

Pandemic Influenza Scientific Advisory Group (SAG): Subgroup on Modelling Modelling Summary

Note:

The attached 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 after each meeting of the subgroup, to record the group's advice in a form which can be immediately used to assist in the formulation of policy.

The document is, therefore, focused on those results which 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 can do now' and 'Policy questions'. 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.

INFLUENZA PANDEMIC PLANNING: SAG Subgroup on Modelling.

Modelling and Implications; High Level Summary – November 2007

1. Introduction

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

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, considering the possible progression of pandemic flu from its country of origin to, and then within, the UK¹. We identify key stages of this progression, and where appropriate we summarise the important operational issues in terms of:

- What we know
- What else we need to know
- What we can do now on the basis of what we know
- Modelling questions
- Policy questions

2. Progression of a pandemic

2.1 *The initial outbreak*

What we know:

- If the first incipient pandemic cases are in a rural part of south east asia, 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 R_0 of up to about 2. Even if the strategy fails to contain the disease, it might delay its progress by around a month.
- The practicality of such measures depends on effective local planning to identify cases, provide antiviral drugs and implement quarantine and other social distance measures.
- Regardless of whether the above containment measures prove to be effective, disease surveillance will be required to estimate important disease parameters such as the (age-specific) attack 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 starts in Asia and takes 2 to 4 weeks to spread to the UK

¹ Sections 2.1 and 2.2 assume the pandemic starts in SE Asia.

(see section 2.2), estimates of the mortality rate will be available by the time it reaches the UK. Attack rates are difficult to estimate, so reasonable estimates for these parameters may take longer to derive.

What we need to know:

- Is containment practical if the first cases are in an urban setting?
- Is there a practical containment strategy if the evolution from an avian flu which can infect humans, to a virus capable of sustaining a pandemic, is gradual?

What we can do now:

- Ensure that all intervention strategies are able to accommodate the full range of possible disease parameters with the ability to take account of surveillance information when it becomes available. Put in place mechanisms to easily modify the response as further information becomes available.
- Assist international efforts to make at least 3 million courses of antivirals available for use in initial containment.
- Encourage construction of realistic and detailed local plans for containment.

2.2 *International spread*

What we know:

- 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 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 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.
- 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.

What else we need to know:

- The nature and extent of the likely influence of seasonality on the transmissibility of pandemic flu.

What we can do now:

- Assume no significant benefit from entry restrictions or screening.

Modelling questions:

- What is the quantitative effect of the likely influence of seasonality on the transmissibility of pandemic flu on the rate of spread to the UK and the impact of travel restrictions?

Policy questions:

- Are international travel restrictions a realistic possibility, and under what circumstances would it be considered appropriate to impose travel restrictions to delay the spread of pandemic flu to the UK?

2.3 *Geographical spread within the UK*

What we know:

- Uncontained, a flu outbreak would be expected to spread to all major UK centres of population within 1 to 2 weeks.
- Mass provision of antivirals to the population would simply postpone the outbreak by the period for which prophylaxis is provided. However, such mass prophylaxis would deplete antiviral stocks very quickly (at a rate of one treatment course per 10 person days).
- Because of the probable multiple importations of pandemic flu, and the concentration of the population in cities, attempts at containment by targeted antiviral prophylaxis and practical social distance measures are very unlikely to succeed.
- 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.

What we can do now:

- Assume, for the purposes of developing intervention strategies, that the outbreak will spread throughout the UK in less than 2 weeks.

2.4 *Spread among, and impact on, the UK population*

What we know:

- A pandemic profile (i.e. the proportion of cases, deaths etc expected each week) has been constructed to guide national planning (see Annex 1). The profile is similar to that of the second wave of the 1918/19 pandemic in London. 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.
- Local epidemics in 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, however, that there may also be a large variation in 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.

- Mass treatment of clinical cases with antivirals would flatten this temporal profile, lowering the peak and lengthening the base.
- The UK case fatality rate (CFR) for previous pandemics was of the order of 0.2 to 2%. In contrast, recent estimates of the case fatality rate for H5N1 avian flu are of the order of 50%. Based on historical pandemics a 'reasonable worst case' for a pandemic would be a CFR of 2.5%. Even if the estimates for H5N1 avian flu are overestimates for a version of the virus 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.
- A pandemic with a CFR above 2.5% cannot be ruled out.
- For previous pandemics, the overall clinical attack rate (cumulative across all waves) has been of the order of 25 to 35% in the UK. A reasonable upper bound for the cumulative clinical attack rate would appear to be 50%. The worst case scenario would be 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 range from 50 to 67%.
- In the absence of a horizon for the availability of vaccine, treatment is the most efficient use of antivirals given the size of the current stockpile. If the available stock is less than the clinical attack rate it will be necessary to limit treatment to priority groups.
- 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. 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 a substantial effect the drug must be administered within 24 hours of the start of symptoms.
- Another possible practical use for antivirals is prophylaxis of essential workers. 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 half the current national stockpile 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 2.5).
- If pandemic flu were to reach the UK, the main intervention would be the treatment of clinical cases with antiviral drugs. However, antiviral prophylaxis of the household contacts of these cases could have a more marked impact on the disease. Such household prophylaxis would be more effective in mitigating and delaying the progress of the epidemic but this would require an anti-viral stockpile of at least twice the size currently available.
- 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.
- The stocks of pre-pandemic vaccine, antivirals and antibiotics currently available or on order are sufficient to provide vaccination, antiviral treatment and antibiotic treatment to ~2%, ~25% and 0.4% of the UK population respectively. Applying these interventions to the corresponding proportions of the population would have a marked impact on the number of hospitalisations and deaths across a range of clinical attack rates, but the impact on the total number of clinical cases is marked only for a virus with low transmissibility and hence with raw attack rates of around 25% without intervention. Under no circumstances would it be possible, given existing stocks and orders, to limit the number of cases, hospitalisations or deaths to the levels expected for seasonal flu.

Moreover, the main impact is generated by the antiviral treatment intervention. If antiviral treatment is less effective than expected, the impact will be low.

- Stockpiling enough pre-pandemic vaccine, antivirals and antibiotics to provide vaccination, antiviral treatment and antibiotic treatment to 40%, 25% and 14% of the UK population respectively would allow a 'targeted' strategy in which the following interventions are applied:
 1. vaccination of all those aged 16 or under and all those aged 65 or over;
 2. antiviral treatment of all clinical cases if the effective attack rate is less than 25% or all high risk cases if the attack rate is higher than this;
 3. antibiotic treatment of all cases with complications.

Together these interventions could be sufficient to limit the number of cases, hospitalisations and deaths to roughly the levels expected for a severe epidemic of seasonal flu if all interventions are effective and the clinical attack rate is not markedly greater than 25%.

- Stockpiling enough antivirals to treat 75% (rather than 25%) of the UK population would allow the above antiviral intervention to be augmented to one involving both treatment of all cases and prophylaxis of their household contacts. Combining this augmented antiviral intervention with vaccination of 100% (rather than 40%) of the population, together with the use of antibiotic drugs for complications, could be sufficient to limit the number of cases, hospitalisations and deaths to the levels of the targeted strategy (when fully effective) even if one component intervention is ineffective. For a 25% to 35% raw (i.e. without intervention) clinical attack rate, the impact of this combination is such that only localised outbreaks of seasonal flu proportions would be expected with all interventions effective.
- 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 more than one intervention proves to be less than fully effective.
- In addition to the medical countermeasures of vaccine, 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 school closures and restrictions on mass gatherings.
- 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 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 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.
- 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 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.

- In the early stages of a pandemic, the groups for whom the risk of complications or death is greatest will not be known. As the outbreak progresses, surveillance data will accumulate, and it will become possible to identify risk groups and estimate key disease parameters. If the pandemic starts in Asia, reasonable estimates of some (but probably not all) disease parameters should 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.
- Contact tracing (including serology of contacts) of the first few hundreds of cases in the UK will be essential for the accurate determination of disease parameters.
- The estimated impact of antiviral treatment and household prophylaxis assumes treatment within 24 hours of the first symptoms and that those with clinical symptoms are treated at home. Greater delay or the greater mixing of those with clinical symptoms will reduce the impact of any antiviral policy.
- Absenteeism directly due to illness would be expected to peak at between 15-17% for two to three weeks at the height of the epidemic. This corresponds to a 50% attack rate but employers should be advised to plan to this rate to take account of local geographical and temporal variation.
- Small organisational units should plan to a higher figure of 30-35%.
- For a typical organisation additional absenteeism due to those who need to stay at home to look after ill children might increase absenteeism from 15-17% to 20%.
- If schools were closed, absenteeism due to those staying at home to look after children could rise to 17-18% throughout the period of school closure, though evidence from school holidays and teachers strikes suggests this may be an overestimate.
- 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.

What we can do now:

- Develop a flexible system that would enable antiviral treatment to be targeted dynamically at different priority groups as required, restricting use to priority groups if attack rates are high but ensuring high coverage if attack rates are low.
- Ensure that any such system is flexible enough to accommodate household prophylaxis.
- Ensure that there are robust data collection systems in place that will be able to capture information regarding attack rate, disease pattern and severity, and mortality, in a timely and reliable way. This should include contact tracing (including serological investigation of contacts) of the first few hundreds of cases.
- Plan to the planning assumptions in Annex 1 recognising that these will need revision on the basis of surveillance information from both the UK and abroad.

Policy questions:

- How would the response change for an extreme pandemic (i.e. with a CFR above the historical range i.e. up to 2.5%)?

2.5 *The second wave*

What we know:

- Some supplies of vaccine specific to the pandemic virus may be available for a second or third wave of a pandemic - if they arise. Of the three pandemics of the 20th Century only that of 1918/19 generally produced second waves and thus in only one of these pandemics would a specific vaccine be of value in controlling the pandemic. (The second wave of 1968/9 in the UK was a special case.)
- It is expected that vaccine will start to become available approximately 4-6 months after the start of the pandemic. 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 of vaccine, which may take an additional 10-12 months.
- The impact of vaccination with a pandemic-specific vaccine, if it were available, is entirely dependent on the timing and size of any second and subsequent waves in relation to the first wave and hence inherently difficult to estimate.
- Surveys of patterns of immunity through and following the first and subsequent waves are therefore essential to planning a pandemic specific vaccination strategy.
- 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. (For example, 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.
- 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.

What we can do now:

Set up arrangements for the required surveys of levels of immunity across the population.

Annex 1: Advised planning assumptions

Up to 50% of the population ill (with serological rates up to 80-85%).

Of which, from 10% up to 25% are expected to have complications, half of these bacteriological. (With possibly as little a 35% overlap between the 'at risk groups' and those who actually get complications.)

Peak illness rates of 10 - 12% (in new cases per week - of the population) in the peak fortnight.

Absences rates for illness reach 15-20% in the peak weeks (at a 50% overall 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.)

Case hospitalisation demand rates in the range 0.55% to 4% with an average six day length of stay.

- but, of which 25% would, if the capacity existed, require intensive care for 10 days.

Case fatality rates in the range 0.4% to 2.5%.

Profile of weekly numbers of cases, hospitalisations, deaths etc. as proportion of total over single wave pandemic:

