

Antivirals

Evidence summary

This document summarises the evidence presented in:

Development of decision support documents to assist decision making during a pandemic influenza response: evidence for personal protective equipment and antiviral measures, Kathryn Glass, Stephanie Davis, Laura Martich, Geoffry N Mercer, National Centre for Epidemiology and Public Health, Australian National University

Mathematical modelling of antivirals for a public health response to an influenza pandemic, Jodie McVernon and James McCaw, Vaccine & Immunisation Research Group, Murdoch Children's Research Institute; and Melbourne School of Population and Global Health, The University of Melbourne

and

Review of current evidence on the use of neuraminidase inhibitors held in the National Medical Stockpile, in a pandemic, Jodie McVernon, Allen Cheng, James McCaw, Rob Moss and Aeron Hurt, Melbourne School of Population and Global Health, the University of Melbourne; Department of Epidemiology and Preventive Medicine, Monash University; and World Health Organization Collaborating Centre for Reference and Research on Influenza

The full reports and other supporting documents are available via request from the [Australian Government Department of Health website](#).

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1 Introduction

1.1 Antiviral medicines

Several different classes of antiviral medicines are effective against influenza and more are currently in clinical development.

The neuraminidase inhibitors oseltamivir and zanamivir are licensed globally, and act by impeding virus exit from infected host cells, thereby preventing viral replication¹. They are considered safe for short and long-term use (greater than 4 weeks for prophylaxis) but antiviral resistance continues to be an issue (see Section 6 of this summary). An earlier class of medicines, M2 proton channel inhibitors, have been discontinued due to more significant toxicity and resistance problems^{2,3}.

Antiviral medications are used for treatment of infected cases, prophylaxis of already or potentially exposed contacts. Treatment with antivirals aims to reduce symptoms in individuals and, hence, lower morbidity and mortality rates. Prophylactic use of antivirals aims to reduce infection and potentially lower the disease attack rate.

1.2 Menu of actions for antivirals

Four actions involving antivirals are included in the menu of actions under ‘Pharmaceutical measures’:

- antivirals for treatment of cases
- antivirals for postexposure prophylaxis for contacts
- antivirals for postexposure prophylaxis for high-risk groups
- antivirals for pre-exposure prophylaxis for healthcare workers.

Evidence relating to each action is summarised in Sections 2–5 of this summary, respectively. Issues that apply across actions are described in Section 6.

1.3 Evidence

While useful data were gathered during the 2009 pandemic, and reported in the literature, about the effectiveness of antiviral prophylaxis and treatment, it is not always clear how these data can be extrapolated to suit Australia’s needs. For this reason, detailed mathematical modelling has been used to examine a range of scenarios to determine how best to use antivirals to prevent and respond to an influenza pandemic. The evidence for this summary is therefore based on literature reviews of the effectiveness of antiviral measures in an influenza pandemic; and mathematical modelling studies of antivirals for a public health response to an influenza pandemic.

A literature review was conducted in 2015 in the *Review of current evidence on the use of neuraminidase inhibitors held in the National Medical Stockpile, in a pandemic* to ensure AHMPPI pandemic planning assumptions, specifically antiviral interventions, are informed by the most current evidence and best practice. The report also modelled the outcomes of currently used distribution strategies, identifying which approaches were the most effective in reducing morbidity and mortality across different pandemic scenarios, and identifying at-risk groups to prioritise for treatment during a pandemic response.

The modelling studies simulated several different pandemic impact scenarios based on variations of transmissibility and clinical severity (Figure 1).

Low transmissibility scenarios	Medium transmissibility scenarios	High transmissibility scenarios
Scenario 6 (low transmissibility, high clinical severity)		Scenario 7 (high transmissibility, high clinical severity)
Scenario 3 (low transmissibility, medium clinical severity)	Scenario 4 (medium transmissibility, medium clinical severity)	Scenario 5 (high transmissibility, medium clinical severity)
Scenario 1 (low transmissibility, low clinical severity)		Scenario 2 (high transmissibility, low clinical severity)

Figure 1 Pandemic impact scenarios

The model described in the report *Development of options on how to define pandemic impact for Australian purposes* was used,^a with two additional features:

- the size of the antiviral stockpile available for treatment and community prophylaxis was varied to assess the effects of smaller (or larger) stockpiles
- use of the stockpile was explored within pre-specified pandemic scenarios, representing a variety of pandemic impact levels.

Modelling considered three different strategies: treatment of severe cases only, treatment of all identified cases, and treatment and prophylaxis of identified cases and their contacts. The same scenarios were also used to determine the appropriate quantity of antivirals in the National Medical Stockpile.

This modelling was extended in 2015 by stratifying data by the at-risk groups listed below, and modelling the group characteristics against three out of seven pandemic scenarios identified in Figure 1 (Low Transmission/High Severity; Medium Transmission/Moderate Severity; High Transmission/High Severity):

- 6.5% aged 0-4 years (young children)
- 13.7% aged 66 years or older (elderly)
- 10% of the remaining population (5-65 years) at high risk, who have greater risks of requiring hospitalisation, being admitted to ICUs and dying
- 325,000 health care workers
- The remainder of the population who have no significant risk factors

Modelling considered four antiviral strategies for these groups during the Targeted Action Phase (Figure 2), assuming the first four weeks of a pandemic (the ‘Initial Action Phase’) would provide all identified cases with treatment and post-exposure prophylaxis to all identifiable contacts:

^a Available at [Department of Health website](#).

Strategy	Description of Strategy
Rx All/PEP Eld, HR	Treatment of all identified cases regardless of risk stratum or care setting, and prophylaxis for individuals in the 'Elderly' and 'High-Risk' strata.
Rx All	Treatment of all identified cases regardless of risk stratum or care setting, and no recommendation for prophylaxis.
Rx At-Risk, Hosp	Treatment of all identified cases in the 'Children', 'Elderly', 'High-Risk' and 'Health Care Worker' strata, and of all cases in hospital and ICU settings.
Rx Hosp	Treatment of all cases in hospital and ICU settings.

Figure 2 Pandemic antiviral strategies

The full literature reviews and modelling study reports, and other supporting documents, are available by request via the [Australian Government Department of Health website](#).

2 Antivirals for treatment of cases

2.1 Literature

A meta-analysis of trials of neuraminidase inhibitors assessed the benefits of antivirals in reducing the duration of illness if taken within 48 hours of symptom onset.³ A separate review found that both zanamivir and oseltamivir reduce the duration of illness by around 1–2 days if taken within 48 hours of symptom onset⁴. Greater reductions in the likelihood of severe outcomes (critical care requirement or death) are possible if the antivirals are taken earlier. A third review confirmed the benefits of the neuraminidase inhibitors in children and high-risk population groups⁵.

The Cochrane review of the effectiveness of neuraminidase inhibitors for treatment of seasonal influenza conducted in 2012 found consistent efficacy of neuraminidase inhibitors against symptoms, with insufficient power from trial data to confirm effectiveness of oseltamivir against complications⁶. In mild influenza infection, the benefits of neuraminidase inhibitors administered within 48 hours of illness onset are a reduced duration of illness of between half to one day in high-risk populations, adults and children, allowing resumption of usual activities somewhat earlier than in the absence of treatment^{7,8,9,10}. A recent placebo-controlled trial of oseltamivir treatment in children aged 1–3 years demonstrated substantial improvements in symptom resolution of 3.5 days in vaccinated children, and 4 days in unvaccinated children¹¹. The efficacy of oseltamivir and zanamivir in children has been demonstrated to be equivalent, for treatment of influenza A(H3N2), A(H1N1) and B¹².

Ecological observations in Mexico related the doubling of case fatality between the first and second pandemic waves to a decline in medicine distribution, in confirmed cases from 50% in the first wave and 9% in the second wave¹³.

Studies examining the timing of antiviral treatment on health outcomes in particular risk groups (children, pregnant women, the elderly, transplant and other immunocompromised patients) largely showed that treatment reduced complications and mortality^{14,15,16,17,18,19,20}. But of 10 studies identified by the literature review, one study showed no benefit²¹ and one other study showed treatment worsened chance of survival²². A study comparing treatment of pregnant women in Australia and New Zealand with treatment in the United Kingdom suggested that, within this demographic, antiviral use was lower in Australia and New Zealand²³.

2.2 Modelling

Consistent with previous findings, treating only the severely ill (i.e. hospitalised people) rarely impacted on the characteristics of the epidemic at the population level. An exception was under scenario 6 with high clinical severity and low transmissibility. In this scenario, hospitalised cases constituted a substantive proportion of all infections, and combined with low intrinsic transmissibility, the small proportional reduction in transmission leads to a substantial reduction in overall infections.

Providing treatment for all identified cases (both hospitalised and community based [mild and moderate]) had a varied impact on the characteristics of the epidemic. Thus, under

low-transmissibility scenarios significant benefits may be expected, while for higher transmissibility scenarios, the strategy has little population-level impact.

Stockpile capacities of 40–45% per capita were generally sufficient to ensure treatment strategies are implemented, with sufficient excess for continuous provision to healthcare workers. A stockpile size in excess of 50% conferred little additional benefit to the population, given anticipated constraints on medicine distribution capacity. See Section 6.2 for further information on stockpile use.

2.3 Review

The Cochrane Respiratory Infections Group updated its systematic review and meta-analysis of neuraminidase inhibitors for preventing and treating [seasonal] influenza in healthy adults and children in 2014²⁴. While partial and differential reporting of outcome measures makes direct comparisons difficult, the most recent iteration of the Cochrane review provides compelling evidence to support the use of NAIs for treatment and prophylaxis.

Treatment of mild disease does not appear warranted, based on studies of generally healthy participants in randomized controlled trials with high quality evidence. Observed treatment effects in among individuals with laboratory confirmed influenza included modest reduction in symptom duration (approximately 24 hours); moderate reductions in risk of secondary bacterial infections and hospitalization; but moderately frequent gastrointestinal side effects such as nausea and vomiting, the risks of which most likely outweigh the benefits of treatment.

Treatment of moderate-severe disease in the community was beneficial in reducing progression of symptoms, such as development of otitis media, pneumonia and hospitalisation, based on findings in low to moderate quality evidence. Treatment of moderate-severe disease in hospital settings was beneficial in reducing severe clinical outcomes including pneumonia and mortality, based on moderate quality evidence from observational studies of seasonal and pandemic influenza.

The quality of evidence for each finding is important to note. While the treatment outcomes outlined in the Cochrane review are positive overall, the quality of evidence arising from the studies varies greatly due to the limited types of studies conducted (most are observational studies due to ethical and practical issues).

3 Antivirals for postexposure prophylaxis for contacts

3.1 Literature

When given as postexposure prophylaxis, neuraminidase inhibitors reduced the risk of laboratory-confirmed influenza. Nine studies of the effectiveness of neuraminidase inhibitors as postexposure prophylaxis against confirmed influenza infection showed a protective effect^{25,26,27,28,29,30,31,32,33}. Evidence from a ring prophylaxis study in Singapore showed a large decline in the reproduction number when postexposure prophylaxis was implemented. Similarly, studies of postexposure prophylaxis in other schools, summer camps and nursing homes showed a low secondary attack rate following prophylaxis^{18,34,35}.

3.2 Modelling

As consistently demonstrated in previous modelling studies, the additional use of antivirals for timely postexposure prophylaxis of contacts altered the course of epidemics under several scenario assumptions. For epidemics of low transmissibility, prophylaxis (in addition to treatment) greatly increased intervention impact compared with treatment-only strategies.

Existing healthcare sector capabilities are likely to be sufficient to mitigate high clinical severity, low-transmissibility epidemics (Scenario 6), while significantly increased delivery capacity is required for successful mitigation of moderate (Scenario 4) and high (Scenario 7) transmission scenarios. For higher transmissibility epidemics, stockpile expiry is more likely, driven strongly by both initial stockpile size and delivery capacity.

An antiviral strategy involving community distribution to cases and close contacts would need to be deployed as early as possible in the pandemic response to maximise the chances of mitigation success. However, because of the resource-intensive nature of such an activity, close monitoring is needed so that the response can be redirected towards an approach targeted at individuals at high risk of severe outcomes if the antiviral strategy is not succeeding.

Continuous provision of antivirals to all essential service workers throughout a pandemic response would require establishment of a separate stockpile of at least 12.6 million courses, approximately twice the size of that required for healthcare workers, and would also require a responsive distribution strategy. Such a stockpile is far in excess of the number of doses used in case-targeted response strategies, requiring a substantial additional investment in antiviral courses. The corresponding increased requirement for distribution of these doses would likely additionally impact on the ability to deliver a transmission-reducing intervention to the wider community.

3.3 Review

Prophylactic use of neuraminidase inhibitors was associated with an 80% reduction in risk of symptomatic influenza among individuals exposed to a household case, and a 55 to 60% reduction in symptomatic infections when provided to individuals outside household settings²⁴. While no significant effect of prophylaxis against asymptomatic

infection was observed, such instances are unlikely to come to medical attention and therefore from a public health perspective do not represent a burden on clinical services or society.

Across reviews, the efficacy of neuraminidase inhibitors for prophylaxis ranged from 64% (16, 85) to 92% (37,99) representing absolute risk reductions ranging from 1.2% to 12.1%²⁴.

4 Antiviral pre-exposure prophylaxis for healthcare workers

4.1 Literature

A meta-analysis of published randomised trials of neuraminidase inhibitors used as prophylaxis against natural infection found no significant effect on influenza-like illness or asymptomatic infection, but identified protective effects against laboratory-confirmed infection³⁶. Observational studies from the 2009 pandemic did not provide new high-quality evidence regarding the effectiveness of continuous pre-exposure prophylaxis⁹.

In considering the effectiveness of neuraminidase inhibitors in prophylaxis of influenza infections, a 2012 Cochrane review raised concerns regarding publication and reporting biases in the trial program of oseltamivir⁶. The apparent blunting of immune responses to influenza in individuals administered oseltamivir is seen to potentially bias assessment of confirmed infection using seroconversion as an outcome in transmission studies, and the review reached no conclusion about the efficacy of this medicine for pre-exposure prophylaxis⁶. That said, both oseltamivir and zanamivir have been demonstrated to reduce pathogenicity by approximately 50%, resulting in a greater reduction in secondary symptomatic infections than seroconversions, and it is the former that constitute the outcome of primary interest for policy makers, as they impose burden on the healthcare system³⁷.

A study of Australian healthcare workers found that only 17.6% would work unconditionally during an influenza pandemic, with the majority saying that they would work if antivirals were available for prophylaxis or treatment.

4.2 Modelling

Modelling explicitly considered the impact of continuous pre-exposure prophylaxis to healthcare workers on their burden of disease. Measures focused towards healthcare workers included priority review and diagnosis of individuals in the early phases of the pandemic response; preferential distribution of antivirals for both treatment and prophylaxis in the setting of capacity constraints; and priority distribution of vaccine to healthcare workers once available.

An antiviral stockpile containing approximately 8 million doses (i.e. 40% of the population size) was generally sufficient to enable continuous pre-exposure coverage of front-line healthcare workers, along with a targeted postexposure treatment and prophylaxis strategy, where warranted on the basis of anticipated pandemic impact.

Synergistic benefits of targeted pre-exposure prophylaxis and community-based prophylaxis were observed among healthcare workers for all scenarios, resulting in far lower rates of disease than those reported from the general population.

Provision of continuous pre-exposure prophylaxis to healthcare workers until vaccine availability (at 18 weeks following identification of local [Australian] sustained transmission) required between 3.5 and 4 million courses. Such requirements are entirely compatible with use of the stockpile for case-targeted strategies, both treatment and prophylaxis. The model showed that where use for case-targeted strategies

impacted on the stockpile sufficiently to limit availability for healthcare workers, the case-targeted strategy was likely to be ineffective; and a stockpile of 10 million courses (50% per capita coverage) would be likely to be sufficient to allow for both strategies.

4.3 Review

The risk of occupational acquisition of influenza infection by HCWs is low, relative to community settings. In the context of comprehensive infection control measures, neuraminidase inhibitors confer minimal or no further reduction in disease risk. However, perceived safety at work is a critical determinant of HCW willingness to work during pandemic events, particularly for workers responsible for the care of children in the home environment. Neuraminidase inhibitors may be useful in reducing perceived risks, and have been demonstrated to be safe over prolonged (16 weeks) periods of administration, albeit at the cost of frequent side effects³⁸.

5 Antiviral prophylaxis for high-risk or vulnerable groups

5.1 Literature

Continuous pre-exposure prophylaxis has been demonstrated to be effective among high-risk and institutionalised elderly people, groups in whom influenza vaccines are anticipated to be of relatively low effectiveness³⁹. A separate systematic review also reported the protective effects of oseltamivir and zanamivir in at-risk groups⁴⁰.

5.2 Modelling

To simulate protecting those at greatest risk required the development of a stratified model that more accurately captured the increased propensity of individuals with underlying chronic diseases ('at risk') to be hospitalised, and experience severe outcomes including critical care requirement and death.

Measures focused towards at-risk groups included priority review and diagnosis of individuals in the early phases of the pandemic response; preferential distribution of antivirals for both treatment and prophylaxis in the setting of capacity constraints; and priority distribution of vaccine to at-risk groups once available. Greatest benefits are anticipated where distribution of antivirals for treatment and prophylaxis is prioritised to at-risk individuals, resulting in the greatest achievable reductions in hospitalisations and deaths.

5.3 Review

Groups identified to be at highest risk of severe disease during the 2009 pandemic included the very young and old, pregnant women and individuals with chronic disease, immunosuppression or obesity⁴¹. Limited evidence from subgroup analyses indicates that most of these groups are likely to benefit from neuraminidase inhibitor use, although evidence for effectiveness in children is conflicted⁴¹.

Limited data are available from observational studies to inform the effectiveness of antiviral treatment in high-risk groups. Available evidence confirms likely benefits of treatment in:

- Community treatment of individuals with underlying comorbidities, which was associated with a greater reduction in the risk of hospitalisation than was observed in the general population; and
- Hospital treatment of pregnant women, obese individuals and critically ill adults was associated with a reduced mortality risk. Inconsistent findings were reported in the paediatric age group.

6 Overall considerations for antivirals

6.1 Antiviral efficacy

Treatment of mild disease does not appear warranted, based on studies of generally healthy participants in randomised control trials⁶. However, treatment of moderate to severe disease in the community is beneficial in reducing progression of symptoms, based on observational studies of seasonal and pandemic influenza^{42, 43, 44, 45}. Treatment in hospital settings is also beneficial, showing a reduction in severe clinical outcomes based on observational studies of both seasonal and pandemic influenza⁴⁶.

A number of studies also identified demonstrate a correlation between timing of treatment and improvement in health outcomes, where use of antivirals within 48 hours of symptoms is essential to obtaining the best possible outcomes⁴². This highlights the importance of ease of access to antivirals and a sound distribution strategy of treatment to patients with influenza, which will minimise the burden of morbidity and mortality if effective.

6.2 Antiviral safety profile

The safety profile of neuraminidase inhibitors during the 2009 pandemic was as anticipated from clinical trials and previous post-licensure surveillance.

In the United Kingdom ‘first few hundred’ study, 41 of 335 recipients of oseltamivir experienced adverse effects, three-quarters of which were gastrointestinal⁴⁷. Of the 17 individuals reporting adverse events, 15 events were considered moderate and 2 were severe⁴⁷. Review of population-level pharmacovigilance reports during the 2009 pandemic response showed an overall benign safety profile of oseltamivir, particularly in relation to anticipated adverse events such as gastrointestinal and neuropsychiatric effects, although nausea was troublesome for some⁹.

Khazeni et al.⁴⁸ systematically reviewed seven trials on the safety and efficacy of extended duration (>4 weeks) antiviral chemoprophylaxis and concluded that long-term prophylactic use of oseltamivir and zanamivir appears safe in immunocompetent white and Japanese adults, although some nausea and vomiting is to be expected with oseltamivir. Neuraminidase inhibitors have also been linked to neuropsychiatric adverse events, especially in children in Japan. However, large retrospective cohort studies have shown no increase in adverse events related to the central nervous system, or to neuropsychiatric adverse events from oseltamivir^{49,50,51}. In addition, a separate study claimed the evidence strongly supports influenza (rather than oseltamivir) as the cause of neuropsychiatric adverse events and adverse events relating to the central nervous system⁵².

6.3 Antiviral resistance

Antiviral resistance continues to be an issue for neuraminidase inhibitors, particularly during an influenza pandemic⁵³. Fortunately, although levels of resistance to oseltamivir were high before the 2009 H1N1 pandemic^{54,55} relatively little resistance has developed to the new pandemic strain in the 3 years following the pandemic. It is important that global monitoring for the emergence of oseltamivir resistance continues⁵⁶.

Resistance to zanamivir is uncommon; however, zanamivir is not as widely distributed as oseltamivir and there is some speculation that increased use of zanamivir will lead to an increase in resistance⁵⁶. Overall, the prevalence of resistance to the neuraminidase inhibitors zanamivir and oseltamivir was low throughout the 2009 H1N1 pandemic, with the majority of cases occurring in individuals with immunodeficiency.

6.4 Key drivers of antiviral stockpile consumption

The relative number of antiviral courses consumed for treatment of severe (hospitalised) cases, treatment of community-based cases and for postexposure prophylaxis of contacts was reported for alternative medicine distribution strategies, and by pandemic impact scenario. Overall:

- transmissibility was the main driver of consumption, with high-transmissibility pandemics consuming large quantities of antivirals
- both transmissibility and clinical severity were important determinants of mitigation success, with overall stockpile consumption falling in the low-transmissibility, high clinical severity scenario compared with lower clinical severity pandemics, reflecting successful mitigation
- increasing clinical severity was generally associated with a greater proportional requirement on the stockpile for treatment of severe and community cases compared with distribution for prophylaxis, reflecting the model's scaling of clinical severity, and the absence of assumed constraints on medicine delivery in the hospital setting, compared with the community.

6.5 Early benefits of short term intensive antiviral distribution strategies

Given that sustained application of intensive case treatment and prophylaxis strategies is not likely to be feasible, the impact on the clinical attack rate of such strategies on stockpile use over a 2 or 4-week initial response phase was modelled:

- For high-transmissibility scenarios, significant reductions in case load of about 50% were observed 4 weeks into the intervention, both for treatment, and combined treatment and prophylaxis strategies (even where the final clinical attack rate is anticipated to be unchanged by the intervention).
- Even for the high-transmissibility epidemics, the median number of antiviral courses consumed by the community-based interventions was less than 50 000.
- For a combined treatment and prophylaxis strategy under a high transmissibility, low clinical severity scenario, smaller stockpiles (of around 1 million courses) have a 60% chance of being depleted.
- Anticipated cumulative incidence over the first month varied by an order of magnitude between the high and low-transmissibility scenarios, as did antiviral consumption. This finding shows that differences in innate epidemic characteristics, measurable through caseload and antiviral consumption, are likely to manifest early to support decision making.

6.6 Cost-effectiveness

There are few recent detailed studies of the cost-effectiveness of antivirals for treatment or prophylaxis. These studies are inconsistent in the approaches taken, the underlying

assumptions and the final measure. In addition, most of the cost-effectiveness studies include a prepandemic or postpandemic vaccine in conjunction with antivirals, making the cost-effectiveness of antiviral use alone difficult to determine. Therefore, conclusions on cost-effectiveness from the existing studies can only be drawn at a very coarse level. If used for treatment only, antivirals can be cost-effective in some circumstances, usually for high pandemic impact (high transmissibility and high clinical severity) scenarios, and mostly only in particular risk groups. If used for prophylaxis, antivirals are generally found not to be a cost-effective public health measure. There is clearly a need for more research into the cost-effectiveness of antivirals in an Australian (and worldwide) context. The recent Australian-focused papers by Newall et al. and Halder et al. go some of the way to addressing the current deficiency in this area^{57,58,59}.

6.7 Novel antivirals and their potential for use in future pandemic response

Newer neuraminidase inhibitors licensed in Japan are promising additions to the future antiviral response, with both intravenous peramivir and inhaled laninamivir demonstrating similar or superior efficacy to oseltamivir and zanamivir in clinical trials and postlicensure surveillance. A particular advantage of laninamivir is the requirement for a single dose, which may be given by or in the presence of a healthcare worker, potentially increasing treatment compliance in a pandemic event.

Novel antiviral agents acting by a range of host and virus-targeted mechanisms are on the horizon; some are already in Phase II clinical trials. The emerging evidence base on these therapies should continue to be reviewed regularly and considered for inclusion in future Australian pandemic responses.

7 Conclusions

The majority of published studies support the use of neuraminidase inhibitors for the prophylaxis and treatment of influenza in the pandemic setting. However, analysis of the cost-effectiveness of such a response is limited. The requirements of the general community, healthcare workers and at-risk groups are different and each should be considered as part of the phases of a broader antiviral pandemic intervention strategy.

Modelling studies show that influenza response strategies that deliver any measure of community-based antiviral distribution over and above treatment of the severely ill confer additional benefits to the population. Comparing modelling findings from three strategies (treatment of severe cases only, treatment of all identified cases, and treatment and prophylaxis of identified cases and their contacts) indicated that transmissibility is the primary driver of likely success. Low-transmissibility scenarios are amenable to control. Community distribution for treatment provides significant expected benefits at the population level for all low-transmissibility scenarios and the addition of prophylaxis can lead to significant further gains, even with small stockpiles available. For higher transmissibility epidemics, only combined treatment and prophylaxis strategies are capable of materially modifying the course of the epidemic, but effects are modest and stockpile and delivery requirements were more influential.

While an overall reduction in clinical attack rate may not be achieved for high-transmissibility scenarios, a reduction in case load may be achieved over the first month of an intensively applied community-based antiviral delivery strategy.

Compliance with antiviral interventions plays a strong role in determining either success or failure of the intervention to have a population-level impact. This emphasises the importance of communication strategies targeted at both health professionals and the community to ensure an effective intervention. During the 2009 pandemic, there was some evidence of reduced compliance with antiviral prophylaxis due to adverse events, particularly in the United Kingdom⁵⁹. An Australian survey of healthcare workers given oseltamivir as postexposure prophylaxis found that 16% either refused medication or did not complete the course because of adverse events⁶⁰. New generation single-dose neuraminidase inhibitors may hold a key advantage for any future public health response because the therapy can be supervised, ensuring high compliance.

Modelling analysis also showed that a greater burden of disease was observed among risk groups for both the mitigated and unmitigated scenarios reported. For low-transmissibility scenarios, benefits of both treatment only and combined treatment and prophylaxis strategies were observed for all groups. In contrast, for high-transmissibility scenarios, either treatment or treatment–prophylaxis approaches resulted in only modest impacts on the final attack rate among the general population and risk groups. However, even in the absence of apparent changes to the overall clinical attack rate, assumptions regarding the efficacy of antivirals against severe disease resulted in a marked reduction in the number of deaths reported, for all scenarios and could substantially reduce critical care requirement.

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