

Scientific Pandemic Influenza Advisory Committee (SPI): Subgroup on Modelling

Modelling Summary

Introduction

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 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.

1. Purpose

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:

- a) 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 (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).
- b) The practicality of such measures depends on effective local planning to identify cases, provide antiviral drugs and implement quarantine and other social distance measures.
- c) 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 (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.
- d) For low R_0 's of up to about 1.8 and with optimistic assumptions of antiviral treatment's reduction of transmission, international sharing of antiviral stocks might reduce attack rates more than countries retaining their own stockpiles for their own use (Colizza et al. 2007). This reduction would take place both in countries without their own stockpiles and in those with stockpiles. However, the effect is lost for higher R_0 's or less optimistic assumptions of antiviral effectiveness. The effect is also lost if the treatment is not started in each country after the first few cases. Most of the gains of such 'co-operative' strategies can be obtained from the use of a targeted international stockpile in a timely way to contain the disease in the country of origin as discussed above (a) (Cooper et al. 2007 based on model described in Cooper et al. 2006).

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

What we need to know:

- a) Is containment practical if the first cases are in an urban setting?
- b) 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:

- a) 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.
- b) Assist international efforts to make at least 3 million courses of antivirals available for use in initial containment.
- c) Encourage construction of realistic and detailed local plans for containment.

2.2 *International spread*

What we know:

- a) 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).
- b) 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).
- c) 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.
- d) 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.
- e) 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).
- f) 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 (Cooper et al. 2006).
- g) The above delays may be important, in principle, if there is a substantial seasonal effect on the transmissibility of flu (Cooper et al. 2006). If there is, it might 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, making robust predictions of the success of such a strategy early in an actual pandemic would be impossible. Hence, the use of travel restrictions as a lever to shift the season of a UK epidemic is impractical.

- h) Assuming passengers are screened before travel for clinical symptoms, there is no additional advantage in entry screening (Pitman et al. 2005). Even preventing those with clinical symptoms from travelling is only likely to delay the spread of the disease by 1 to 2 weeks.

What we can do now:

- Assume no significant benefit from entry restrictions or screening.

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:

- a) Uncontained, a flu outbreak would be expected to spread to all major UK centres of population within 1 to 2 weeks (Ferguson et al. 2006).
- b) 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).
- c) 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 (Ferguson et al. 2006, Van Tam et al. 2004).
- d) 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).

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

2.4.1 What we know about the impact of an unmitigated pandemic:

- a) 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 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 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) Mass treatment of clinical cases with antivirals would flatten the temporal profile, lowering the peak and lengthening the base (Ferguson et al. 2006; Vynnycky et al. 2005, Gani et al 2005).
- d) The UK case fatality rate (CFR) for previous pandemics was of the order of 0.2 to 2% (Nguyen-Van-Tam and Hampson 2003). In contrast, recent estimates of the case fatality rate for H5N1 avian flu are of the order of 50% (see www.who.int/csr/disease/avian_influenza/).
- e) 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 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.
- f) A pandemic with a CFR above 2.5% cannot be ruled out.
- g) 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% (Mann et al 1981, Longini et al 2004, Monto 1987, Nguyen-Van-Tam JS and Hampson AW (2003), Fleming 2000).
- h) 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 may 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.
- i) 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.
- j) 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 (Department of Health 2006b). 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.
- k) Small organisational units should plan to a higher figure of 30-35% (Department of Health 2006b).
- l) 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% (Department of Health 2006b).

2.4.2 What we know about the impact of pharmaceutical countermeasures:

- a) 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 (treatment courses for 25% of the population) stockpile (Ferguson et al. 2006). If the available stock is less than the clinical attack rate it will be necessary to limit treatment to priority groups (Gani et al 2005).
- b) 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 (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 a substantial effect the drug must be administered within 24 hours of the start of symptoms.

- c) 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 half the current (25%) 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).
- d) When the stockpile builds up towards the intended 50-60% coverage (in terms of treatment courses) post-exposure prophylactic options will become practical. 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 a stockpile for which household prophylaxis is a practical 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), as would antibiotic treatment of those with complications.
- g) The stocks of pre-pandemic vaccine, antivirals and antibiotics currently available or 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, to limit the number of cases, hospitalisations or deaths to the levels expected for seasonal flu (Ferguson et al. 2006). Moreover, the main impact is generated by the antiviral treatment intervention. If antiviral treatment is less effective than expected, the impact will be low.
- h) 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 (Department of Health 2006a):
 - a. vaccination of all those aged 16 or under and all those aged 65 or over;
 - b. 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;
 - c. antibiotic treatment of all cases with complications.
- i) 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% (Department of Health 2006a).
- j) 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 (Ferguson et al. 2006). 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 (Department of Health 2006a). 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 (Department of Health 2006a).

- k) 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 (Department of Health 2006a).
- l) 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 (Ferguson et al. 2006). Greater delay or the greater mixing of those with clinical symptoms will reduce the impact of any antiviral policy.

2.4.3 What we know about the impact of non-pharmaceutical countermeasures:

- a) 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.
- b) The impact of closing schools, especially without any antiviral intervention, depends critically on the mixing between children and adults. Different plausible models (Ferguson et al. 2006; Cauchemez et. al 2008; Gay et al. 2005) give results suggesting a reduction in peak ranging from one tenth to almost one half. In any case the reduction in the total number of cases is little more than one tenth (in the range of 10 to 20%). Most of the 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 one half (Gay et al. 2005). School closure is therefore most usefully employed if children are particularly badly affected.
- c) Closing schools as an adjunct to antiviral treatment might further reduce the peak of the epidemic e.g. taking the most optimistic case, from a near 30% reduction in the peak with antivirals alone to a total reduction closer to 50% (Ferguson et al. 2006). The total number of clinical cases might also be reduced by a factor of around one tenth. Again most of this reduction would be in school age children.
- d) Combined with a household prophylaxis policy (as opposed to simply treating cases), 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) (Ferguson et al. 2006).
- e) 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.
- f) As noted above 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 (Department of Health 2006b). 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%

(Department of Health 2006b). However, 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, giving a total absence level including illness of 30-35% at the peak, though evidence from school holidays and teachers' strikes suggests this may be an overestimate (Department of Health 2006b).

- g) 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).
- h) 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

What we can do now:

- a) 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.
- b) Ensure that any such system is flexible enough to accommodate household prophylaxis when the stockpile has built up to a sufficient level to make implementation practical.
- c) 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.
- d) 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%)?
- How would the response change for a mild pandemic (say 25% attack rate with a CFR less than 0.4%)?

2.5 *The second wave*

What we know:

- a) 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 national epidemics with second waves and thus in only one of these pandemics would a specific vaccine be of general value in controlling the pandemic. (The presence of a second wave of the 1968/9 pandemic in the UK was unusual in global terms.)
- b) 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 of vaccine, which may take an additional 10-12 months.

- c) 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.
- d) Surveys of patterns of immunity through and following the first and subsequent waves are therefore essential to planning a pandemic specific vaccination strategy (Vynnicky et al. 2006).
- e) 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.
- f) 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%) (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 - 12% measured in new cases per week as a proportion of the population) in the peak fortnight (Department of Health 2005).

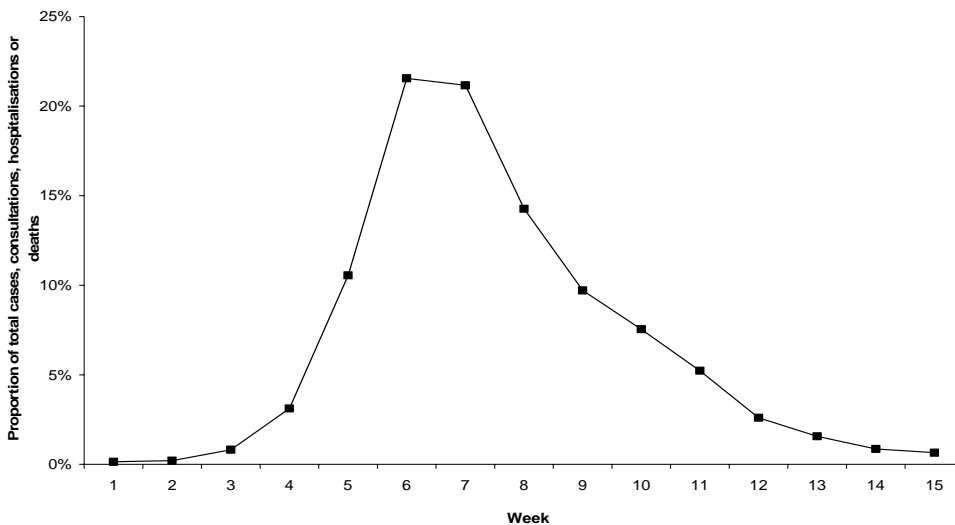
Absences rates for illness reach 15-20% in the peak weeks (at a 50% overall attack rate, assuming an average 7 working day absence for those without complications, 10 for those with, and some allowance for those at home caring for children (Department of Health 2006b).

Case hospitalisation demand rates in the range 0.55% 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.

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

Indicative profile of weekly national numbers of cases, hospitalisations, deaths etc. as proportion of total over single wave pandemic - Department of Health (2005).



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Note: References marked with an asterisk are not currently publicly available, being pre-publication drafts or internal DH reference papers.