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SPI-M Modelling Summary

Prepared by the Scientific Pandemic Influenza Advisory Committee (Subgroup on Modelling)
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Executive summary

This document represents the consensus view of the modelling subgroup of the Pandemic Influenza Scientific Advisory Group. It is not a polished report of the group’s deliberations and conclusions. Rather, it is a working document, updated as necessary after each meeting of the subgroup, to record the group’s advice in a form that can be immediately used to assist in policy formulation and is intended for a technical audience.

The document is focused on those results that directly influence policy. It not only contains statements of what might happen but also the group’s view of the policy implications. This takes the form of notes on ‘What we know’ and ‘Implications for planning’. However, other factors such as practicality, proportionality and questions of value for money are also important in the generation of an effective policy. These factors are outside the remit of the sub-group. (When relevant, modelling of such factors is the responsibility of the Department of Health’s Analytical teams and similar groups in other government departments).

The views of the group should not therefore, be taken as a definitive statement of current government policy but only of the group's advice based on their own scientific understanding.

Sometimes the document lists unresolved modelling questions. These represent either work in hand, or topics to which the group intends to return when higher priority work has been completed.

This is a continuous document, and should not be read as a series of independent statements.
1. Purpose

The purpose of this paper is to summarise the results of epidemiological modelling on Pandemic Influenza and their implications for policy. The view presented in this paper represents a consensus agreed by the Scientific Pandemic Influenza (SPI) subgroup on modelling. The paper is regularly updated on the basis of new results.

The focus of this paper is on the modelling results for significant pandemics, of which there were three in the twentieth century: 1918-19, 1957-58, and 1968-69. Such significant pandemics result in a relatively large number of people becoming clinically ill, suffering complications, requiring hospitalisation, and dying. The more recent H1N1 2009 pandemic was less significant, being, by nearly all measures, of considerably lower impact. The policy importance of the 2009 outbreak was as an exemplar of an event, which, at least in its early development is difficult to distinguish from a significant epidemic similar to the three 20th Century events with the then currently available sources of information.

The general aim is to describe the results as they impact on policy. The goal is to assist in the development of a set of flexible responses that cover (in an appropriate and feasible way) the whole range of risk (e.g. possible disease parameters). Robust solutions that cover a wide range of scenarios are preferred. However, where such solutions cannot be found, the decision points where a choice between different responses needs to be made, and the lead indicators required to inform that choice, should be identified. An important outcome of adopting this kind of approach will be an indication of which areas of the existing plans are sufficiently robust or flexible and which require further development. This development may involve further research / modelling, or it may involve additional policy decisions.

More particularly, the purpose of this paper is to summarise broadly, and at a relatively high level, our current knowledge as it impacts on determining an operational response. As a means of structuring the information, we have taken a chronological approach. We consider the possible progression of a future pandemic flu strain from its country of origin to, and then within, the UK. We identify key stages of this progression, and where appropriate we summarise the important operational issues in terms of:

- What we know
- Implications for planning
- Policy questions
2. Background

What we know:

a) There were three significant pandemics in the twentieth century: 1918-19, 1957-58, and 1968-69-70.

b) In the UK there were three waves associated with 1918-19 pandemic. The wave structure of this pandemic is not well understood. The final 1919 wave may have been a separate pandemic of a different virus to the 1918 waves. The smallest of the waves was in July-August 1918, the largest second wave was from October 1918 to January 1919, and the third wave was from February to April 1919. Estimates of the national clinical attack rate vary, but suggest nationally it was around 25% of the population (totalled over all waves). The highest clinical attack rates were seen in the young. Estimates of the case fatality ratio are around 2%, relatively evenly spread across the population, though with an excess in young adults.

c) In the UK the 1957-58 pandemic came in one wave with most of the deaths occurring from September-February. Estimates of the national clinical attack rate vary, but suggest nationally it was around 30% of the population. Estimates of the case fatality ratio are around 0.1 to 0.2%. These average figures mask the considerable variation by age, most deaths being in the older adult population. However, most illness was in the young.

d) The 1968-69 pandemic came in two waves in the UK, which was unusual in global terms. In England and Wales, the first wave peaked around February-March 1969 followed by a large peak in the 1969-1970 flu season. Estimates of the national clinical attack rate vary, but based on comparisons with the epidemic in the United States, it may have been around 35% of the population. Estimates of the case fatality ratio are around 0.2 to 0.4%. These average figures for mortality mask the considerable variation by age, with again most deaths being in the older adult population. In this case however, illness was spread evenly across age groups.

e) The recent H1N1 2009 pandemic produced no significant signal of excess deaths in the overall population although approaching 700 people in the UK are known to have died from confirmed H1N1. Case ascertainment is unlikely to have been complete, and the true number is almost certainly higher. RCGP rates of consultations were highest in the young. There were significant levels of background immunity amongst adults. The epidemic consisted of two ‘waves’, one immediately following the other. The first ‘wave’ peaked at the beginning of the school holidays in mid-Summer when contact rates in children reduced. Once schools returned in September, infections grew again until mid-October when there were not enough susceptible individuals left to sustain the pandemic. Estimates of the national clinical attack rate vary. Synthetic case figures used to
track the epidemic suggest a clinical attack rate of 1 to 2%. However, modelling suggests that these estimates reflect only around 10% of those infected (Baguelin et al 2010), which is consistent with serological analysis of the first wave (Miller et al Lancet 2010). If, as is typical for influenza, only half of those infected were symptomatic though possibly with very mild symptoms, the clinical attack rate would be around 5 to 10%. If so, estimates of the case fatality ratio are around 0.01% (Presanis et. al. 2011) In terms of age groups, mortality was spread evenly across the age groups although most illness was in the younger groups. An antigenically similar H1N1 virus was responsible for a significant epidemic of seasonal influenza in 2010/11.
3. Progression of a Pandemic

3.1 The initial outbreak

What we know:

a) A pandemic virus could first emerge anywhere in the world. Two of the three pandemics of the twentieth century pandemics may have emerged in China (1957 and 1968). Most of the H5N1 avian influenza cases identified have been in Asia and this might evolve into a virus capable of spreading efficiently in humans. The focus of initial outbreak modelling has hence been on Asian outbreaks, although the conclusions from such modelling results are informative wherever the pandemic starts.

b) If the first incipient pandemic cases are in a rural part of the world, stringent social distance measures, the use of area quarantine and the implementation of a geographically based, large scale, antiviral prophylaxis policy, could contain an outbreak with up to 3 million courses of antivirals for R0 of up to about 2 (Ferguson et al. 2005, Longini 2004). Even if the strategy fails to contain the disease, it might delay its progress by around a month (Ferguson et al. 2005).

c) The practicality of such measures depends on effective local planning to identify the first cases, provide antiviral drugs and implement quarantine and other social distance measures. Such measures were not possible in the 2009 pandemic as there were 6,000 to 32,000 pandemic H1N1 infections in Mexico by late April 2009 when the strain was widely identified and reported (C. Fraser et al. 2009). However, early detection is more likely with a high case fatality ratio virus, which might be responsible for a more significant pandemic.

d) Regardless of whether early containment measures prove to be effective, disease surveillance will be required to estimate important disease parameters such as the (age-specific) clinical attack rates and mortality rates, as well as measures of disease severity and descriptions of clinical pattern. It is uncertain exactly how long it will take to derive reasonable initial estimates for these and other parameters. It seems reasonable to assume that, if the disease is recognised early and takes 2 to 4 weeks to spread to the UK (see section 3.2), initial upper bound estimates of the mortality rate (and the general qualitative nature of the pandemic) may be available by the time it reaches the UK. More useful estimates may not be available until there have been significant cases in the UK. Clinical attack rates (and therefore case fatality ratios) are particularly difficult to estimate, so reasonable estimates for these parameters may take longer to derive. Indeed clinical attack rate (and therefore case fatality ratio) estimates may not be available until after the pandemic.
e) Initial severity estimates will be problematic for numerous reasons. Not all early cases will be confirmed in a laboratory, and those with milder symptoms may never contact health services. The delay in the reporting of death from the onset of symptoms will affect any estimates of case fatality ratio. Outbreaks that have completed can be difficult to locate. Background immunity is likely to be unknown. Laboratory tests may still be in development and not widely available. Different health systems may show different propensities to consult healthcare, leading to different ‘denominator’ information.

Implications for planning:

I. Encourage arrangements that facilitate the early collection and sharing of data (similar to that described in Annex 4) between nations.

II. Ensure that all intervention strategies are able to accommodate the full range of possible disease parameters, including the possibility of outbreaks without significant impacts in terms of hospitalisations and mortality. Put in place mechanisms to easily modify the response as further information becomes available.

III. Assist international efforts to make at least 3 million courses of antivirals available for use in initial containment.

IV. Encourage construction of realistic and detailed local plans for containment in the source country. (This is different to attempting to contain the virus once it is widespread which has little chance of success, see section 3.3d).

3.2 International spread

What we know:

a) The UK generally has a high volume of international travel, and so is likely to be one of the earlier countries to receive infectious individuals. For example, the UK was one of the first countries in Europe to have confirmed H1N1 cases in 2009, the first confirmed cases occurring within a week of the recognition of a public health emergency of international concern.

b) Simulations of outbreaks beginning in rural parts of Asia suggest that 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 (Cooper et al. 2006, Ferguson et al. 2006 and broadly in agreement with Colizza et al. 2007). However, in a mild pandemic such as 2009 it might take some time for even significant levels of infection to be recognised as an international health emergency, and the time from recognition to arrival in the UK might be much shorter. Indeed, some (unconfirmed) cases may already be present in the UK before such recognition.
c) Imposing a 90% restriction on all air travel 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 (Cooper et al. 2006, Ferguson et al. 2006).

d) Restrictions limited to travel to the UK from Southeast 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.

e) 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 into the UK.

f) 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 (Cooper et al. 2006).

g) Estimates on the delays caused by different travel restrictions depend on various assumptions, including the transmissibility and generation time of the influenza virus. For lower transmissibility, although there may be some quantitative changes to the estimates above, these would not, in general, be large enough to make a difference for policy decisions.

h) While clearly possible in principle, for all practical levels of restriction, there is little probability of a country missing the pandemic altogether due to travel restrictions. (Cooper et al. 2006).

i) Screening is less effective than restricting travel generally. Preventing those with clinical symptoms from travelling is only likely to delay the spread of the disease by 1 to 2 weeks. Assuming passengers are thus screened before travel for clinical symptoms, there is no additional advantage in entry screening (Pitman et al. 2005).

Implications for planning:

I. Assume no significant benefit from international travel restrictions, exit or entry screening.
3.3 Geographical development of the pandemic, within the UK

What we know:

a) A pandemic flu outbreak would be expected to have been seeded (through international and internal travel) in all major UK centres of population within 1 to 2 weeks (Ferguson et al. 2006). It would then take some further time to show significant activity across the country, as was seen in 2009.

b) Larger population centres are likely to be seeded with more cases early on during the pandemic. Therefore, the pandemic may take hold sooner in urban areas. Hence, at the early stages of the pandemic, case numbers may be larger in urban areas. Such differences in case numbers will primarily reflect the timing of the start of the local pandemic, as opposed to a larger overall clinical attack rate.

c) Mass provision of antivirals to the population would simply postpone the outbreak by the period for which prophylaxis is provided (Vynnycky et al. 2005, Longini et al 2004). However, such mass prophylaxis would deplete antiviral stocks very quickly (at a rate of one treatment course per 10 person days).

d) Because of the probable multiple importations of pandemic flu, and the concentration of the population in cities, attempts at containment (similar to those explained in section 3.1b above) by antiviral prophylaxis and practical social distance measures are almost certain to fail (Ferguson et al. 2006, Van Tam et al. 2004).

e) Even very substantial reductions in internal travel between localities (of say ~90%) would have little effect on the length and peak size of the epidemic in each local area. However, coupled with the elimination of international travel, they could significantly spread out a national epidemic by desynchronising the epidemics in the local areas. Such restrictions are probably impractical. More realistic reductions in such travel would have a negligible effect on the national epidemic (Health Protection Agency 2005).

f) Transmission and development of the outbreak may be effected by changes in contact patterns, caused, for example, by school or seasonal holidays.

Implications for planning:

I. Assume, for the purposes of developing intervention strategies, that clinical cases will appear throughout the UK in less than 2 weeks.

II. Assume no benefit of internal travel restrictions.
### 3.4 What we know about the impact of an unmitigated pandemic

a) A pandemic profile (i.e. the proportion of infections, clinical cases, hospitalisations and deaths expected each week) has been constructed to guide national planning (see Annex 3). The profile is similar to that of the second wave of the 1918 to 1919 pandemic in London. This profile represents the build-up that might be expected for a national epidemic. About 22% of new cases occur in each of the peak weeks.

b) Local epidemics in former PCT sized areas would be expected to be more highly peaked than the national epidemic, with a peak number of cases up to 50% higher. Similarly, they would be expected to be of shorter duration, perhaps by a third, than the national epidemic. Empirical evidence from 1918 suggests, however, that there may also be a large variation in epidemic profile from PCT to PCT. In 1918, two thirds of modern PCT sized areas had less peaked rates of mortality than suggested by the national planning profile, and a third more highly peaked mortality.

c) As discussed in section 3.5, the mass treatment of clinical cases with antivirals could flatten the temporal profile, lowering the peak and lengthening the base if there is a high take up of treatment (Ferguson et al. 2006, Vynnycky et al. 2005, Gani et al. 2005). In 2009 few of those infected were treated in the period of mass treatment (e.g. via NPFS) because few of those infected consulted the healthcare system. Hence the overall impact of antivirals on transmission and in turn the attack rate was negligible in 2009.

d) The UK case fatality ratio (CFR) for four pandemics in the last 100 years was of the order of 0.01 to 2% (Nguyen-Van-Tam and Hampson 2003, see also section 2 above). In contrast, recent estimates of the case fatality ratio for H5N1 avian flu are of the order of 50 to 60% (see www.who.int/csr/disease/avian_influenza/).

e) There has been a general (but not uniform) decline in influenza (pandemic and seasonal) and pneumonia mortality since the 1918 pandemic. However, the extent to which this decline can be attributed to the improved underlying health of the public, better healthcare or to changes in pathogen severity is unclear.

f) Based on historical pandemics a ‘reasonable worst case’ for a pandemic would be a CFR of 2.5%. However, even if the estimates for H5N1 avian flu are overestimates for a naturally occurring viral strain adapted for efficient human to human transmission, an H5N1 pandemic would be expected to be towards the higher end of the range of historically observed CFRs.

g) A pandemic with a CFR above 2.5% cannot be ruled out.

h) Mortality rates often vary by age. Age-specific mortality curves for 1957-58 and 1968-69 show a U-shaped pattern with a slightly increased case fatality ratio in
the very young and then increasing case fatality ratio with increasing age. The 1918 pandemic on the other hand had a more equally spread mortality rate with particularly high mortality rates seen in young adults (Monto 1987).

i) For the well documented pandemics over the last 100 years, the overall clinical attack rate (cumulative across all waves) has been of the order of 5 to 35% in the UK. Interpreting public health records from pre-20th century outbreaks is problematic but suggests a higher rate for the pandemic of 1889, in the range of 35 to 50% in the UK (Valleron, A.J. et al. 2010, Finnie 2011, Parsons, H. F. 1891, 1893). As seen in 2009, there can be low impact pandemics with low clinical attack rates. A reasonable upper bound for the cumulative clinical attack rate for planning purposes would be around 50%. The reasonable worst case scenario with peak impact at any given time is hence a single wave pandemic with a clinical attack rate of 50%. The proportion of the population infected would be higher: estimates of the proportion of infected individuals who go on to become clinical cases generally range from one third to two thirds. (Mann et al. 1981, Longini et al. 2004, Monto 1987, Nguyen-Van-Tam and Hampson 2003, Fleming 2000, Carrat et al. 2008).

j) Clinical attack rates may vary by age both due to different mixing patterns between age groups as well as partial immunity that can be distributed unevenly between age groups. Illness generally peaks in school children and/or young adults.

k) In the early stages of a pandemic, the groups for whom the risk of complications or death is greatest will not be well known. However, groups identified as being at a higher risk of complications or death from seasonal influenza are likely to be at a higher risk of complications or death from the pandemic strain. As the outbreak progresses, surveillance data will accumulate, and it may become possible to better identify risk groups and estimate key disease parameters. If the pandemic starts abroad, reasonable estimates of some (but probably not all) disease parameters may be available by the time the disease reaches the UK. However, if the pandemic starts in the UK, no such estimates will be available initially.

l) The provision of good background serology data will be key to providing estimates of initial immunity, which will be important for estimating the clinical attack rate.

m) Contact tracing (including serological and virological testing of contacts) of the first few hundreds of cases in the UK, community surveys and individual outbreak analysis will be essential for the accurate determination of disease parameters, most importantly generation time and the proportion of cases showing clinical symptoms.

n) Given a cumulative 50% attack rate over a single wave as in the ‘reasonable worst case’ discussed above, absence directly due to illness would be expected to peak at 17% for two to three weeks at the height of the epidemic (Department
Employers should also be advised to take account of the possibility of local geographical, behavioural and temporal variation. Small organisational units (5 to 15 staff) should plan to a higher level of absence of 30 to 35% (Department of Health 2006b).

For a typical organisation, additional absence (again in the reasonable worst case) due to those who need to stay at home to look after ill children might increase absenteeism from 17 to 20% (Department of Health 2006b).

Both the positive (reduced transmission) and negative (reduced productivity) effects of absenteeism may be amenable to modification by suitable behavioural interventions. Setting priorities for the objectives of such interventions is hence essential to avoid ‘mixed messages’.

3.5 What we know about the impact of pharmaceutical countermeasures

A policy of rapid treatment of those ill is the most efficient use of antivirals for stockpiles, corresponding to treatment courses for less than 50% of the population (Ferguson et al. 2006). If the available stock is less than the clinical attack rate of influenza like illness (taking account of losses due to wastage), it will be necessary to limit treatment to priority groups (Gani et al. 2005).

Although the main purpose of antiviral treatment is to reduce the severity of the disease, treating all clinical cases with antivirals might also decrease the overall attack rate (assuming a high uptake of treatment) (Ferguson et al. 2006, Gani et al. 2005). There is considerable uncertainty over the extent of the reduction possible. Some models suggest a relative reduction of up to one third. This suggests, for example, that treating all cases in an outbreak for which the attack rate would be 50% without treatment would require enough antiviral courses for ~35% of the population. To obtain the most effect, the drug must be administered within 24 hours of the start of symptoms. Delivery within 48 hours (advised by NERVTAG as a plausible practical assumption) is less effective but still beneficial and cost-effective. In addition, to obtain a substantial effect, a sizable proportion of those infected must take the drug. In 2009 there was little impact on transmission because few of those infected showed ILI and only a proportion of those took antivirals.

Another possible practical use for antivirals is prophylaxis of essential workers leading to a possible two thirds reduction in both peak and total clinical attack rates for the groups receiving prophylaxis (Ferguson et al. 2007). The cost, in terms of antiviral stocks, of such prophylaxis is a function of the number of workers who are classified as essential, the duration over which they are offered prophylaxis, and whether prophylaxis is additionally provided for their close
contacts. The costs in terms of antiviral treatment courses would be large, for example around half the current Tamiflu stock for front line NHS workers alone. A further problem is that unlike those treated, workers who receive prophylaxis for the duration of the first wave and do not develop clinical or sub-clinical infection would not be immune at the start of a second wave (see section 3.5).

d) Stockpile levels in excess of 50% coverage (in terms of treatment courses) are sufficient to allow post-exposure prophylactic options to be considered. Post-exposure antiviral prophylaxis of the household contacts of cases could have a more marked impact on the disease than simply treatment of cases (Ferguson et al. 2006). Such ‘household prophylaxis’ would be more effective in mitigating and delaying the progress of the epidemic than antiviral treatment alone (Ferguson et al. 2006).

e) Given any stockpile for which household prophylaxis is a possible option (i.e. more than 50% coverage in treatment courses), starting with prophylaxis and, if necessary, reverting to treatment (and if necessary targeted treatment of at risk groups/children) is likely to result in the smallest number of deaths. On the other hand, the greatest reduction in peak attack rate is more likely to be obtained by continuing the household prophylaxis strategy to stockpile exhaustion.

f) Prior vaccination with a poorly matched (pre-pandemic) vaccine and antibiotic treatment of those with complications would also be important in controlling the overall impact on hospitalisations and deaths (Ferguson et al. 2006, Vynnycky et al. 2006).

g) For a 1918 like pandemic, a policy of timely household antiviral prophylaxis, limited school closures (see section 3.6), and antibiotic treatment of complications could be expected to essentially halve the attack rate and reduce the number hospitalisations and deaths by 80 to 90% compared with no intervention. Even for a more extensive pandemic, such a combined intervention might lead to reductions in the number of cases in excess of 40% and in deaths and hospitalisations by more than 80% (Department of Health 2006a).

h) Stockpiling enough pre-pandemic vaccine for 40% of the UK population would allow a ‘targeted’ strategy of vaccination of all those aged 16 or under, and all those aged 65 or over.

i) For a 1918 type of epidemic the combination of interventions, including pre-pandemic vaccine, might suppress the national epidemic entirely leading to only local outbreaks of seasonal influenza proportions¹. For a more extensive pandemic, such a combined strategy might still reduce the number of cases by around 60%, and deaths and hospitalisations by 80 to 90%.

¹ Scenarios where pre-pandemic vaccination is considered use the low assumption of 20% efficacy.
j) Pre-pandemic vaccination of 100% (rather than 40%) of the population (again with the use of antiviral household prophylaxis and antibiotic drugs for complications) would lead to a substantially greater 80 to 90% reduction in the number of cases and around a 95% overall reduction in deaths and hospitalisations. (Department of Health 2006a).

k) Indicative results summarising subsection 3.5c to 3.5j above for the combined interventions are shown in Annex 1.

l) Such combined interventions would still have significant impacts, even if one intervention was less effective than expected. In addition, stockpiling enough antivirals to treat more than 75% of the population increases the likelihood of still exerting reasonable control over the scale and severity of the national outbreak, even if antiviral prophylaxis or vaccination proves to be less than fully effective (Department of Health 2006a) and/or there are significant antiviral losses in treating non-pandemic influenza like illness and wastage.

m) The estimated impact of antiviral treatment and household prophylaxis, discussed above and in Annex 1, assumes treatment within 24 hours of the first symptoms and that those with clinical symptoms are treated at home (Ferguson et al. 2006). Greater delay or the greater mixing of those with clinical symptoms will reduce the impact of any antiviral policy.

n) Those infected will show a range of symptoms. Some of those with clinical symptoms may not fulfil the criteria to be classified as a clinical case and not all clinical cases may present to primary medical services. This will affect the proportion of those with clinical symptoms who receive treatment with antivirals and hence the estimated impact of the policy.

o) The above estimates of impact assume that the uptake of pharmaceutical measures is prompt and universal. In the UK in 2009, uptake of antivirals was low and that of vaccine only reached ~40% in the at risk groups identified for vaccination by the end of the epidemic. Low uptake, as well as failing to be able to deliver interventions in a timely manner, will necessarily reduce the impact of these countermeasures.

p) As the effectiveness of pharmaceutical countermeasures is well established and there are diminishing returns from information campaigns, establishing a high take-up of antivirals and vaccine should be a priority target of efforts at guiding behaviour.

3.6 What we know about the impact of social distance measures:

a) In addition to the medical countermeasures of vaccination, antivirals and antibiotics, various social distance measures might be used to reduce interpersonal contacts and hence the progress and extent of the epidemic. Two
such measures are restrictions on mass gatherings, and school closures of various kinds - individual classes, local, regional, national, pre-emptive, scheduled or reactive (Cauchemez et al. 2009).

b) The impact of any intervention including closing schools depends critically on the mixing between children and adults, as well as the age dependence of any background immunity.

c) Assuming little or no background immunity, different plausible models (Ferguson et al. 2006, Cauchemez et al. 2008) give results suggesting a reduction in peak of up to 50%, depending on when and for how long schools are closed. The corresponding reduction in the total number of cases is in the range of 10 to 20%. Much of the reduction in the total number of cases would be in school age children.

d) On the other hand, if there were significant background immunity amongst adults there may be a more considerable impact on the pandemic. For example, in the UK in the 2009 pandemic, school holidays (possibly in combination with general summer holidays) suppressed the epidemic over August (Eames 2012). However, to be used successfully as a suppression strategy, closures would need to be maintained until pandemic specific vaccines were available. Indeed, the ill-timed closing of schools might make the epidemic worse.

e) School closure is therefore most usefully employed if children are particularly badly affected, or if there is known to be significant background immunity in adults.

f) The impact of any school closure policy would depend on the timing and length of the school closures in the specific circumstances of the epidemic. However, In the case of mitigating (rather than suppressing) an epidemic, 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 (Ferguson et al. 2006). 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.

g) Combined with a household prophylaxis policy rather than simply treating cases, closing schools would have a more significant effect on the profile of the epidemic and the overall number of clinical cases (in adults as well as children), (Ferguson et al. 2006) as shown in Annex 1.

h) As noted above, absence directly due to illness could peak at up to 17% for two to three weeks at the height of the epidemic (Department of Health 2006b, SQW Consulting 2007). Under the same reasonable worst case assumptions, for a typical organisation, additional absence due to those who need to stay at home to look after ill children might further increase absence from 17 to 20% (Department of Health 2006b). However, if schools were closed, absence due to those staying at home to look after children could rise to 15 to 20% throughout the period of
school closure, independently to the extent and severity of the epidemic (Department of Health 2006b, Sadique et al. 2008). In an epidemic approaching the reasonable worst case, a total absence level including illness and those caring for children might approach 30 to 35% at the peak, though evidence from school holidays and teachers’ strikes suggests this may be an overestimate (Department of Health 2006b, SQW Consulting 2007).

i) If schools are closed it will be important to discourage the gathering of children into school-like childcare settings e.g. mass childcare provision by employers (Inglesby et al. 2006) as this would negate any health benefit of the policy.

j) 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 would have otherwise attended the events but very little for the overall community. Some benefit might also be expected from the reduction in travel to such events. However, the benefits of even major reductions in all travel are small. 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.

k) Voluntary home isolation, i.e. people staying at home if they show flu like symptoms, will decrease the number of contacts between infected and uninfected individuals, and hence is likely to decrease the spread of infection.

l) The combined effects of various social distancing measures (including closing schools, cancelling large public events, closing places of entertainment, and home isolation) if started very early on in a locality affected by influenza may have a significant impact on reducing transmission. In some US cities in the 1918 to 19 pandemic it is thought that the combined measures reduced R to less than 1 (from an R0 value of 1.4 to 2) however such measures would need to be maintained until sufficient quantities of pandemic specific vaccine became available. In the US cities, when the measures were relaxed there was a second wave of infection.

m) All social distance measures depend on compliance by the population which, in turn, depends on the social acceptability of the measures. Without good behavioural research on these it is difficult to predict the impact of such measures being deployed in a future pandemic.

Implications for planning:

1. Develop a flexible system that would enable antiviral prophylaxis, antiviral treatment for all, or antiviral treatment to be targeted dynamically at different
priority groups as required. Begin with household prophylaxis but revert to more restricted use if indicated by stockpile usage and surveillance information.

II. Ensure that there are robust data collection systems in place that will be able to capture information regarding attack rate, disease pattern, severity, mortality, the propensity to seek healthcare and the background level of immunity in a timely and reliable way. This should include contact tracing (including virological/serological investigation of contacts) of the first few hundreds of cases.

III. Plan to the planning assumptions in Annex 2, and Annex 3, recognising that these will need revision on the basis of surveillance information from both the UK and abroad.

IV. While there is a role for the less disruptive social distance measures in any pandemic (i.e. voluntary home isolation), school closures and the cancelling of public events are generally only justified in very severe pandemics because of their severe social impact over an extended period of time (e.g. until pandemic specific vaccine becomes available).

Policy questions:

1. How would the response change for an extreme pandemic (i.e. with a CFR above the historical range of up to 2.5%)? When would long term social distance measures be justified?
2. How can the response be tailored to the range of possible pandemics from events similar to 2009 to those similar to the reasonable worst case?
3. What is the social acceptability of pharmaceutical countermeasures and social distance measures, in particular school closures, in pandemics of different severity?

4. The second wave

What we know:

a) Some supplies of vaccine specific to the pandemic virus may be available before a second or third wave of a pandemic - if they arise. In the 2009 pandemic vaccine only became generally available sometime after the peak of the second wave in the UK. Without the suppression effect in the holiday period (see section 3.6d) the vaccine would have arrived after the vast majority of the epidemic was over.

b) Of the three pandemics of the 20th Century, only that of 1918 to 19 generally produced national epidemics with second waves and thus in only one of these pandemics would a pandemic specific vaccine be of general value in controlling the pandemic.
c) It is expected that vaccine specific to the pandemic virus will start to become available approximately 4-6 months after the start of the pandemic (WHO website, DH 2005 website). Even if there is time to produce some vaccine before the start of the second wave, there may not be time to produce a large amount, which may take 8-12 months.

d) The main impact of vaccination with a pandemic-specific vaccine, if it were available, is therefore entirely dependent on the timing and size of any second and subsequent waves in relation to the first wave (and vaccine manufacturing and delivery schedules) and hence inherently difficult to estimate.

e) The priority groups for vaccination will depend on the previous history of the pandemic. Between waves it may be preferable to vaccinate those groups with the greatest transmission to prevent a further wave.

f) Some limited impact will occur if a substantial quantity of vaccine becomes available within, rather than before, a second wave (or extended first wave). The rapid final delivery to those to be immunised would be essential to obtain a significant effect. In this case the vaccine should be targeted at those most at risk of serious illness.

g) Surveys of immunity patterns through and following the first and subsequent waves are essential to planning a pandemic specific vaccination strategy (Vynnycky et al. 2006).

h) The number of individuals who develop immunity to the pandemic strain in response to the first wave and subsequent waves will depend on the overall attack rate, which in turn will depend on the intervention strategies adopted (e.g. containment strategies involving pure prophylaxis would, if successful, leave relatively few people immune). The proportion of the population who are immune to the pandemic strain at the start of a second wave could therefore vary widely, depending on the intervention strategies adopted during the first wave.

i) If strategies controlling the epidemic are successful (i.e. complete coverage with pre-pandemic vaccine coupled with household prophylaxis) widespread vaccination with the pandemic specific vaccine will be necessary to provide sufficient population immunity to allow suspension of antiviral interventions.

Implications for planning:

I. Set up arrangements for the required robust surveys of the background level of immunity across the population that was present before the first (and possibly only) wave.

II. Set up arrangements for robust surveys of the level of immunity across the population during and after the first (and possibly only) wave.
III. Ensure arrangements exist for the rapid immunisation of the population as vaccine becomes available and that these can cope with different prioritisation strategies.

Annex 1: Indicative impacts of countermeasures

This annex provides a graphical illustration of the indicative impacts of different countermeasures, both individually and in combination. The analysis follows from the discussion in the main text of this report, and is presented for three different clinical attack rates: 50%, 35% and 25%.

The four countermeasures considered are:

<table>
<thead>
<tr>
<th>Countermeasure</th>
<th>Effect on disease</th>
<th>When it is most effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivirals (AV)</td>
<td>Reduces severity of disease and can reduce the overall attack rate.</td>
<td>Depending on stockpile size and size of the pandemic, antivirals may be used for just ‘at risk’ or to treat all those infected. Best used within 48 hours of symptom onset, and ideally within 24 hours for maximum effect (the tables assume the latter). Needs to be given to the majority of infected people to have sizeable impact.</td>
</tr>
<tr>
<td>Antibiotics (AB)</td>
<td>Treats bacterial complications, reducing hospitalisation and deaths.</td>
<td>Antibiotics would be used to treat those with complications. Only effective if complications are bacterial and not viral.</td>
</tr>
<tr>
<td>Pre Pandemic Vaccine (PPV)</td>
<td>Reduces number of cases, hospitalisations and deaths</td>
<td>Pre pandemic vaccine use may be targeted at ‘at risk’ or used for everyone. The efficacy for PPV may be low if it provides a poor match to the prevailing strain.</td>
</tr>
<tr>
<td>Household prophylaxis with anti-virals</td>
<td>Mitigate and slow the progress of the disease more than antiviral treatment</td>
<td>For any stockpile where household prophylaxis is possible (i.e. more than 50% coverage), beginning with prophylaxis and, if necessary, later reverting to reactive treatment is likely to minimise the number of deaths. The household prophylaxis scenarios also assume a policy of reactive school closure.</td>
</tr>
</tbody>
</table>
The following options of combinations of countermeasures are considered:

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
<th>Percentage of population covered by stockpile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Antivirals (Reactive)</td>
</tr>
<tr>
<td>0</td>
<td>No intervention</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>Reactive treatment with antivirals, no vaccine or antibiotics</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>Reactive treatment with antivirals, no vaccine or antibiotics</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>Reactive treatment with antivirals and antibiotics, no vaccine</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>Reactive treatment with antivirals and antibiotics. Targeted vaccine.</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>Reactive treatment with antivirals and antibiotics. All vaccinated</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>Antiviral household prophylaxis, reactive antibiotics &amp; no vaccine</td>
<td>80%</td>
</tr>
<tr>
<td>7</td>
<td>Antiviral household prophylaxis, reactive antibiotics &amp; targeted vaccine</td>
<td>80%</td>
</tr>
<tr>
<td>8</td>
<td>Antiviral household prophylaxis, reactive antibiotics &amp; all vaccinated</td>
<td>80%</td>
</tr>
</tbody>
</table>

**Note:** Reactive school closure is also assumed in the household prophylaxis scenarios.
The incremental nature of these options can also be illustrated in diagrammatic form:

The effects of each option are measured by the expected numbers of clinical cases, hospitalisations and deaths.

Specific assumptions are taken from the main text of this report, and typically reflect the most likely outcome for any level of intervention, together with a margin for uncertainty. This is shown in the following diagrams. The coloured bar indicates high and low estimates using different hospitalisation and case fatality rates. A population of 60 million is assumed.

**Illustrative effects of countermeasures** - A. Raw clinical attack rate of 50%
B. Raw clinical attack rate of 35%
C. Raw clinical attack rate of 25%
### Hospitalisations

<table>
<thead>
<tr>
<th>Options</th>
<th>AV (%)</th>
<th>AB (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>25</td>
<td>100</td>
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<tr>
<td>5</td>
<td>50</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

**Local outbreaks of seasonal flu proportions only**

### Deaths

<table>
<thead>
<tr>
<th>Options</th>
<th>AV (%)</th>
<th>AB (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>25</td>
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<tr>
<td>3</td>
<td>50</td>
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<td>100</td>
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<tr>
<td>4</td>
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<td>7</td>
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<td>25</td>
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</tr>
<tr>
<td>8</td>
<td>80</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

**Local outbreaks of seasonal flu proportions only**

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**Countermeasure options - % population covered by stockpile**
Annex 2: Advised National Planning Scenario for the Reasonable Worst Case

The reasonable worst case is a concept developed for emergency planning in the UK. This concept is designed to exclude theoretically possible scenarios, which have so little probability of occurring that planning for them would lead to a disproportionate use of resources. They are not predictions of what will happen but of the worst that might realistically happen, and therefore we would expect most pandemics to be less severe and less widespread than the reasonable worst case. By planning for the reasonable worst case planners are assured that they have a high probability of meeting the demands posed by the hazard should it occur.

- Up to 50% of the population ill (with infection attack rates up to 80-85%) (Department of Health 2006c).
- Of which, from 10% up to 25% are expected to have complications, half of these bacteriological (with possibly as little as a 35% overlap between the ‘at risk groups’ and those who actually get complications (Meier et al. 2000)).
- Peak illness rates of around 10 to 12% (measured in new clinical cases per week as a proportion of the population) in each of the weeks in the peak fortnight (Department of Health 2005).
- Absences rates for illness reach 15 to 20% in the peak weeks (at a 50% overall clinical attack rate, assuming an average 7 working day absence for those without complications, 10 for those with, and some allowance for those at home caring for children (Department of Health 2006b)).
- Case hospitalisation demand rates up to 4% with an average six day length of stay but, of which 25% could, if the capacity existed, require intensive care for 10 days (i.e. require level 3 critical care).
- Case fatality ratios up to 2.5%.

An indicative planning profile of weekly national numbers of cases, hospitalisations, deaths etc. as proportion of total over single wave pandemic - Department of Health (2005).
IMPORTANT NOTE: The above chart is NOT a forecast. Its purpose is to provide a reasonable worst case for planning purposes. Below are examples of historical profiles from previous pandemics.

Historical Profiles from Previous Pandemics:
(Dates have been suppressed to emphasise the overall profile)
Annex 3: Additional advice on Local Planning Assumptions for English PCT sized areas

- Up to 50% overall clinical attack rate in a 'reasonable worst case'.
- Peak demand in a 'reasonable worst case' of about 13% of population becoming ill in each of peak weeks.
- Local epidemics in some PCT sized areas could be, both up to 50% more highly peaked than the national epidemic, and of a shorter duration, perhaps by a third.
- There may be a large variation in epidemic profile from PCT to PCT. A large proportion of PCT sized areas may have less peaked epidemics than suggested by the national planning profile and similarly a large proportion may have more highly peaked epidemics.
- Planning should take account of the possibility of both short 'highly peaked' local epidemics and also local epidemics more protracted than suggested by the planning profile.

Various examples of possible local profiles both more and less highly peaked than the (national) planning profile are shown below:
Annex 4: Data Required for Real Time Modelling in an Influenza Pandemic

In a pandemic, real time modelling should be possible. This document highlights the information that will be required. It outlines the surveillance information that is required to make predictions of the future course of the UK epidemic and also that required to provide ‘nowcasts’ of the state of the UK epidemic at any time. It does not specify data types or formats, so for example age information may be supplied as age or date of birth. These matters will be agreed in data specification documents for each data source.

It should be noted that if comparable forecasts are to be made available for the different Devolved Administrations, comparable data will also be required. Comparing data across the UK will also be challenging if the interventions across the four countries differ.

Data for real time modelling in a pandemic will come from two sources, aggregate data during the majority of the UK epidemic and individual data mainly from the first few hundred cases placed on an individual case database, the ‘FF100’ database. The data is split between basic data required to analyse and forecast numbers of cases and deaths, and an extended data set, which would also allow forecasts of the demand for secondary care and absence in both the NHS and elsewhere, as well as a more detailed analysis of development of the UK epidemic.

1. Aggregate level data

   **Basic Data**

   - Flu-Service (from switch-on in a given area) positive identifications of pandemic influenza
     - By age group, sex and risk group (AS&RG), linked with data on broad geographical area (region) (GA);
     - By district and postcode where possible (noting that sample sizes may limit the scope for highly disaggregated analysis);
     - Numbers identified with complications and referred to GPs (by AS&RG)
     - Children referred to GPs for assessment;
     - Delay from symptom onset to treatment;
     - Virological confirmation (of sample).

   - GP consultations for ILI, pneumonia and respiratory infections (generally), as well as other conditions that may be associated with the pandemic strain (e.g. encephalitis or diarrhoea, as identified by the analysis of individual level data). These will include both cases sent by the flu-service (if operational) and any additional cases.
     - By age group, sex and risk group, broad geographical area (region);
     - By district and postcode where possible;
     - Rates and numbers;
     - Virological confirmation (of sample).
• Deaths (all cause and ILI related)
  o By age group, sex and risk group;
  o By broad geographical area (region);
  o By date of death and symptom onset.

• Antivirals
  o Courses collected:
    ▪ For treatment;
    ▪ For prophylaxis (if any);
  o By age group, sex, risk group and broad geographical area (region), with further geographical disaggregation if possible.

• Vaccines given
  o By age, sex, risk group and broad geographical area (region), with further geographical disaggregation if possible;
  o Completed courses;
  o Through time, i.e. how many completed courses have been given to whom, by when;
  o Ideally, some assessment of reliability of data feeds from employers, to inform interpretation.

• Epidemiological and clinical studies
  o Immediate, high priority serological study by age and risk group, to assess pre-existing immunity to pandemic virus (requires prioritisation of assay development);
  o Rapid serological survey following first wave of epidemic, by age and risk group, to assess:
    ▪ Immunity (vaccine and natural)
    ▪ Vaccine efficacy
    ▪ Vaccine safety

Extended Data

• Surveys (telephone and/or web based) to include measures of respiratory illness, fever, GP consultations, use of Flu-Service, extent and time of absence from work and length of illness (by ASRG&GA). Given its national and international connections, London may offer good sampling opportunities.

• Hospital Admissions (by ASRG&GA)

• Hospital beds occupied (by ASRG&GA)

• ICU Admissions (by ASRG&GA and level of care category)

• ICU beds occupied (by ASRG&GA and level of care category)

• Length of stay Hospital and ICU admissions (by ASRG&GA)

• GP referrals to hospital (by ASRG&GA) required to assess demand – these data are not currently available but may be in future.
School closures:
  - no. of schools (by type and region) currently closed on a given day.

Absence levels (number of workers absent on a given day):
  - For general workplace;
  - For NHS staff and other essential services;
  - Data on absence for both these categories are not currently available, but may be in future.

Lab reports (by ASRG&GA) (including systematic surveys of the population):
  - Of virus isolations or antibody to pandemic strain;
  - Antiviral resistance monitoring.

Epidemiological and clinical studies
  - Ongoing serological survey (by ASRG&GA), to assess:
    - Immunity (vaccine and natural);
    - Vaccine efficacy;
    - Vaccine safety.

2. Basic individual-level data from FF100 case investigations and outbreak analysis.

Initial cases will be investigated epidemiologically, and their contacts traced. It is expected, however, that such data will stop being collected as the demands on services increase. As the status of patients change, (e.g. they become virologically confirmed, recover or die, etc.) then the relevant data items need to be updated, and the dates of the update needs to be recorded (even if the patient’s status does not change).

This investigation will include, as is most appropriate for each case/contact, testing for virus and antibodies.

Particularly in the case of the FF100 dataset, establishing a reliable and complete dataset of a few individuals and their contacts including virological (and if necessary serological testing) is more important than an incomplete data on a larger number of cases.

The essential requirements of the resulting dataset are:

Cases:
  - Unique individual identifiers (to prevent duplication)
  - Age, sex, location
  - Date of onset
  - Suspected or confirmed case (updated as information becomes available. At least weekly).
  - Whether antivirals were given, and if so:
    - When were they first given in relation to onset
  - Whether vaccine was given
  - Date of death or resolution
  - Date of hospitalisation
    - Date of admission to critical care high dependency unit
  - Date of discharge from hospital
    - Date of discharge from critical care
  - Other clinical features of disease
Contacts:

- Unique individual identifiers (to prevent duplication)
- Age, sex, location
- Date or dates of contact with known cases
- Whether they have previously been infected
- If they received prophylaxis
- Their status (with regular updating of):
  - If they become infected (from viral testing or antibody testing 3 weeks after initial exposure);
  - If they become a clinical case.

If they become a case, then the required data for cases should then be collected (maintaining the data on previous prophylaxis if any).
Annex 5: Glossary

**R0: Basic Reproductive Number.** (also known as the basic reproduction number or basic reproduction rate): This is the average number of secondary infections produced by a single infected individual while they are infectious, in an entirely susceptible population. This is a measure of the degree of transmissibility of an infection.

**Case Fatality Ratio (CFR):** (also known as the case fatality rate). The proportion of those who have been clinically attacked, who die because of influenza.

**Clinical Attack Rate (CAR):** (also known as the clinical attack ratio). The proportion of the considered population infected and showing symptoms over a specified period of time. Some may not develop symptoms severe enough to be readily identified as influenza. The measured clinical attack rate is thus not always the number who actually develop symptoms, but the number remembering symptoms retrospectively, or the number seeking healthcare.

**Clinical Case:** Someone infected and showing symptoms severe enough to be readily identified as influenza.

**Infection Attack Rate:** (also known as serological attack rate). The proportion of the considered population infected over a specified period of time, many of whom may not show clinical symptoms.

**Influenza Like Illness (ILI):** The specific definition for influenza like illness may vary by data source. However in the UK it is often defined as a temperature of 38°C or greater, plus two or more of the following: unusual tiredness, headache, runny nose, sore throat, shortness of breath or cough, loss of appetite, aching muscles, diarrhoea or vomiting.

**Reproductive Number:** (Also known as the reproduction number). This is the average number of secondary infections produced by a single infected individual while they are infectious, given the population’s characteristics (e.g. immunity). This is a measure of the degree of transmissibility of an infection in the given population.

**Reasonable Worst Case (RWC):** A concept developed for emergency planning in the UK. This concept is designed to exclude theoretically possible scenarios which have so little probability of occurring that planning for them would lead to a disproportionate use of resources. The RWC is not a prediction of what will happen but of the worst that might realistically happen, and therefore we would expect most pandemics to be less severe and less widespread than the RWC. By planning for the RWC, planners are assured that they have a high probability of meeting the demands posed by the hazard should it occur.
Annex 6: References

- Baguelin et al. (2010) Vaccination against pandemic influenza A/H1N1v in England: A real-time economic evaluation. Vaccine currently available online only
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• Nguyen-Van-Tam, J.S. et al, (2004) Tackling the next influenza pandemic: Ring prophylaxis may prove useful early on, but is unlikely to be effective or practical to implement once the pandemic is established. BMJ e-letter
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Note: References marked with an asterisk are not currently publicly available, being pre-publication drafts or internal DH or Cabinet Office reference papers.