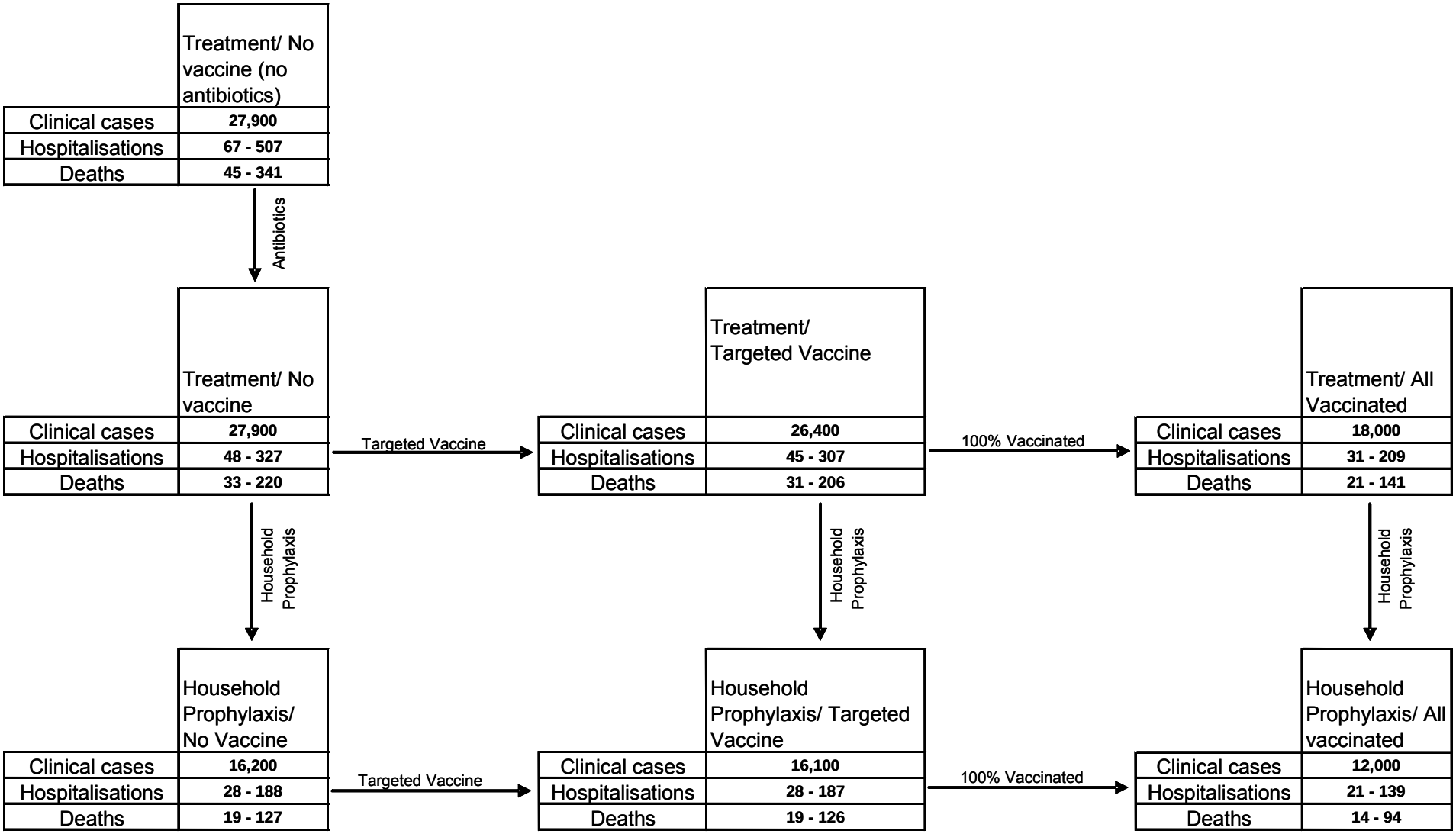


Figure 7: Modelled number of clinical cases, hospitalisations and deaths with intermediate steps for an unmitigated clinical attack rate of 50%



Section C – Evidence underpinning Social Measures

9. Social Measures

9.1 So-called social (or non-pharmaceutical) measures are potential tools which could mitigate the impacts of a pandemic by possibly reducing the rate of spread of the virus and the numbers of clinical cases. They include: international travel restrictions, health screening at ports, border closures, domestic travel restrictions, school closures, personal hygiene advice and advising against mass gatherings. The evidence base for these measures has been reviewed by DH's Scientific Advisory Group Modelling Subgroup drawing on published papers by UK and US modellers as well as other review papers published by the WHO Writing Group[88] [89].

9.2 Overall the scientific evidence base for developing policy and/or guidance on social measures is limited. Even more limited is the evidence on the cost impacts of these measures, and the understanding of how people will think and behave in response to social measures. A better understanding of these social and psychological factors is a key gap in our understanding.

International travel restrictions

9.3 The aim of international travel restrictions would be to slow the spread of the pandemic, ideally to delay its arrival until a vaccine was available (although the evidence suggests it is extremely unlikely that sufficient time could be bought). With this in mind this section of the paper considers restrictions on humans movement into the country

9.4 It is unrealistic that international travel restrictions would prevent entirely the spread of pandemic influenza. It is important to note that international travel restrictions only act to delay an epidemic. They do not reduce the size of the within-country epidemic once it occurs. The evidence base includes experience from earlier pandemics of attempts to keep out, or slow down arrival of the virus. This measure has usually been modelled in terms of restrictions on air travel.

9.5 The SAG Modelling Subgroup paper[90] summarised the available modelling evidence[91] as follows:

[88] World Health Organization Writing Group. Non-pharmaceutical interventions for pandemic influenza, international measures. Emerg Infect Dis 12, 81-7 (2006)
[89] World Health Organization Writing Group. Non-pharmaceutical interventions for pandemic influenza, national and community measures. Emerg Infect Dis 12, 88-94 (2006)
[90] on www.dh.gov.uk
[91] Ferguson et al 2006 Strategies for mitigating an influenza pandemic. Nature 442:448-452; Cooper BS, Pitman RJ, Edmunds WJ, Gay NJ (2006) Delaying the International Spread of Pandemic Influenza. PLoS Med 3(6): e212; Colizza V, Barrat A, Barthelemy M, Valleron AJ, Vespignani A (2007) Modeling the Worldwide Spread of Pandemic Influenza: Baseline Case and Containment Interventions. PLoS Med 4(1): e13

- Having taken 2 to 4 weeks to build up in the country of origin pandemic flu could take as little as 2 to 4 weeks to spread from Asia to the UK, with the peak of the UK epidemic following about 50 days later.
- Imposing a 90% restriction on *all* air travel to (reduce the number of inbound travellers to) the UK would delay the peak of a pandemic wave by only 1 to 2 weeks. On the other hand a 99.9% travel restriction might delay a pandemic wave by 2 months.
- Restrictions *limited to travel to the UK from south east Asia* (should the epidemic begin there) will be necessarily less effective as there will be indirect flows of people into the UK from Asia, as well as people infected in epidemics in other countries. It is unlikely that such limited restrictions would be more than 90% effective in reducing the overall flow of those infected into the country. The likely effect would therefore be a delay of about 1 to 2 weeks in the peak of a pandemic wave.
- Putting restrictions *on all air travel from the country in which the pandemic strain originates* is likely to produce delays similar to those expected for restrictions on all travel from South East Asia (if that were the origin), into the UK.
- If restrictions on travel from *all countries which had epidemics* of pandemic flu were put in place internationally the effect could be somewhat greater: a 90% reduction might delay the spread by 3 to 4 weeks and a 99.9% effective ban by 3 to 4 months.
- For all practical levels of restriction, there is little probability of a country missing the pandemic altogether due to travel restrictions; however some poorly connected countries might miss an epidemic given a 99.9% ban.
- The above delays may be important if there is a substantial seasonal effect on the transmissibility of flu. If there is, it may be possible to "buy" enough time to shift what would otherwise have been a winter outbreak to the spring (or a spring outbreak to the summer), when the lower transmissibility would result in a smaller outbreak. Although this seasonal effect is potentially significant, strong evidence for such an effect has not yet been presented.

9.6 Since the SAG advice, modelling by Epstein et al[92] also assessed the impact of international air travel restrictions on the global transmission of pandemic flu. These authors also concluded that such restrictions may provide a small delay in the (global) spread of the pandemic. They went on to consider the interaction that this may have with the assumed seasonality of influenza to show that travel restrictions can even be harmful (by delaying importation until the height of the influenza season when transmissibility is assumed to be greater). The authors provide a very rough estimate of the possible cost of such a policy on the US economy and concluded that it would be of the order of 0.8% of Gross National Product – mainly driven by substitution effects. There is no other available evidence on cost implications and this is a particular gap in current knowledge.

[92] Epstein JM, Goedecke DM, Yu F, Morris RJ, Wagener DK, Bobashev GV 2007. Controlling pandemic flu: the value of international air travel restrictions. PLoS One 5: 1-11

9.7 Evidence from previous pandemics presents a mixed picture of the impacts of measures which have sought to delay or prevent the introduction of pandemic influenza[93]. In the 1918 pandemic, some island countries enacted maritime quarantines that appear to have delayed the introduction of the virus. Australia's quarantining of arriving ships in October 1918 is thought to have delayed the arrival of the virus there until January 1919. Other examples from 1918 include Madagascar, Samoa and New Caledonia where quarantining of incoming travellers either delayed or stopped the infection. The policy was less successful when applied on continents/mainland. Limited data from the 1957 pandemic also shows a mixed picture of benefits.

9.8 Overall, the WHO concluded that quarantine of incoming travellers did not substantially delay introduction, except in some island countries, and that the principal focus of interventions against pandemic influenza spread should be at national and community levels rather than international borders. The practical and compliance aspects of international travel restrictions would also need to be considered. Moreover, no practical level of travel restriction is likely to allow a country to avoid a pandemic altogether. The limited health benefits also need to be considered against the wider social and economic consequences.

Border closures

9.9 The closure of UK borders would have an impact on both the movement of people and the movement of goods. The same scientific evidence base applies to border closures as for international travel restrictions, including the wider social and economic impacts. As for restricting international travel, there would be considerable practical implications and compliance issues to overcome for a policy of border closures to be implemented.

9.10 Closing UK borders would lead to shortages of essential goods such as medicines and foods, and British Nationals would be unable to return, unless quarantine was imposed on arrival. Foreign nationals would not be allowed to leave and may call for assistance from government. At least transient losses to export income from a policy of closing borders to movement of goods over two months to non-EU countries would be £13bn, and to both EU and non-EU countries £32bn[94].

Health screening at ports of entry

9.11 Screening at ports is another possible measure to control the spread of the virus, either by:

[93] World Health Organisation Writing Group. Non-pharmaceutical interventions for pandemic influenza, international measures. Emerg Infect Dis 12, 81-7 (2006)
[94] CCS/FCO Economic Impact of an Influenza Pandemic on the UK – paper to DHSC in 2005 which was peer-reviewed by HMT and DTI economists.

- screening passengers on exit to prevent those who are symptomatic from travelling overseas (although those who were infected and incubating the virus and not yet showing symptoms would still be able to travel);
- screening passengers on entry to prevent those who are symptomatic from entering, or at least being identified and offered medical care. Again, asymptomatic cases would get through.

9.12 The SAG Modelling Subgroup paper[95] summarised the available evidence as follows:

- Assuming passengers are screened before travel for clinical symptoms, there is no additional advantage in entry screening. Even preventing those with clinical symptoms from travelling is only likely to delay the spread of the disease by 1 to 2 weeks.

9.13 The paper concluded that policy makers should assume no significant benefit from entry restrictions or screening.

9.14 Simply on the basis that those people infected and incubating the virus before becoming symptomatic would be deemed by exit or entry screening to be fit to travel or enter (respectively), there is limited benefit from health screening at ports.

9.15 The Health Protection Agency have estimated the possible effect of entry screening for pandemic influenza on the UK, under the assumption that symptomatic patients will not be allowed to board flights[96]. They concluded that entry screening would fail to detect most cases (>80% missed). The primary reason is that screening is unable to detect individuals who are, or who will become, infectious but are currently asymptomatic. The short period between generations of cases of influenza means that it would take little time for those missed by screening to infect secondary cases 'replacing' those detected.

9.16 Screening measures were used during the SARS outbreaks in 2003 which should have been much easier to control by travel restrictions and screening than influenza supports this view. Entry screening data from 4 Asian locations and Canada during SARS has been compiled in the table below.

[95] on www.dh.gov.uk

[96] Pitman RJ, Cooper BS, Trotter CL, Gay NJ, Edmunds WJ. Entry screening for SARS or influenza, policy evaluation. BMJ. 2005; 331:1242-3

Screening Tool	Total Screened	SARS cases detected
Thermal scanning	> 35,000,000	0
Health Declarations[97] (Actively administered at port of entry)	>45,000,000	4 (all had either symptoms or contact with a case of SARS)
Health Alert Notices[98] Mainland China Thailand	 450,000 1,000,000	 4 possible 24 possible

Table 4: Entry screening data from four Asian locations and Canada during the SARS outbreak in 2003.

These data include 5 persons with SARS who entered Canada but did not have signs or symptoms at international airports. As a result, Canadian authorities concluded that border screening for SARS was insensitive and not cost effective and that surveillance allowing for early detection of imported cases was preferable[99].

9.17 Exit screening data from 3 Asian locations and Canada during SARS are summarised in the table below[100].

Screening Tool	Total Screened	SARS cases detected
Health Declarations (Actively administered at port of entry)	> 2,400,000	1 (China-Taiwan)
Thermal scanning	> 7,900,000	0

Table 5: Exit screening data from three Asian locations and Canada during the SARS outbreak in 2003.

9.18 The conclusions were that:

- Screening of travellers through health declarations or thermal scanning had little documented effect on detecting SARS cases.
- The indirect public health benefit of screening in terms of deterring travel by ill persons and in building public health confidence remains unquantified.

9.19 Implementing any form of screening would place a significant burden on several sectors which will already be experiencing increased demand during the pandemic. DfT figures show that in 2004 nearly 105 million people

[97] A questionnaire completed by the traveller to report health information e.g. symptoms and history of exposure

[98] Handed out to travellers on arrival. A summary of signs and symptoms indicating when to seek medical advice.

[99] St John RK, King A, de Jong D, Bodie-Collins M, Squires Sg, Tam TW. Border screening for SARS. Emerg Infect Dis. 2005;11: 6-10.

[100] Bell DM, World Health Organisation Working Group on prevention of international and community transmission of SARS. Public health interventions and SARS spread 2003. Emerg Infect Dis 2004; 10: 1900-6

arrived in the UK (and a similar number left the UK), around three quarters of them through Heathrow, Gatwick, Stansted and Manchester airports, the Channel Tunnel and the port of Dover. Instituting screening at these six points alone would create significant practical problems, since, for example, Heathrow handles around 80,000 arrivals (and a similar number of departures) each day, and the Channel Tunnel infrastructure has not been designed for the application of health checks. There would be further problems if the decision were taken to apply screening not just at the above ports, but at all points of entry to the UK (26 major airports with potentially a further 300 airports/landing strips servicing international flights and over 1,000 sea ports).

9.20 In summary, the available evidence indicates that neither entry nor exit screening is likely to be effective in delaying the international spread of the virus, and there are considerable downsides in terms of economic impact. However, WHO continues to advise the possible screening of travellers departing countries with transmissible human infection[101].

Domestic travel restrictions

9.21 Travel restrictions within a country slow the spread of the virus somewhat. Again, they do not reduce the size of the epidemic within a locality – they simply decrease the degree of synchrony between local epidemics.

9.22 The SAG considered specific work commissioned from the HPA and also the work described by Ferguson et al in Nature, considering a UK epidemic[102].

9.23 A study by Camitz and Liljeros in 2006 modelled internal travel restrictions on the speed and spread of an outbreak of disease similar to SARS i.e., moderately infectious. They found that a ban on journeys of more than 50km would drastically reduce the speed and spread of outbreaks even when compliance was less than 100%[103]. However, the characteristics of SARS are very different from those of influenza as the number of people affected grows slowly in SARS. In influenza ten times as many people are affected every 12 days. Much smaller delays are expected in an influenza pandemic. DN: Given these differences not clear of the relevance –why not delete?

9.24 Evidence from previous pandemics indicates that some countries, e.g. some states in Australia and Canada in 1918, attempted to restrict travel into their territory (for example by not allowing rail travel and setting up road blocks). These measures were not effective in checking the spread of disease:

[101] World Health Organisation Writing Group. Non-pharmaceutical interventions for pandemic influenza, international measures. Emerg Infect Dis 12, 81-7 (2006)

[102] Ferguson et al 2006 Strategies for mitigating an influenza pandemic. Nature 442:448-452

[103] Camitz M and Liljeros F 2006. The effect of travel restrictions on the spread of a moderately contagious disease. BMC Medicine 4:32

isolating individuals and families or quarantining entire communities did not work[104].

9.25 Any small benefit from domestic travel restrictions needs to be considered against the wider levels of disruption and achievable level of compliance. This measure also needs to be considered in the context of the key message of 'stay at home if you are ill'. A survey in the USA provided some evidence about public behaviour in a pandemic, and indicated that 94% of 1,697 interviewed would stay at home for 7-10 days if they had pandemic flu[105].

School closures

9.26 Children excrete more influenza (and other) viruses, and for longer than adults. This, linked with their lower personal hygiene, and large groups confined for significant periods of time, results in infections spreading quickly when children mix in school or childcare groups. In addition, as children are likely to have no residual immunity to a new influenza virus (unlike some older adults), they are likely to be amongst the groups most affected by a pandemic virus. The vulnerability of children to a particular strain of virus will not be known until the time of the pandemic; if it takes 2-3 weeks from the beginning of a pandemic for it to reach the UK, there should be some indications in that time of whether children are among the more, or less vulnerable groups.

9.27 Schools often close during influenza epidemics and pandemics. This happens naturally in response to large numbers of staff and pupils being ill. The SAG Modelling Subgroup paper[106] summarised the available modelling evidence, as follows:

- The impact of closing schools, especially without any antiviral intervention, depends critically on the mixing between children and adults. Different plausible models give results suggesting between a 10% and 30% reduction in the peak. In either case the reduction in the total number of cases is the range of 10%. Most of this reduction (in the total number of cases) would be in school age children, where the reduction in the number of clinical cases might be as high as 50%. School closure is therefore most usefully employed if children are particularly badly affected.
- Closing schools as an adjunct to antiviral treatment might reduce the peak of the epidemic by an additional 10% (e.g. taking the most optimistic case, from a 30% reduction in the peak to 40%). The total number of clinical cases might also be reduced by 10%. Again most of

[104] Whitelaw TH. The practical aspects of quarantine for influenza. Can Med Assoc J. 1919; 9: 1070-4; McGinnis JP. The impact of epidemic influenza, Canada, 1918-19. Hist Pap Can Hist Assoc. 1977; 19:120-41; Sattenspiel L, Herring DA. Simulating the effects of quarantine of the spread of the 1918-19 flu in central Canada. Bull Math Biol. 2003; 65:1-26

[105] Harvard School of Public Health Project on the Public Health and Biological Security. Pandemic Influenza Survey, September 2006. http://www.hsph.harvard.edu/panflu/panflu_charts.ppt

[106] on www.dh.gov.uk

this reduction would be in school age children, where the reduction in the number of clinical cases might be as high as 50%.

- Combined with a household prophylaxis policy, closing schools can have an important effect on the profile of the epidemic and the overall number of clinical cases (in adults as well as children).
- Closing schools reactively (after a case of flu in the school) for three weeks produces almost the same effect as longer or more widespread closures. However, a school may have to close a number of times under such a policy and longer or more widespread closures may be more practical.

9.28 The importance of the assumptions on the mixing of children in modelling are demonstrated by three recent modelling papers reporting very different conclusions on the effect of school closures on transmission of influenza during a pandemic. A paper by Glass et al. suggested that a combination of nation-wide closing of schools, children being isolated at home and avoidance by adults not involved in their care would have a significant protective effect on the community, with up to 93% reduction in transmission. A paper by Germann et al suggested a 32% reduction in cumulative attack rate, whereas Ferguson et al, considered more plausible by the SAG, suggested a small reduction in cumulative attack rate, but a more substantial reduction in peak attack rates (of up to 40% with antiviral treatment)[107].

9.29 The HPA will soon publish their analysis based on Christmas holidays and seasonal influenza data which was in general agreement with Ferguson et al on the combined effect of antiviral treatment and school closures. This analysis was also considered plausible by SAG.

9.30 US plans for 'Community Mitigation' include school closures, although they tended to be more optimistic about the impacts of closures on disease spread compared with the views of the SAG.

9.31 Overall, therefore there is mixed evidence on the impacts of school closures on the course of an influenza epidemic or pandemic with UK modellers taking a more conservative view than some US modelling. The effectiveness of such a policy would depend crucially on keeping children at home when schools shut to reduce their exposure to infection in other settings.

9.32 There is limited evidence on the impact of school closures on parent-workers' absences and the economy. Estimates based on analysis of the Labour Force Survey suggest that ~16% of the workforce would be affected by a school-closure policy, possibly rising to ~30% in the health and social care sectors. The cost of this enforced absenteeism in terms of lost production being around £1bn per week of school closure (Sadique et al. submitted). Soon-to-be-available results from a desk study commissioned by CCS on impacts of school closures on parent–worker absence in the Critical National

[107] Ferguson et al 2006 Strategies for mitigating an influenza pandemic. Nature 442:448-452; Germann et al. Mitigation strategies for pandemic influenza in the United States. PNAS 2006; 103: 5935-40; Glass et al Emerg Inf Dis (in press tbc) Design of targeted social distancing strategies for pandemic influenza.

Infrastructure (CNI) should help to fill this gap. Soon-to-be-available results from a desk study commissioned by CCS on impacts of school closures on parent–worker absence in the Critical National Infrastructure (CNI) suggest much lower levels, with a peak of 6% additional absences in the CNI workforce due to school and group childcare closures, with little variation between sectors. Experts agree that behavioural responses to a pandemic, including the response of parents following school closures, remains a significant gap in our understanding and one where further research is required.

Closed residential institutions

9.33 Influenza will spread rapidly in closed residential institutions. In 1957, in residential schools, attack rates reached 90%, often affecting the whole school within a fortnight. Similar spread is likely in other closed communities such as residential care facilities, barracks and prisons.

Mass gatherings

9.34 There is no modelling evidence on the impact of banning mass/public gatherings on the spread of influenza, not least because of the considerable challenges for modelling such measures. The SAG Modelling Subgroup paper[108] summarised the available modelling evidence as follows:

- Little direct evidence is available on the effects of cancelling large public events. However, the results might be expected to be similar to those for closing schools, albeit on a considerably more limited scale. Some benefit might be expected for those who attend the events but very little for the overall community. Some benefit, although very small, might also be expected from the reduction in travel to such events. These conclusions are consistent with the lack of important observable differences between the course of seasonal flu outbreaks in London, where there is considerable mixing on commuter trains and underground railways, and the course in other parts of the UK.

9.35 Observations from previous pandemics have been taken as some indication that closing public places along with a range of other measures might be of benefit. Avoiding crowds was suggested by a WHO expert committee in 1959, in the light of observations during the 1957 pandemic, as a means of reducing the peak incidence of an epidemic and extending its duration[109].

9.36 Evidence from the 1918 pandemic on the use of public health measures (including banning mass gatherings) from cities in the US has been considered by various authors. A report in 1927 concluded that closing

[108] on www.dh.gov.uk

[109] World Health Organisation. Expert committee on respiratory virus disease: first report. World Health Organ Tech Rep Ser. 1959; 58:1-59

schools, churches and theatres was not demonstrably effective in urban areas but might be effective in smaller towns and rural districts, where group contacts are less numerous[110].

9.37 In a more recent paper on the 1918 pandemic in the USA, the authors 'fitted an epidemic model to weekly mortality in 16 cities with nearly complete intervention-timing data and estimated the impacts of the interventions, at least in combination. The model could reproduce the observed epidemic patterns well although this does not mean that the interventions were actually responsible for the observed reductions. Assuming that the interventions were effective, the authors found the time-limited interventions used reduced total mortality only moderately (perhaps 10-30%) and that the impact was often very limited because of interventions being introduced too late and lifted too early. San Francisco, St Louis, Milwaukee and Kansas City had the most effective interventions, reducing transmission rates by up to 30-50%'. The authors also noted that they had to assume that individuals reactively reduced their contact rates in response to high levels of mortality during the pandemic[111]. However, even assuming their effectiveness suggested by this analysis does not clarify the benefits of banning mass gatherings in isolation.

9.38 Overall, the evidence is limited about the public health benefits of banning mass gatherings. There is also no direct evidence that banning mass gatherings would <u>not</u> make a difference to a pandemic.

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[110] Jordan EO. Epidemic influenza: a survey. Chicago: American Medical Association, 1927
[111] Bootsma MCJ, and Ferguson NM (2007). Proc Natl Acad Sci USA published online April 2007

Annex A
Steps towards adapting to the human host – further details

1. If it is to become a human pandemic strain, the current H5N1 virus will need to develop greater affinity for humans and efficient human transmission behaviour, whether by reassortment or genetic drift. Influenza viruses attach to, and hence infect host cells by binding to specific receptors. Human (seasonal) influenza viruses have a preference for receptors which are more abundant in the upper airways. These receptors are denoted "α 2,6". If a virus attaches in the upper airway and multiplies at that site, it seems likely that this explains why some viruses (such as normal seasonal influenza) can be passed easily from person to person[112].

2. In contrast the H5N1 virus binds most easily with receptors which are more abundant lower down in the airway in humans. These receptors are denoted "α 2,3"[113]. This fact may explain why it is currently difficult for humans to contract H5N1 and why it does not spread easily from person to person. However, if the H5N1 virus changed so that it began to bind most easily to α 2,6 receptors (those in the upper airway), it would most likely behave more like a seasonal influenza virus, that is transmit easily from person to person.

3. Whether such a change to the H5N1 virus is possible and if so how easily could this happen are key questions related to the risk that H5N1 poses. Recently, scientists have reported finding some H5N1 strains (isolated from infected birds and infected humans) which have a preference for receptors in the upper airway of humans (α 2,6). Therefore this change is possible and has already happened on a small scale. However, since these isolates have not yet caused a pandemic, it would appear these are not the only changes needed.

4. Scientists have studied the 1918 pandemic virus (H1N1) and found that mutations on just two proteins on the haemagglutinin (H) on the surface of that virus caused a binding preference for α 2,6 receptors to be switched to a preference for α 2,3[114]. When tested in the ferret model (ferrets were infected with these viruses) the virus with a preference for α 2,6 spread from ferret to ferret and was virulent, whereas the virus with a preference for α 2,3 was still virulent but did not spread.

5. Since two small protein mutations produced enough change in the 1918 virus to alter its transmissibility, it may be that only a relatively small change is needed for the H5N1 virus changes to be able to transmit from person to person[115].

[112] Baigent SJ, McCauley JW. Influenza type A in humans, mammals and birds: determinants of virus virulence, host range and interspecies transmission. 2003 Bioessays 25, 657 (2003).
[113] Yamada S, et al. Haemagglutinin mutations responsible for the binding of H5N1 influenza A viruses to human-type receptors. 2006 Nature 444, 378-382 (2006).
[114] Tumpney TM, Maines TR, Van Hoeven N, Glaser L, Solorzano A, Pappas C, Cox NJ, Swayne DE, Palese P, Katz JM, Garcia-Sastre A. A two-amino acid change in the haemaggutinin of the 1918 influenza virus abolishes transmission. Science 2007;315:655-9.

[115] Zambon M. Lessons from the 1918 influenza. Nature Biotechnology 2007;25(4):433-4.

Therefore it seems possible that a small change in the H5N1 virus could be the start of the next pandemic, but this event is entirely unpredictable.

ANNEX B
Further information on studies investigating the dosage of vaccine required to induce requisite antibody levels

I. GSK's AS03-adjuvanted, split virion H5N1 vaccine induced an HI geometric mean titre (GMT) ≥40 in 70% of vaccines following two doses at antigen concentrations as low as 3.8 µg. This was not achieved after the first dose. No unadjuvanted formulation achieved this even after the second dose[116].

II. Preliminary results from Baxter suggest that their whole-virus H5N1 influenza candidate vaccine is highly immunogenic and elicits functional antibodies to H5N1 even at the lowest dose level of 3.75µg. Importantly, preliminary analysis of serum samples obtained from the study subjects suggests both the neutralization of the pandemic virus contained in the vaccine and cross-neutralization against widely diverse strains of H5N1, including both Hongkong/156/97 and Indonesia/05/05[117].

III. GSK's alum-adjuvanted, whole virion H2N2 vaccine induced HI GMTs titres ≥40 in 82% of vaccines after two vaccine doses at an antigen concentration of 1.9µg[118].

IV. GSK's whole virus H5N1 vaccine induced HI GMTs ≥40 in 70% of vaccines following two doses at antigen concentrations of 15 and 27 µg with and without alum adjuvant (the alum-adjuvanted 3.8µg vaccine induced 69.4% seroprotection). The authors noted that two doses are required to achieve these titres[119].

V. Berna Biotech's whole virion H9N2 vaccine and Solvay's sub unit H9N2 vaccine (both unadjuvanted) were unable to induce HI titres meeting any of the EMEA's criteria after a single dose in an immunologically naïve population (those aged under 32 years). However, one out of three of the EMEA's criteria were met after two doses[120].

VI. Sanofi Pasteur's H5N1 sub unit H5N1 vaccine was tested at 7.5, 15, 45 and 90 µg. Two intramuscular applications of the highest dose still only resulted in HI GMTs ≥40 in 58% of vaccines[121].

VII. Sinovac's (a Chinese manufacturer) alum-adjuvanted, whole virion H5N1 vaccine induced HI GMT ≥40 in 78% vaccines following two doses at antigen concentrations of 10µg (seroprotection was only 38% after a single dose)[122].

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[116] Borkowski et al - data presented to International Conference on Influenza Vaccines for the World – IVW200618-20 October, 2006, Vienna, Austria

[117] Baxter website - http://www.baxter.com/about_baxter/news_room/news_releases/2006/10-04-06-h5n1_trial.html

[118] Hehme et al, Virus Research 2004 Vol 103, July: 163-171

[119] Hehme et al - data presented to International Conference on Influenza Vaccines for the World – IVW200618-20 October, 2006, Vienna, Austria

[120] The Lancet, 2003: 362: 1959-1966

[121] Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M. Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. N Engl J Med 2006;354(13):1343-51.

VIII. A Japanese alum-adjuvanted, whole virion H5N1 vaccine induced "serum antibody responses to an extent by one [15µg] or two [5µg] shots with the high or medium dose, respectively, of the vaccine preparation, meeting all of the three EMEA criteria"[123]. (However very few specific details are available in the abstract).

IX. Novartis' MF59-adjuvanted H5N3 vaccine induced SRH titre >25mm^2 in 50% of vaccines after a single dose of 7.5µg adjuvanted vaccine. Two doses achieved seroprotection of 100%. Unadjuvanted vaccine induced 0% and 36% seroprotection after one and two doses respectively[124]. An SRH titre of 14mm^2 remained 16 months after the second dose and all three EMEA criteria were met after a booster at 16 months[125].

X. CSL has stated that clinical trials of its alum-adjuvanted, split virion H5N1 vaccine required show that "Two doses, in addition to an [adjuvant] will almost certainly be necessary to produce an immune response" and "A good level of protection was achieved in about half the participants in this trial at the standard dose (15 mcg) plus the adjuvant"[126].

XI. In a clinical trial of split virion H5N1 vaccine at 7.5, 15 and 30 µg, with or without alum adjuvant, the maximum response was HI GMTs ≥40 in 67% of vaccines in the 30 µg adjuvanted dose, for which two doses were needed. Adjuvant did not improve responses in the lower dosage regimes. Two vaccinations of 7.5 µg did result in HI GMTs ≥40 in more than 40% of vaccines[127].

[122] The Lancet 2006: 368: 991-997
[123] Masato Tashiro- data presented to International Conference on Influenza Vaccines for the World – IVW200618-20 October, 2006, Vienna, Austria
[124] The Lancet 2001; 357: 1937-1943
[125] Vaccine 2003; 21: 1687-1693
[126] CSL website - www.csl.com.au/Technical_Information.asp
[127] Bresson JL, Perronne C, Launay O, Gerdil C, Saville M, Wood J et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomised trial. Lancet 2006;367(9523):1657-64.

ANNEX C
Additional information on investigations demonstrating cross protection of pre-pandemic vaccines in human and animal studies

I. Mice immunised with H5N2 vaccine survived lethal challenge with a Hong Kong 1997 (clade 1) H5N1 virus[128] and a Vietnam 2003 H5N1 virus[129].

II. Mice immunised with H5N1 Vietnam 2003 vaccine survived challenge with lethal doses of a 1997 Hong Kong strain and a 2005 Indonesia (clade 2) H5N1 strain[3]. Further studies have shown that vaccination of mice with Indonesia 2005 H5N1 vaccine induces cross-protection against the Vietnam 2004 strain[3]. Protection across H5N1 variants was also confirmed in a ferret model where a single, alum adjuvanted whole-virus vaccine dose produced by reverse genetics from the Hong Kong 2003 strain, protected against challenge with Vietnam 2004 strain. An unadjuvanted 2-dose regime equally resulted in cross-protection[130].

III. GSK has recently reported the results of human studies showing that a candidate adjuvanted H5N1 vaccine is able to induce substantial level of immunity against a drift strain (different clade) using the neutralisation assay[131].

IV. H5N3 vaccine has been shown to induce neutralising antibodies in human sera against H5N1 strains from Hong Kong 1997 to Vietnam 2004[132]. Even though H5N3 vaccine also protected ferrets from lethal doses of H5N1 strain from Vietnam 2004, serum samples did not react in HI or virus neutralisation tests demonstrating neither provides a correlate or cross-protection in ferrets[133].

V. Vaccination (two doses) of mice and ferrets with a live H5N1-derived vaccine attenuated to be trypsin dependent, four weeks later fully protected against lethality and pulmonary replication of challenges with wild type H5N1 clades 1, 2 and 3[134].

[128] Vaccine 2006. 17 November, Vol 24, Issues 47-48, Pages 6859-6866
[129] Vaccine 2006. 10 November, Vol 24, Issues 44-46, Pages 6588-6593
[130] Govorkova EA, Webby RJ, Humberd J, Seiler JP, Webster RG. Immunization with reverse-genetics-produced H5N1 influenza vaccine protects ferrets against homologous and heterologous challenge. J Infect Dis 2006;194(2):159-67.
[131] Denis MJ. Heterologous Cell-mediated Immunity Priming Using Adjuvanted H5N1 Candidate Vaccine. Presented at: "IX International Symposium on Respiratory Viral Infections"; Causeway Bay, Hong Kong 2007.
[132] J. Infectious Disease 2005; 191: 1210-5
[133] Lipatov AS, Hoffmann E, Salomon R, Yen HL, Webster RG. Cross-protectiveness and immunogenicity of influenza A/Duck/Singapore/3/97(H5) vaccines against infection with A/Vietnam/1203/04(H5N1) virus in ferrets. J Infect Dis 2006;194(8):1040-3.
[134] Suguitan AL Jr, McAuliffe J, Mills KL, Jin H, Duke G, Lu B et al. Live, attenuated influenza A H5N1 candidate vaccines provide broad cross-protection in mice and ferrets. PLoS Med 2006;3(9):e360.

VI. Mice immunised with an H5N1 whole virus vaccine from Hong Kong 2003 showed protective immunity when challenged with H5N1 from Turkey 2006. Antibody responses and protective effects were enhanced by the addition of alum adjuvant. However, mice immunised with H5N1 whole virus vaccine from Vietnam 2004 had lower levels of serum antibodies and less protective immunity against H5N1 from Turkey 2006, regardless of the addition of alum[135].

VII. Mice immunised with a liposomal vaccine containing ectodomains of matrix 2 proteins from H1N1, H5N1 and H9N2 strains were (partially) protected from the origin strains as well as from an H6N2 variant. Antiserum from the immunised mice provided protection (100% survival) to naïve mice challenged with H6N2[136].

VIII. Immunisation of mice against the NA of a human H1N1 strain by DNA vaccination resulted in partial protection against avian H5N1 strain from Vietnam 2004. Sera transferred from immunised mice to naive animals conferred similar protection against H5N1 mortality. Analysis of human sera showed that antibodies able to inhibit the sialidase activity of avian N1 exist in some individuals[137].

[135] Ninomiya A, Imai M, Tashiro M, Odagiri T. Inactivated influenza H5N1 whole-virus vaccine with aluminum adjuvant induces homologous and heterologous protective immunities against lethal challenge with highly pathogenic H5N1 avian influenza viruses in a mouse model. Vaccine 2007;25(18):3554-60.

[136] Ernst WA, Kim HJ, Tumpey TM, Jansen AD, Tai W, Cramer DV et al. Protection against H1, H5, H6 and H9 influenza A infection with liposomal matrix 2 epitope vaccines. Vaccine 2006;24(24):5158-68.

[137] Sandbulte MR, Jimenez GS, Boon AC, Smith LR, Treanor JJ, Webby RJ. Cross-Reactive Neuraminidase Antibodies Afford Partial Protection against H5N1 in Mice and Are Present in Unexposed Humans. PLoS Med 2007;4(2):e59.

ANNEX D – Information on the assumptions used to construct the scenarios for combined clinical countermeasures modelling

1. Each disease scenario comprises two elements: a clinical attack rate (an index of the extent of illness) and a case fatality rate (an index of the severity of illness). We used 25% as the lower bound for the clinical attack rate because the three 20th century pandemics all had attack rates close to 25% in the UK. We additionally considered an attack rate of 35% because international data suggest that the attack rate may have reached 35% for some of the 20th century pandemics in the US. Finally, we used 50% as the upper bound for the clinical attack rate because the WHO has advised health departments to plan for a 50% attack rate as a worst case.

2. We used 0.37% as the lower bound for the case fatality rate because 0.37% is the estimated case fatality rate for seasonal flu in years where flu A predominates (corrected for the likely influence of routine vaccination) and 2.5% as the upper bound because estimates of the case fatality rate for 1918/1919 (the most severe of the three 20th century pandemics) generally fall between 2.0 and 2.5% for the UK.

3. To derive the number of hospitalisations for the low severity scenario (case fatality rate of 0.37%) we used a case hospitalisation rate of 0.55%. This figure is the estimated hospitalisation rate for seasonal flu in years where flu A predominates (corrected for the likely influence of routine vaccination). For the high severity scenario (case fatality rate of 2.5%) we simply "scaled up" the low severity case hospitalisation rate of 0.55% to give a hospitalisation rate for the high severity scenario of 3.72% (0.55% x 2.5%/0.37%).

4. We assumed a case-complication rate of 10% for the low-severity scenario and ~28% for the high-severity scenario. The lower figure of 10% is an estimate of the case-complication rate for seasonal flu. The corresponding estimate for the population at risk of developing complications represents ~22% of the total UK population. Hence the upper figure of ~28% (which is derived by assuming that 25% of non-hospitalised and 100% of hospitalised cases have complications) allows for a substantial increase in the size of the high risk population, a substantial increase in the proportion of those at risk who develop complications, or a more modest increase in both of these components.

Number of deaths, hospitalisations and clinical cases

5. For all calculations we assumed a reference UK population of 60 million.

6. For face masks we assumed no effect on the extent or severity of illness.

7. For (pre-pandemic) vaccination we assumed:
   - A 20% reduction in susceptibility to infection
   - No reduction in the probability of becoming a clinical case
   - No reduction in the severity of illness

- That in all cases the impact of vaccination is expressed solely in terms of the expected impact on the number of clinical cases (and the consequent effect on the number of hospitalisations and deaths).

8. For antiviral treatment we assumed:
    - A 50% reduction in the probability of being hospitalised or dying
    - A moderate effect on transmission – consistent with a 60% reduction in infectiousness from the start of treatment, with treatment starting 24 hours after the onset of symptoms (see Ferguson et al.[138])
    - That where targeting of antiviral treatment is required (because the total stockpile is insufficient to treat all clinical cases) all patients at risk of hospitalisation or death are treated.

9. For antiviral prophylaxis we assumed:
    - That post-exposure prophylaxis of household contacts is combined with a) antiviral treatment of all clinical cases and b) school closures.

10. For antibiotic treatment we assumed:
    - That 50% of complications are bacterial
    - That antibiotics are 75% effective in preventing hospitalisation or death in those with bacterial complications
    - That all hospitalisations and deaths occur in those with complications
    - That where the stock of antibiotics available is insufficient for all those with complications to be treated, antibiotic treatment is successfully targeted at the 50% of complications that are bacterial.

[138] Ferguson NM et al (2005) Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 437(7056): 209-14