

# Pandemic controllability: a concept to guide a proportionate and flexible operational response to future influenza pandemics

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## ABSTRACT

The 2009 H1N1 influenza pandemic posed challenges for governments worldwide. Strategies designed to limit community transmission, such as antiviral deployment, were largely ineffective due to both feasibility constraints and the generally mild nature of disease, resulting in incomplete case ascertainment. Reviews of national pandemic plans have identified *pandemic impact*, primarily linked to measures of transmissibility and severity, as a key concept to incorporate into the next generation of plans. While an assessment of impact provides the rationale under which interventions may be warranted, it does not directly provide an assessment on whether particular interventions may be effective. Such considerations motivate our introduction of the concept of pandemic *controllability*. For case-targeted interventions, such as antiviral treatment and post-exposure prophylaxis, we identify the visibility and transmissibility of a pandemic as the key drivers of controllability. Taking a case-study approach, we suggest that high-impact pandemics, for which control is most desirable, are likely uncontrollable with case-targeted interventions. Strategies that do not rely on the identification of cases may prove relatively more effective. By introducing a pragmatic framework for relating the assessment of impact to the ability to mitigate an epidemic (controllability), we hope to address a present omission identified in pandemic response plans.

**Keywords** communicable diseases, pandemic influenza, management and policy, research

## Introduction

Following the emergence of the influenza A(H1N1)pdm in 2009, national governments have been evaluating the strengths and weaknesses of their pandemic plans.<sup>1–5</sup> In Australia, as in most other jurisdictions, pre-2009 plans focused primarily on responding to a severe pandemic with a 1918-like signature of high severity and high clinical attack rate.<sup>6–9</sup> The generally mild nature of the 2009 pandemic posed challenges for targeted case-based intervention strategies designed to limit transmission such as antiviral deployment, reactive quarantine and selective school closures.<sup>1,5,10,11</sup>

Public health agencies including the US Centers for Disease Control and Prevention (CDC), European CDC, World Health Organization and the Australian Government's Office of Health Protection have identified the concept of *pandemic impact* as a key issue for further consideration in developing the next generation of pandemic plans.<sup>12–16</sup> The impact of a pandemic derives from a number of factors,

including the transmissibility<sup>17,18</sup> and pathogenicity<sup>19</sup> of the virus, the age-specific incidence of disease,<sup>20,21</sup> health and socio-economic status of the population<sup>22–27</sup> and timing of virus introduction relative to the annual seasonal cycle of influenza.<sup>22,28–30</sup>

Expanding on concepts articulated during the 2009 pandemic,<sup>31</sup> here we identify an additional epidemiological measure, *controllability*, which may be influential in determining response strategies. We argue that the concept of controllability, complementary to impact, adds pragmatic value to current revisions of pandemic plans. Its inclusion will aid decision-makers considering whether and how to implement alternative responses to an emergent pandemic.

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## Pandemic impact

Influenza pandemics, sporadic in their occurrence over the course of human history, have varied in their impact on the human population.<sup>32–34</sup> The 1918 influenza pandemic was characterized by high clinical infection counts and high mortality. In contrast, the 2009 H1N1 pandemic had an overall mortality rate similar to that seen in yearly seasonal epidemics, while the distinct age profile provided a clear indication of its non-seasonal nature.<sup>35,36</sup> While it is recognized that pandemics exact substantial societal and economic costs,<sup>37</sup> for the purposes of this work we will confine the definition of *impact* to a consideration of transmissibility and severity, respectively, capturing the burden of morbidity and mortality. Our focus aligns with the recently introduced framework for the assessment of impact by Reed *et al.*,<sup>16</sup> who mapped past pandemics onto transmissibility-severity axes and evaluated the data requirements for real-time estimation of impact.

Virus transmissibility, captured by the basic reproduction number ( $R_0$ ) (assuming the population is fully susceptible), is the prime determinant of the total number of individuals infected over the course of a pandemic. The time course of infections depends further upon the average time between onset of symptoms in sequential generations of infection.

Clinical severity may be considered as the risk of severe outcome [e.g. hospitalization, intensive care unit (ICU) admission or death] per infected individual. The case-fatality ratio (CFR), which measures the risk of death given clinical infection, has been widely utilized as the primary measure of clinical severity,<sup>35</sup> but measures such as the infection-fatality ratio (IFR)<sup>36</sup> may also be appropriate, particularly from a transmission modeling point of view where the number of infections (clinical or otherwise) is imputed. However, the CFR (and IFR) has been seen to vary by orders of magnitude, both in its global average value across pandemics and by geographic location within pandemics.<sup>33</sup>

## Real-time modeling to assess impact

The 2009 pandemic was the first to occur in the era of ubiquitous computational resources, highly developed national pandemic preparedness plans and with the availability of detailed virological surveillance data. Although algorithms to infer the reproduction number from real-time epidemiological surveillance data were available,<sup>38,39</sup> limitations to their use were rapidly identified,<sup>20,40</sup> with extensions to account for age- and mixing effects developed during or following the pandemic.<sup>11,20,41</sup> Whether robust inferences on transmissibility can be made during the earliest stages of a pandemic remain an open challenge.<sup>35</sup>

Estimation of the CFR in real time is also fraught with challenges,<sup>35,42</sup> based on uncertainties in the estimation of deaths and cases, inaccurate ascertainment of cause of death, delays to death from the time of infection and reporting bias.<sup>43</sup> Early estimates of the 2009 pandemic CFR from Mexico were alarmingly high.<sup>44</sup> As methodological flaws were addressed,<sup>45</sup> estimates did indeed decrease.<sup>44,46–48</sup>

## Pandemic intervention strategies

Knowledge of the likely impact of a pandemic will clearly motivate public health officials to implement responses that may themselves be socially and/or economically costly. These costs must be balanced against the burden of a high severity pandemic on medical services, business continuity and social stability.

Intervention measures designed to save lives and maintain core health-care facilities and staff—such as the use of antiviral agents for treatment—would likely be recommended for use wherever available. However, it is less clear under what circumstances, if any, pandemic intervention strategies designed to modify the course of the outbreak itself may be effective (and warranted). Lipsitch *et al.*<sup>35</sup> have developed a decision-making framework that maps transmissibility and severity to the ‘overall scale of response’. Their proposed framework identifies the characteristics of a pandemic that would conceivably warrant intervention. The estimated effectiveness of control measures is considered as an additional element within this framework, but is not directly tied to the drivers of impact.<sup>35</sup> A working group convened during the 2009 pandemic suggested that decisions on attempted containment should be based on worst-case estimates for the CFR and best-case estimates for  $R_0$ , noting that the latter is a key driver of controllability.<sup>31</sup>

We suggest that the factors that contribute to impact may also critically determine the *controllability* of an epidemic and therefore controllability should be considered as an additional element in the decision-making process.

## Visibility and controllability versus severity and impact

Identification of the predicted impact of a nascent pandemic may help guide a decision on whether or not intervention is warranted, but it cannot directly inform on whether or not an intervention is likely to succeed. For example, case-targeted interventions rely on the timely and sustained identification of a reasonable proportion of all infectious cases<sup>10</sup> and so a primary driver of *controllability* for this intervention is the *visibility* of the pandemic.

Visibility encompasses both sociological and biological phenomena. The proportion of cases (of a given clinical severity) that choose to present to health authorities and thus become ‘visible’ and amenable to intervention will vary based on many factors, including cultural and social factors, the current (time-dependent) level of public perception of risk (itself likely positively correlated with the CFR), accessibility of health-care services and any effect of government information campaigns. A successful transmission reducing intervention also requires timely identification of cases, and so factors such as the proportion of transmission that pre- and post- dates onset of symptoms will also contribute to controllability.<sup>49</sup>

Impact and controllability are distinct but intertwined concepts. Combined with an assessment of transmissibility, severity helps to determine impact, while visibility (for case-targeted interventions) helps to determine controllability. To further explore this relationship between *controllability* and *impact*, we now take a case-study approach, using a previously published model of antiviral distribution and school-based intervention strategies.<sup>10,50</sup>

## Case studies

### Background

The Australian Government’s *Health Management Plan for Pandemic Influenza 2008* identified the distribution of antiviral agents for treatment and post-exposure prophylaxis as one of a number of strategies designed to reduce the community spread of influenza.<sup>6</sup> Selective school closure was also envisaged to play a role in community mitigation. These recommendations were informed, in part, by earlier modeling studies conducted by the authors.<sup>9,51,52</sup> In light of the 2009 experience, the model framework was updated to consider how varying levels of severity, and crucially, visibility, along with ‘real-world’ constraints in the health sector’s capacity for diagnosis and drug delivery, may modify the likely utility of interventions and the circumstances under which they may be effective.<sup>10</sup>

Here we employ that modeling framework to consider the ability of different interventions to mitigate key characteristics of epidemics including the total and clinical attack rate and time to peak incidence. We run the model repeatedly, sampling disease and intervention parameters from appropriate distributions to simulate a range of possible future pandemic scenarios of widely varying impact. Model outputs under application of interventions are related to baseline epidemic scenarios to allow the assessment of *controllability* and how it varies with different assumptions for transmissibility and

visibility. The sensitivity of model outputs to uncertain epidemic and intervention parameters is examined to provide guidance to public health authorities on key requirements for real-time decision support and current limitations in response capability.

### Interventions

We consider two contrasting frontline interventions designed to modify the transmission of an influenza pandemic: community-based antiviral distribution and ‘school-based measures’, the latter intended to capture a range of possible interventions designed to reduce transmission among the child and adolescent populations. The antiviral strategy is targeted towards identified cases and their contacts, while school-based measures can be deployed to a segment of the population without need for identification of particular infected individuals.

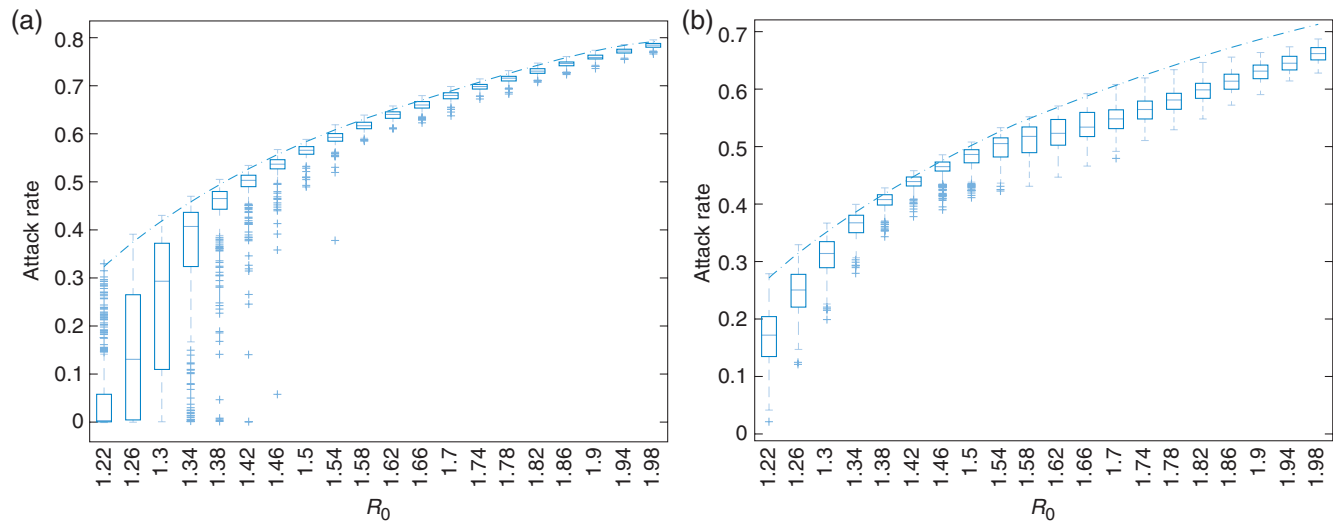
We assume that treatment with antiviral drugs results in a modest reduction in transmissibility and provision of post-exposure prophylaxis to suspected contacts of cases results in a reduced susceptibility.<sup>10</sup> Logistical constraints on case identification and drug delivery are imposed and have important implications for the overall ability of the response to modify the course of the epidemic, particularly for higher values of  $R_0$ .

School-based measures are employed for a fixed period (weeks to months) following a delay to their introduction, reducing child–child mixing while active. We consider two alternative age-mixing models in which to deploy school-based measures: homogenous mixing and enhanced child–child mixing.

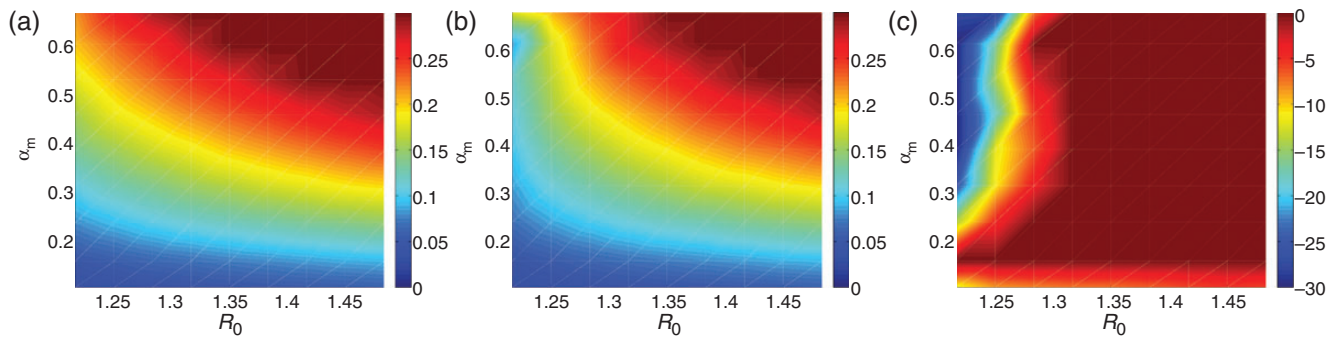
For both interventions we assume the availability of a strain-specific vaccine after 18 weeks of transmission, representing a definitive control measure. Full details of the mathematical model are presented in the Supplementary data .

### Findings and analysis

Transmissibility, characterized through the basic reproduction number  $R_0$ , is a key driver of *impact* and *controllability*. Figure 1 plots the association between  $R_0$  (sampled from [1.2, 2.0]) and impact, as measured by the overall attack rate (total infections) with all other parameters (biological, epidemiological and intervention) co-varied over plausible ranges. An antiviral intervention (Fig. 1a) is only able to meaningfully reduce the attack rate if  $R_0 < 1.5$ . Furthermore, if  $R_0 < 1.25$ , the intervention may be expected to definitively control the epidemic. In contrast, a school-based measure (Fig. 1b) implemented for a period of 12 weeks is never expected to control the



**Fig. 1** The distribution of attack rates (all cumulative infections, clinical or otherwise) as a function of transmissibility ( $R_0$ ). Each box plot shows the range of outcomes from the set of simulations, with the bar indicating the median, boxes covering the inter-quartile range, whiskers extending to the adjacent values and crosses indicating outliers. The dash-dotted line indicates the median attack rate over all simulations in the absence of intervention. Note that a strain-specific vaccine is rolled out to the population at Week 18 of the simulation, providing definitive control. **(a)** A targeted antiviral intervention, providing treatment to identified cases and post-exposure prophylaxis to contacts of identified cases. For high  $R_0$  ( $>1.5$ ), the box plots are tightly constrained (i.e. all simulations give roughly the same result) and overlap with the baseline (no intervention) median result. For low  $R_0$  ( $<1.25$ ), the intervention is expected to significantly reduce the attack rate. For intermediate values of  $R_0$ , between 1.25 and 1.5 the intervention may reduce the attack rate—the broad inter-quartile range, and significant tail of outliers extending towards very low attack rates indicates that the utility of the intervention is highly dependent upon other model parameters that are sampled in the scenarios. **(b)** A school-based measure (reduced child–child mixing) implemented for 12 weeks from the initiation of transmission under the baseline assumption that child–child mixing is enhanced compared with adult–adult mixing. The intervention's effect is less substantial than in **(a)**, and unable to completely control the epidemic. However, it is maintained over the broad range of  $R_0$  values considered. The relative reduction in intervention success for intermediate values of  $R_0$  is a complex result of the interplay between the timing of exponential growth, intervention withdrawal (at 12 weeks) and vaccine introduction (at 18 weeks), and is explored in detail in the Supplementary data.



**Fig. 2** Impact and controllability, assessed by the median clinical attack rate over the LHS sample as a function of  $R_0$  (transmissibility) and  $\alpha_m$  (visibility). **(a)** Baseline (no intervention) median clinical attack rate. **(b)** The median clinical attack rate with the antiviral intervention. **(c)** The mean percentage change in the median clinical attack rate (calculated from the difference between plots **(a)** and **(b)**). The median value for the outcome measure (clinical attack rate) over the LHS samples increases with increasing  $R_0$  and  $\alpha_m$ , indicating higher impact of simulated pandemics in the upper right region of the  $R_0$ – $\alpha_m$  plane (equivalent figures with severity in place of visibility are provided in the Supplementary data). Only for low transmissibility and high visibility scenarios (upper left) is the antiviral intervention able to modify the course of the pandemic (the larger negative values in plot **(c)**). Note that the narrow horizontal strip at the bottom of plot **(c)** is simply a boundary effect due to the plotting routine, and not an indication of control in this region.

epidemic, but its modest effect is sustained across a wider range of values for  $R_0$ .

Having established that transmissibility is a key driver of both impact and intervention success, we introduce a second

axis, the *visibility* of the epidemic, measured as the proportion of all non-hospitalized infectious cases that present to medical authorities ( $\alpha_m$ ). As detailed in the Supplementary data, visibility in our model is assumed to be correlated with



the underlying severity of the epidemic, in principle allowing for controllability to be linked to outcomes such as ICU admissions or death.

Figure 2 demonstrates how *impact* and *controllability* may differ. We consider an antiviral intervention including both case treatment and post-exposure prophylaxis of contacts and take the median clinical attack rate as a measure of *impact*. In the absence of intervention (Fig. 2a), impact increases with increasing transmissibility ( $R_0$ ) and visibility ( $\alpha_m$ ). Figure 2b shows the median clinical attack rate in the presence of the antiviral intervention. If we consider the *controllability*, a material change in the outcome is only evident if  $R_0$  is low and visibility is high (large negative values in upper left corner of Fig. 2c). That is, high-impact epidemics are uncontrollable, whereas lower impact pandemics of high *visibility* may be controllable. We present equivalent figures with *severity* in pace of *visibility* in the Supplementary data.

While case-targeted interventions may only be effective at modifying population transmission in high visibility scenarios, interventions that do not require the identification of individual infectious cases may have different controllability profiles. Figure 3 shows how controllability for a school-based measure maps to the axes of transmissibility ( $R_0$ ) and visibility ( $\alpha_m$ ). Using the time-to-peak incidence as a measure of pandemic impact, we find a uniform median percentage delay may be expected, in particular independent of the visibility ( $\alpha_m$ ). Note however that this finding is critically dependent upon the assumed mixing pattern in the population, and only holds if child–child mixing is naturally enhanced compared with adult–adult and child–adult mixing (Fig. 3a). Where child–child mixing is not enhanced, school-based measures are seen to be ineffective (Fig. 3b).

Figures 2 and 3 display median results over many simulations. Parameters other than  $R_0$  and  $\alpha_m$  also contribute to variation in the outcome (Fig. 1). We may explore this variation in detail using partial rank correlation coefficient analysis, as discussed in the Supplementary data.

## Discussion

### Main findings of this study

We have introduced the concept of *pandemic controllability* to address a present omission in pandemic response plans identified following reviews of the 2009 H1N1 influenza pandemic,<sup>1–5</sup> arguing that *pandemic impact*, while an appropriate measure to assess the likely burden on health-care systems and the population, is but one part of the equation. Our framework is designed to support planners with their attempts to characterize the circumstances under which interventions—designed

to minimize societal disruption and reduce the impact of the pandemic—are both warranted and achievable.

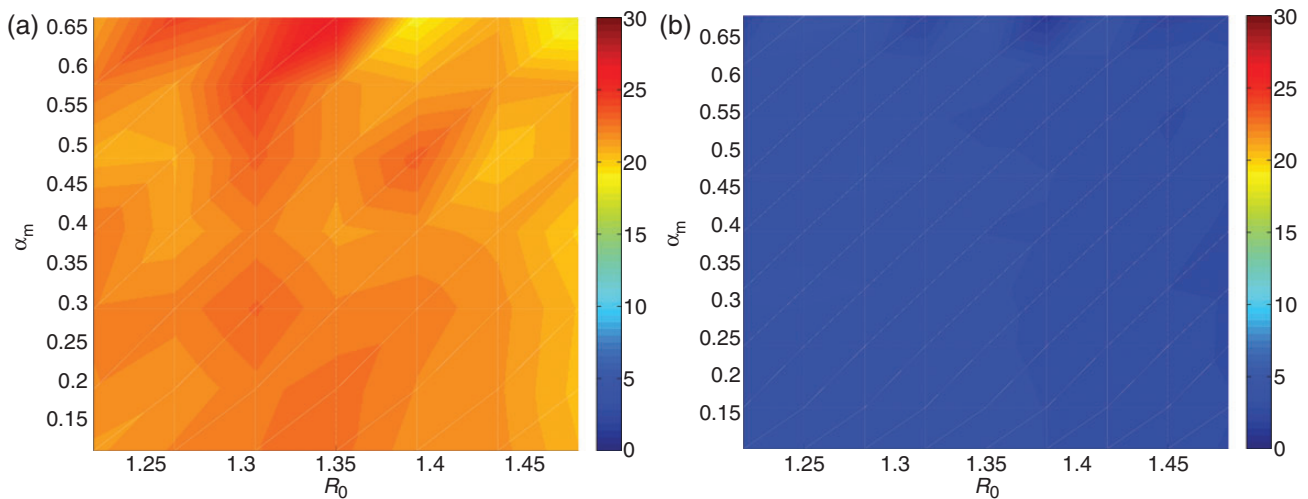
Given that interventions come at a (potentially great) societal and economic cost, only pandemics of sufficient *impact* and for which interventions are anticipated to be both achievable and effective warrant deployment of extensive mitigation strategies.<sup>35,37,53–58</sup> The concept of *controllability* should play a central role in considering how to intervene. Extending the concept as introduced in ref. 31 we have argued that different interventions have different controllability profiles and so the relationship between impact and controllability is dependent upon the intervention under consideration.

Furthermore, as the decision to intervene must be made early, almost certainly before strong evidence on likely future unmitigated impact is available, our results highlight that the development of decision algorithms for refocusing of efforts to provide direct protection to those most at risk is critical for improving public health response strategies. Such algorithms should consider multiple measures of severity—e.g. deaths, ICU admissions, the CFR or IFR—to ensure a precautionary approach to refocusing interventions.

Taking a case-study approach, we have demonstrated how two particular intervention strategies—targeted population distribution of antiviral agents and school-based measures—may differ in their ability to control epidemics of varying characteristics. We demonstrated that targeted case-based intervention strategies, such as wide-scale community provision of antiviral agents, are only likely to be effective in limiting transmission if an epidemic is of low transmissibility and high visibility. As such, epidemics of greatest anticipated impact are likely not controllable (with antivirals alone). This finding must be considered in relation to the high anticipated demand from the public for such interventions in high impact scenarios, and of course, the direct protective effect of antivirals for limiting severe outcomes or death.<sup>59</sup> In contrast, strategies designed to reduce transmission in the general population, or specific sub-populations such as schools, may be effective whether or not a pandemic is ‘visible’ as the decision to deploy an intervention and the efficacy of that intervention is less dependent on the identification of individual cases. Accordingly, such interventions remain effective at materially reducing transmission over a broad range of assumed impacts. Any recommendation to deploy such interventions, targeted or otherwise, must still be weighed against their societal and economic cost.

### What is already known on this topic

The concept of pandemic *impact* has recently been explored by multiple independent authorities, including the US



**Fig. 3** The average percentage change in the time-of-peak of the epidemic with school-based measures under two assumptions on mixing. The start time and duration of the intervention are randomly sampled over plausible ranges as described in the Supplementary data. **(a)** Enhanced child–child mixing assumption. The underlying age-dependent mixing between children is assumed to be enhanced compared with between adults. Measures to reduce child–child mixing result in an appreciable delay to epidemic peak, constant in percentage terms at around 20%. Note that for increasing  $R_0$ , the time to peak shortens and thus so does the absolute delay achieved by the intervention. **(b)** Homogeneous mixing assumption. The underlying age-dependent mixing is assumed to be uniform. A reduction in child–child mixing has (on average) a negligible effect on the epidemic regardless of assumed transmissibility or severity.

CDC,<sup>15,16</sup> European CDC,<sup>14</sup> World Health Organization<sup>12</sup> and the authors in conjunction with the Australian Government.<sup>13</sup> All of these assessments have suggested that the two key elements of impact are transmissibility (e.g.  $R_0$ ) and severity (e.g. CFR). Gathering the appropriate information in a timely manner to assess these two key drivers of impact has been identified as a priority for national surveillance and real-time data analysis endeavors.

How an assessment of *impact* relates to the ability to mitigate an epidemic has received less attention.<sup>31</sup>

### What this study adds

Our study, by introducing *controllability* as a context and intervention-dependent concept, addresses this gap. We have explored the relationship between impact and controllability using a case-study approach and suggested a framework under which to use scenario analysis techniques and mathematical modeling to develop flexible and proportionate response strategies for incorporation into pandemic management plans.

Our results indicate that rapid assessment of epidemic growth rates and case ‘visibility’ (i.e. the proportion of all infectious cases that come to the prompt attention of health authorities), as well as case severity, is critical to inform the likely success of an intervention.

### Limitations of this study

Our study has two primary limitations. From a policy and planning perspective, a formal cost–benefit analysis is still

arguably necessary before a particular course of action could be recommended in a given pandemic situation, even where likely to be effective. Given that such an assessment is anticipated to be impossible to achieve in real time,<sup>11,35</sup> development of a fully integrated pre-emptive modeling and scenario analysis strategy remains a worthy goal.

The second limitation of our study is that we have only explored a limited set of mitigation strategies using one particular modeling framework based on knowledge of the Australian context.<sup>10</sup> All models are necessary simplifications of ‘real-world’ complexities, and should be considered as useful frameworks within which to explore alternative scenarios, to gain key insights into epidemic drivers and potential mechanisms of disease control. As such, each will differ when determining scenarios which are *controllable* or otherwise. For robust, country-specific policy development, findings from a suite of modeling analyses drawn from different research groups and building on independent evaluations of the epidemiological literature should be considered.

### Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

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