

The use of antivirals to reduce morbidity from pandemic influenza

Raymond Gani, Iain Barrass, Steve Leach

Health Protection Agency Centre for Emergency Preparedness and Response, Porton Down, Salisbury, Wilts, UK.

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Introduction

The threat from pandemic influenza has been increasingly highlighted over the last few years as the H5N1 highly pathogenic avian influenza virus has continued to spread and human infections have continued to occur. The WHO recommended to national governments that they formulate pandemic influenza contingency plans, which many governments have since done. These plans have tended to be based around broad assumptions of what the characteristics of the next pandemic could be and have focussed on operational issues relating to the management of the pandemic and its impact on public health and other socio-economic factors. Contingency plans are subject to continuous refinement and updating, with a number of factors determining how often they are updated. These may include refinements in the understanding of the disease and different estimates of a new pandemic's impact, developments in emergency response management capabilities or changes to intervention strategies. One recent development has been consideration of the mass use of neuraminidase inhibitor (NI) antivirals to treat clinical cases of influenza. NI antivirals reduce the period of symptomatic illness for influenza A and mitigate against more severe clinical outcomes. They are currently recommended for use in the UK for treatment of seasonal influenza in at-risk adults who are able to begin treatment within 48 hours of onset of symptoms. Due to the way the NI antivirals interfere with the virus, it is believed that their effectiveness against a pandemic strain will be equivalent to their effectiveness against seasonal strains. Given this, and that there is unlikely to be a vaccine available in sufficient quantities in time to prevent substantial numbers of cases or deaths, many countries are considering, or have begun, stockpiling NI antivirals for use during a pandemic.

Two of the key issues that need to be considered are firstly, the potential impact that antiviral treatment will have on an ensuing new pandemic and secondly, what might be the optimum stockpile sizes. The first point depends on the severity of the pandemic and requires appropriate estimates for the potential public health and other impacts of the pandemic on the population. There are a number of indicators of severity that could be considered and measured, such as the number of hospitalisations, deaths, days off work, *etc.*, and antiviral use will impact on each of these in different ways. For example, depending on stockpile size, treatment of clinical cases would be expected to have a proportionately larger impact on hospitalisations and deaths than on the number of clinical cases *per se*, as treatment in this way can only be administered once cases have clinically identifiable disease, any reduction in the overall number of cases that might occur being as a consequence of a reduction in symptomatic infectious period of the treated cases. By contrast, early post-exposure prophylaxis of the contacts of cases might be expected to have a bigger

impact on the overall number of clinical cases than the previous strategy as the antivirals are then being administered to individuals prior to, and inhibiting, the development of clinical symptoms. Therefore, it is important that a clear idea is formulated as to what is wanted to be achieved through antiviral use. The issue of size of the antiviral stockpile is one that needs to be balanced against a number of competing demands. One strategy that a number of countries are considering is to stockpile enough antiviral treatments for all anticipated clinical cases. Alternative and/or parallel strategies being considered are the treatment of key workers, health care staff and at-risk groups. The increasing adoption of these strategies has increased the global demand for antivirals, in particular for oseltamivir (Tamiflu). This has resulted in orders for antiviral stockpiles to be negotiated to be delivered in phased instalments. This raises the additional question of whether optimal strategies might change as stockpile sizes increase over time.

In this paper we address one aspect of contingency planning and that is the use of antiviral stockpiles to treat clinical cases to reduce hospital admission rates. Here we show how different sized stockpiles may be targeted at different age and risk groups in order to minimise excess hospital admissions throughout a pandemic. We do this for a generic planning scenario and then investigate similar strategies in relation to specific scenarios based on data from previous pandemics.

Methods

A mathematical model was derived in order to simulate an influenza pandemic and this model along with the model parameters are published in Gani *et al.* (2005). Four pandemic scenarios were modelled. The first was a baseline scenario as suggested by WHO (WHO 1999) which consisted of a large single wave lasting for about three months with an overall clinical attack rate of 25%. Further scenarios modelled were based on the major waves of the three 20th century pandemics as they were experienced in the UK and reflected in national data.

The first 20th century pandemic began in 1918 and occurred in three waves. The first wave occurred during the summer of 1918 and, at the time, was considered to be typical for pandemic influenza, with the exception that there was a tendency for those around 20-30 years old to experience higher attack rates. The second wave, occurring in late autumn, was considerably more severe with high mortality rates leading to around 150,000 deaths in the UK alone. The third wave, which occurred in the spring of 1919, was less severe than the second and was considered to be reverting to a form more typical of seasonal influenza, albeit with a high mortality rate. Across the three waves of the 1918 pandemic an estimated 200,000 deaths occurred in the UK, representing more than 0.5% of the population at the time (Anon. 1920).

The two subsequent pandemics in 1957 and in 1968 were less severe but still led to high levels of excess mortality and morbidity. The 1957 pandemic peaked in the autumn of 1957 with a small secondary wave in spring 1958 and resulted in about 30,000 deaths in the UK (Anon. 1960). The last pandemic in 1968 was characterised by a small herald wave in spring 1969 followed by large peak during the 1969/70 seasonal influenza season (Taylor, 1971). Given that second wave of the 1957 pandemic and the first wave of the 1968 pandemic were relatively small, the waves that were modelled here were the large first wave of the 1957 pandemic and the second wave of the 1968 pandemic, as well as the entire three waves of the 1918 pandemic and the WHO planning scenario.

Four treatment strategies were modelled based on some of those being considered by the public health authorities. The first was to treat all clinical cases, the second to treat children and the elderly (i.e. 1-14 year olds and 65+ year olds), the third to treat those at risk from severe outcomes, who represent the group that would typically be targeted for vaccination during the influenza season, and the fourth was to treat the working population, defined as those aged 15-64 years old.

Results

The simulated results from the WHO baseline scenario are shown in Fig. 1. The point where the estimates from the models shown in the figures become horizontal indicates that the stockpile size has exceeded the requirements for that scenario or treatment strategy. The results in Fig. 1a cover a range of clinical attack rates from 20% to 40% and represent the proportion of the population that would develop clinical illness in the absence of any interventions. As the size of the stockpile increases, the numbers of clinical cases decrease. This is not due to the impact of treatment at an individual level as only clinical cases are treated, but the impact at the population level as treatment of clinical cases leads to them becoming less infectious resulting in fewer secondary cases and thus a smaller epidemic with a lower total number of clinical cases. The results in Fig. 1b show the impact of different sized antiviral stockpiles on the hospitalisation rate for the different treatment strategies. For smaller stockpiles less than around 7,000 per 100,000 population (i.e. 7% stockpile), the best strategy would be to treat at-risk groups. For 7% to around 10%, the best strategy would be to treat children and the elderly, and for larger stockpiles to treat all clinical cases. At no point is treating the working population the most effective use of antivirals in preventing hospitalisations.

Estimates of the impact on hospitalisation rates of the different strategies when based on modelling that employed the characteristics of the main wave of the 1957 pandemic (see Gani *et al*, 2005, for further details) are shown in Fig. 2. Due to this scenario having a higher transmission rate and clinical attack rate of around 31% than the baseline scenario, the stockpile requirements for the different strategies here are generally higher than for the WHO scenario, as shown in Fig. 2a. However, the relative order of effectiveness of different strategies remains the same, with treating those at-risk for smaller stockpiles, treating children and the elderly for slightly larger stockpiles, then all clinical cases for the largest stockpiles. Again, treating the working population is always less effective. Fig. 2b shows the temporal dynamics of a selection of the treatment strategies, and demonstrates how the dynamics of the pandemic may be changed by the impact of antiviral treatment on the infectiousness of clinical cases, in some cases delaying and blunting peak hospitalisation rates.

Figure 3 shows the simulations for a pandemic with the characteristics of the main wave of the 1968 pandemic. Due to the differences in the age specific attack rates from the previous pandemics, at no stockpile size is the strategy to treat only children and the elderly optimal. Treating the at-risk groups remains the best strategy for stockpile sizes of up to around 12%. For larger stockpiles, treating all clinical cases is the best strategy, as shown in Fig. 3a. A selection of treatment strategies is shown in Fig. 3b to show the impact on the temporal dynamics of hospitalisations for different stockpile sizes.

Data from the 1918 pandemic was relatively sparse compared to the other pandemics with little information on hospitalisation rates. However data was available for recorded deaths due to influenza across the three waves of the pandemic and so

the model was adapted to reflect death rates. Antiviral treatment was assumed to prevent deaths to the same extent as hospital admissions. The potential impacts of two different antiviral stockpile sizes on death rates are considered in Fig. 4: a 10% stockpile and a 20% stockpile, along with the case where there is no stockpile. As before, only clinical cases are treated. With a 20% stockpile, there are sufficient treatments to treat all cases and total mortality is reduced by around 53%. However, with the smaller stockpile of 10%, the reduction in deaths is only around 17% and this is because the stockpile becomes exhausted during the second wave (which had the higher case fatality rate), before the majority of deaths have occurred.

Conclusions

Whilst the characteristic of the next pandemic are unknown, these simulations based on previous pandemics suggest that stockpiles large enough to treat at least 25% of the population might be sufficient to treat all clinical cases. For stockpiles of the order of 15-25%, treating all clinical cases would be the best strategy for reducing hospitalisation even though the stockpile may not be large enough to treat all clinical cases. For stockpiles less than about 15%, and dependent on the characteristics of the pandemic, targeted treatment strategies become more effective. Treating only children and the elderly may be marginally better, as shown for the WHO scenario and the 1957 pandemic, but for smaller stockpiles, treating the at-risk groups becomes the most effective use of antivirals.

However, each pandemic has been unique, and optimal treatment strategies are likely to have varied between them as has been illustrated here. Whilst the results provided here are useful in helping to scope and quantify resource and planning requirements ahead of time, it should be recognised that these results are of necessity based on limited data from previous pandemic and inter-pandemic influenza, expert opinion and clinical trials. Such assessments should be recalculated in the earliest phases of a pandemic using real-time data to either confirm or update the assumptions used and ensure that the model parameterisation is appropriate for the new pandemic strain. Therefore, were a pandemic to occur, intensive analysis of its dynamics and clear identification of the groups at-risk of more severe outcomes would be required at the start of the pandemic.

References

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Figure 1: Estimated impact of different stockpile sizes on (a) number of clinical cases with different clinical attack rates in the absence of interventions and (b) estimated number of hospitalisations for a clinical attack rates in the absence of interventions of 25% when different treatment strategies are adopted.

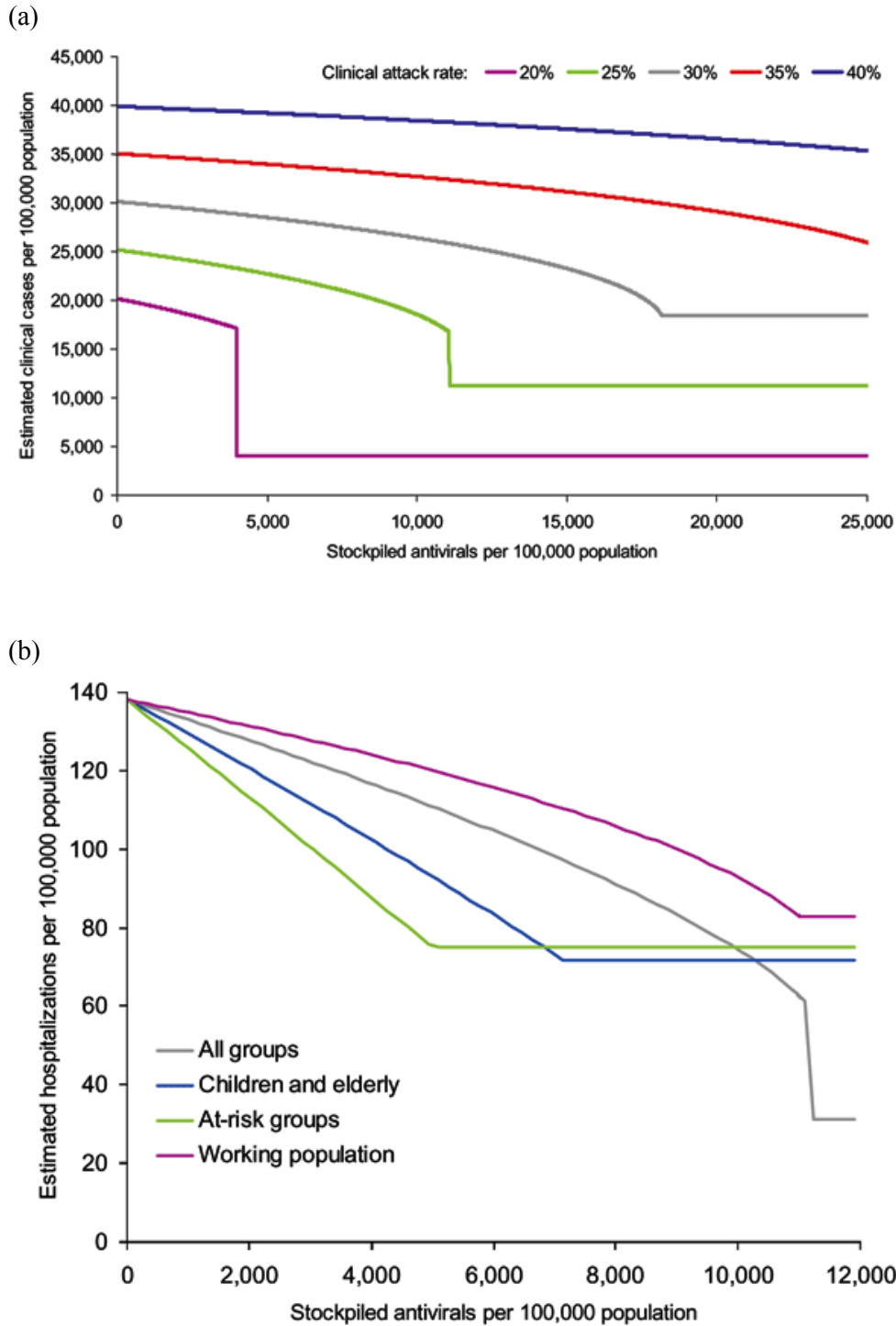


Figure 2: Estimated impact of different stockpile sizes for a pandemic with the characteristics of the main wave from the 1957 pandemic on (a) the estimated number of hospitalisations for different treatment strategies and (b) the impact of the temporal distribution of hospitalisation with a selection of treatment strategies and stockpile sizes.

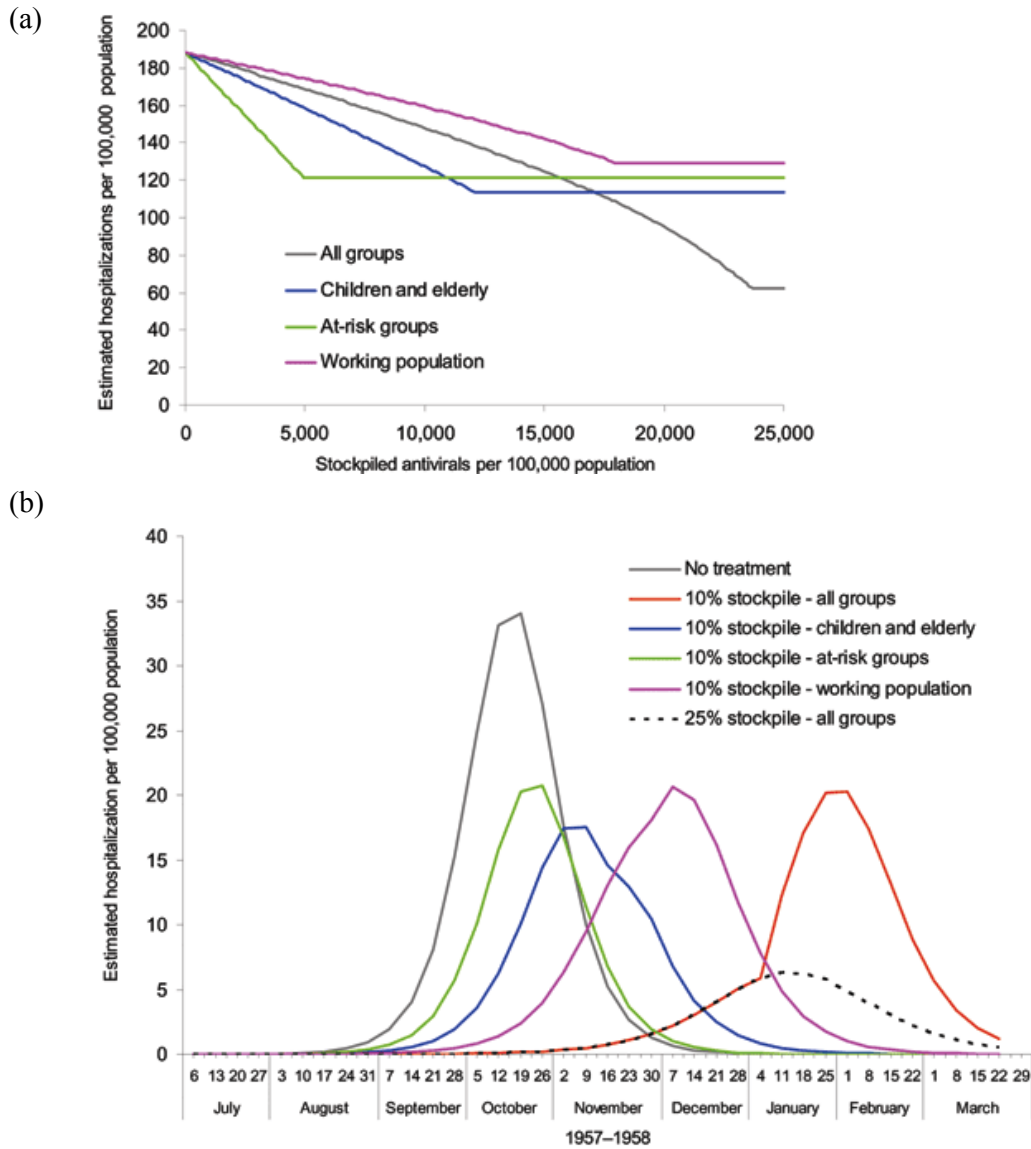
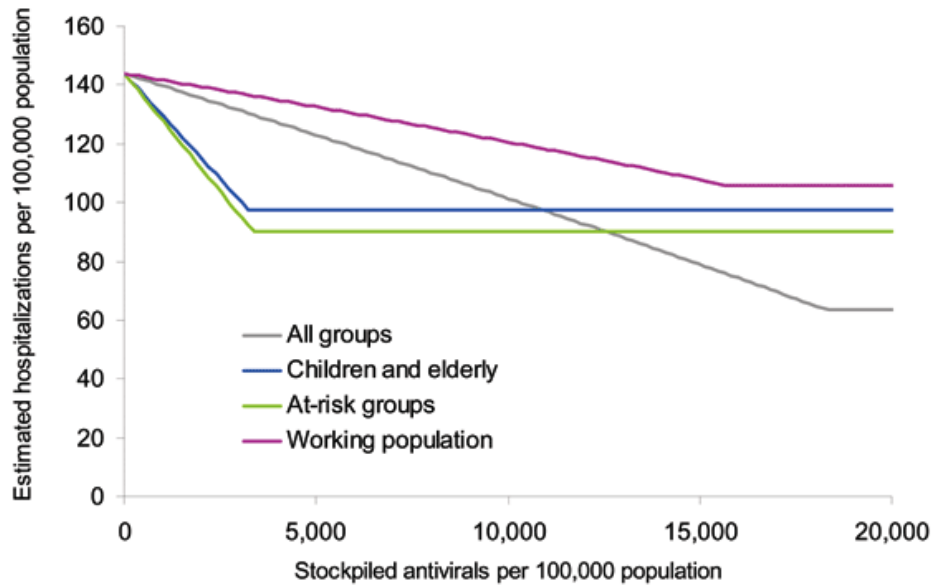


Figure 3: Estimated impact of different stockpile sizes for a pandemic with the characteristics of the main wave from the 1968 pandemic on (a) the estimated number of hospitalisations for different treatment strategies and (b) the impact of the temporal distribution of hospitalisation with a selection of treatment strategies and stockpile sizes.

(a)



(b)

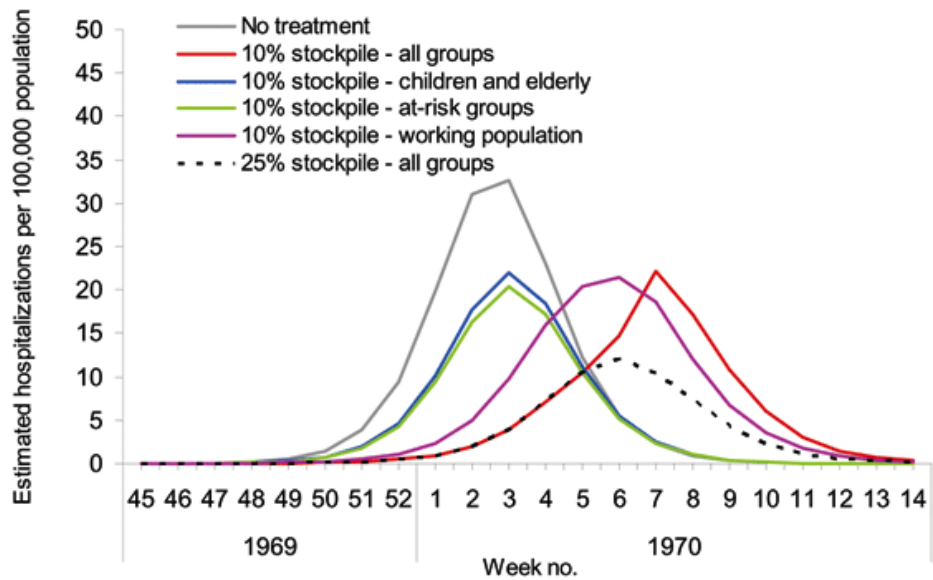


Figure 4: Estimated impact of antiviral treatment of a stockpile which covers 10% of the population and one which covers 20% of the population on the number of deaths from a pandemic with the characteristics of the 1918 pandemic.

