

Relaxation of anti-COVID-19 measures reveals new challenges for infectious disease outbreak forecasting

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Since early 2020, countries around the world have seen unprecedented government-imposed restrictions and behavioural changes that have changed transmission dynamics of infectious diseases. These have posed unique challenges for routine seasonal infectious disease forecasting systems that have seen the relevance of their rich long-term pre-COVID-19 datasets questioned for prediction in this new era.

For the mosquito transmitted viral disease dengue, COVID-19 interventions have substantially suppressed transmission since early 2020¹, but it is unclear how long these suppression effects will last and what will happen when dengue virus transmission rebounds. D-MOSS (www.d-moss.org) is one of the few operational real-time dengue forecasting systems and has been issuing forecasts and informing preventative mosquito control in Vietnam since July 2019. Like many outbreak forecasting systems, D-MOSS uses advanced statistical modelling techniques to identify relationships between a long, province-level dengue case dataset and known drivers of transmission such as temperature, rainfall, and recent case trajectory². Between July-December 2019 D-MOSS successfully identified 144 of 212 outbreaks (68%) across Vietnam with a one-month lead time. Between January 2020 and December 2021, D-MOSS has retained its ability to predict the less frequent, lower intensity outbreak that have occurred (127 of 220, 58%).

The Vietnamese government began relaxing domestic COVID-19 restrictions in September 2021 with all international travel restrictions repealed by February 2022. Since February 2022, seasonal dengue outbreaks have returned, however, the intensity, timing, and frequency of these outbreaks is higher than expected. A total of 199,518 cases and 78 fatalities were reported across Vietnam 1st January - 5th September 2022, peaking in late July (instead of the usual November) at over five times their pre-COVID-19 average for the time of year. Importantly D-MOSS has, uncharacteristically, failed to predict many of these outbreaks with a decline in predictive performance to 46% (100 of 219 outbreaks) at one month lead time, reducing to 13% at a four-month lead time. Such dengue dynamics are not unique to Vietnam, with many countries experiencing abnormal seasonal outbreaks following relaxation of COVID-19 restrictions³.

The 2022 outbreaks and D-MOSS's failure to predict them likely share common causes. The D-MOSS model predictions suggest that the 2022 outbreaks cannot be explained by climatic drivers alone, and normal mosquito trap indices and a continued predominance of DENV1 and DENV2 serotypes suggest vector and virus factors are not outside historical ranges, despite the influence of a protracted three year La Niña event on climate conditions in the region. This could point to declining host immunity, from reduced natural exposure to dengue virus over the past two years, as an explanation for these outbreaks. Large epidemic cycles driven by natural fluctuations in host immunity are normal in many dengue-endemic areas⁴, but Vietnam usually experiences 10-12 years between major epidemics and only three dengue seasons have passed since the last major outbreak (2019). Suppression of dengue transmission by COVID-19 measures could have allowed susceptibility to build up more rapidly and could shorten the gap between major dengue epidemics over the coming years. Longitudinal seroprevalence surveys to measure population-wide immunity would be needed to test this hypothesis⁵. Additionally, delays in dengue case reporting in early 2022 may also be hampering reactive mosquito control and D-MOSS's ability to accurately extrapolate trends from recent data.

Both issues could be addressed by adding complexity to the forecasting model. Including models that explicitly account for immunity, such as dynamic compartmental mathematical models, within the ensemble forecast⁶ could better quantify susceptibility and including a data delay model would improve the utility of recently reported data even if the reports have yet to be finalised^{7,8}. These are sensible solutions that would have helped D-MOSS better predict the 2022 outbreak, but the next outbreak may be due to different causes that require different modelling adaptations.

Instead, perhaps this highlights some of the major challenges, and perhaps limits, to disease forecasting outside the context of relatively stable endemic transmission. Most space-time statistical disease models rely heavily on structured random effects to explain past variation in cases that cannot be explained by the limited range and specificity of environmental and socioeconomic variables available to modellers. These random effects are vulnerable to changes in surveillance and are difficult to reliably extrapolate because they do not identify a causal driver of transmission.

In an ever more volatile changing climate, unprecedented events will be ever more common. Over-reliance on temporal random effects in forecasting models may make predictions less resilient to changing climates and an increasingly dynamic emerging infectious disease

landscape. Since July 2022, short-term (one month lead time) D-MOSS predictive performance has improved (63%), but long lead time performance remains low (8%) and the long-term consequences of COVID-19 disruption to the predictability of dengue dynamics remains uncertain. This improvement could be due to closing of the immunity gap or could reflect the higher model predictive skill Aug-Nov during the usual dengue season in Vietnam where climate exerts a stronger influence on transmission.

While forecasting and predictive models still offer great hope in transforming a wide range of clinical and public health fields, recent events are a reminder of their limitations and the importance of expert judgement and local knowledge of the decision-makers who are responsible for translating these predictions into preventative actions.

Declaration of interest

We declare no competing interests.

References

- 1 Chen Y, Li N, Lourenço J, *et al.* Measuring the effects of COVID-19-related disruption on dengue transmission in southeast Asia and Latin America: a statistical modelling study. *Lancet Infect Dis* 2022; **22**: 657–67.
- 2 Colón-González FJ, Bastos LS, Hofmann B, *et al.* Probabilistic seasonal dengue forecasting in Vietnam using superensembles. *PLoS Med* 2021; **18**: e1003542.
- 3 PAHO. PLISA Health Information Platform for the Americas: Reported cases of dengue reported by countries in the Americas by last available Epi Week. 2022. <https://www3.paho.org/data/index.php/en/mnu-topics/indicadores-dengue-en/dengue-nacional-en/252-dengue-pais-ano-en.html> (accessed Sept 27, 2022).
- 4 Van Panhuis WG, Choisy M, Xiong X, *et al.* Region-wide synchrony and traveling waves of dengue across eight countries in Southeast Asia. *Proc Natl Acad Sci U S A* 2015; **112**: 13069–74.
- 5 Morrison AC, Minnick SL, Rocha C, *et al.* Epidemiology of dengue virus in Iquitos, Peru 1999 to 2005: Interepidemic and epidemic patterns of transmission. *PLoS Negl Trop Dis* 2010; **4**. DOI:10.1371/journal.pntd.0000670.
- 6 Funk S, Abbott S, Atkins B, *et al.* Short-term forecasts to inform the response to the Covid-19 epidemic in the UK. *medRxiv* 2020; **9**: 2020.11.11.20220962.
- 7 Beesley LJ, Osthusid D, Del Valleid SY. Addressing delayed case reporting in infectious disease forecast modeling. *PLOS Comput Biol* 2022; **18**: e1010115.
- 8 Lauer SA, Sakrejda K, Ray EL, *et al.* Prospective forecasts of annual dengue hemorrhagic fever incidence in Thailand, 2010–2014. *Proc Natl Acad Sci U S A* 2018; **115**: E2175–82.