

7 February 2025

Dear Editor,

Please find enclosed, our manuscript entitled “Estimating the global demand and potential public health impact of oral antiviral treatment stockpile for influenza pandemics: a mathematical modelling study”, which we would be grateful for your consideration for publication at *Lancet Infectious Disease*.

The continual threat of a global influenza A virus pandemic stems from the large diversity of influenza A virus subtypes circulating among their reservoir species that can spillover into poultry and mammals. Stockpiling oral influenza antiviral drugs is often considered by governments as part of pandemic preparedness efforts. Due to their antiviral activity against a wide range of influenza A virus subtypes, widespread distribution of these drugs during an influenza pandemic could be useful for minimizing hospitalizations and deaths, especially during the early stages of the pandemic when vaccines are not yet available.

Given uncertainties about the characteristics of a future influenza pandemic, mathematical modelling can generate an evidence base to inform stockpile sizing options. To that end, there is a large body of modelling work from the last two decades, that typically focuses either on one or a handful of country archetypes, providing oral influenza antiviral stockpile sizing recommendations ranging from as little as 15% per-capita to >140% of the country’s population size. Notwithstanding the difficulties in meaningfully synthesizing the wide range of stockpile sizing estimates for public health recommendation, previous studies assumed that most symptomatic individuals would seek treatment promptly after infection within two days of symptom onset. Based on the COVID-19 pandemic, there is now empirical evidence to show that this is an idealized assumption even at the height of a pandemic. Additionally, many of these previous studies made exaggerated assumptions about the transmission reduction effects of antiviral treatment, largely due to a lack of direct evidence. However, in September 2024, a randomized clinical trial on baloxavir marboxil showed that it could reduce transmission risk of treated patients by 29%. This new empirical evidence created an opportunity to re-interrogate and improve previous pandemic preparedness antiviral stockpiling recommendations.

To guide future pandemic antiviral stockpiling recommendations, we sought to estimate peak country-specific antiviral demand and potential impact, defined as the percentage of pandemic deaths averted, for 186 countries using a new multiscale modelling framework we developed for this study. Unlike previous studies, our multiscale model realistically accounts for variation in changes to infectiousness dynamics due to heterogenous timing of treatment by antivirals and the consequent impact it would have on transmission dynamics. Furthermore, this is the first study that incorporates the latest direct estimates of transmission reduction effects by antiviral treatment.

We first used our model to estimate the maximum demand and impact of distributing either oseltamivir or baloxavir marboxil for treatment in four pandemics scenarios (i.e. 1918 A/H1N1-like, 1968 A/H3N2-like, 2009 A/H1N1-like and a COVID-19-like influenza pandemic) under the idealized assumption that public health infrastructure is sufficiently well resourced to promptly identify and treat almost all symptomatic individuals promptly after infection in the country. We then analysed how deviations from this idealized scenario would alter antiviral demand and impact, including delays in population distribution of antivirals since pandemic initiation, individual delays in seeking treatment, as well as changes in antiviral distribution strategies such as drug rationing by age groups, extending the treatment window of drugs from the current indicated use of two days to eight days, and providing post-exposure prophylaxis to household contacts. We also investigated how antiviral resistance could diminish the impact of drug stockpiles.

Like previous studies, we find that oral antivirals can potentially lower the disease burden of future influenza pandemics substantially. However, unlike previous studies our results provide substantially improved estimates of antiviral stockpile demand and impact because of realism of our modeling framework and new clinical data. We find that baloxavir marboxil, owing to its transmission reduction effects, can potentially double the percentage of mean pandemic deaths averted relative to oseltamivir, reducing deaths by 37% – 68% while requiring treatment stockpiles amounting to 7%–34% per-capita, which is ~5%–10% fewer courses than an oseltamivir stockpile. Rationing drugs for use by the most vulnerable, often those aged 65 years and above, is commonly implemented under limited drug availability. However, we find that restricting access does not necessarily lower treatment demand and instead can actually increase pandemic deaths. Providing post-exposure prophylaxis to household contacts could additionally reduce pandemic deaths but only under excess drug availability and only in countries with large average household sizes. Finally, while mass distribution of antivirals could potentially lead to the spread of treatment-emergent resistance, distributing baloxavir marboxil could still save a substantial amount of lives, reducing average pandemic deaths by at least 24% as compared to no intervention at all.

A preliminary version of this work was previously shared with the European Commission’s Health Emergency Preparedness and Response Authority (HERA) upon request for EU Member States’ consideration of their influenza antiviral stockpile needs. We expect this work will be of great interest to a wider global audience, including governments worldwide, clinicians, epidemiologists, public health experts, and generally anyone interested in pandemic mitigation and preparedness. We believe that *Lancet Infectious Disease* is the right forum to reach the widest possible audience.

Thank you for your consideration and we look forward to your decision.

Sincerely,

Alvin X. Han, Katina D. Hulme and Colin A. Russell