

Reply to “Use of Prediction Models for Risk Analysis and Decision-Making in Public Health—The Catch-22 Conundrum”

We are pleased that our editorial¹ has triggered a debate on the usefulness of prediction models to guide disease preventive operations. Indeed, we believe that any disease preventive programme should be regularly and critically reviewed to ensure that the approaches to protect our population are firmly grounded on all available evidence.

Mathematical models have and will continue to impact on our understanding of disease epidemiology as well as generate new hypotheses that shape studies to improve disease prevention. The question before us is whether such models are ready to be applied as predictive tools for epidemics to scale the intensity of control measures. While the authors have acknowledged that mathematical models are imperfect, they contend that such predictive models should still nonetheless be used to guide disease control operations. As an example, they reported their recent experience in having removed more than 20,000 adult mosquitoes using their Gravitrapp, as well as stockpiling of diagnostic kits, insecticides and insect repellents. While this is indeed laudable, it also raises the question of what would happen if the model inaccurately predicts low dengue incidence for the year?

The use of mathematical models to predict disease incidence and guide public health operations is, in many ways, similar to the development of biomarkers as prognostic tools to guide case management. Demonstration of statistically robust, reproducible sensitivity and specificity is an absolute requirement, both from a scientific and ethical standpoint, before any biomarker can be applied clinically. Can similar studies be carried out to demonstrate the robustness of any predictive models?

Indeed, this was a question that was addressed recently, shortly after our editorial was published in April this year. Reich and colleagues developed a real-time forecasting model for dengue and applied it in 77 provinces in Thailand.² The authors observed mixed performance of the model across the provinces. Their finding suggests heterogeneity in the various factors that influence the performance of their model, making prospective validation of any predictive model through studies in different countries or regions, difficult. These findings also suggest that models that are tailored to cater to the nuances in each geographic location,

such as the one described by the National Environment Agency (NEA), could have greater accuracy in prediction compared to models that apply generic parameters. However, statistical validation of such models will require long periods of prospective testing for robustness.

Perhaps it may be more helpful to compare predictive models that cater to the uniqueness of a specific locality, such as Singapore, to personalised medicine. Personalised medicine stratifies disease into different groups for management, based on a plethora of genetic, protein or even metabolomic signatures. In such instances, biomarkers are identified from the molecules that play key mechanistic roles in pathogenesis, which is especially useful when the prevalence of cases that display specific bio-signatures, is low. Here, the similarity between predictive models and personalised medicine ends; unlike biomarkers that are grounded on disease mechanisms, predictive models rely on parameters that have shown statistical association with, but not causation of dengue epidemics.

The factors that influence dengue transmission and hence, risk of epidemics, are not completely understood. Herd immunity against each of the 4 dengue virus (DENV) serotype, as pointed out by the authors, obviously plays a major role. Indeed, we and others have examined how the low herd immunity, as a consequence of the low *Aedes* mosquito population density in Singapore have profoundly shaped the re-emergence of dengue in Singapore.³⁻⁶ A less well-defined but probably underestimated factor is the fitness of the virus. DENVs are not monolithic; genomic differences give rise to strains that differ in epidemiological fitness. We showed recently that as few as 3 nucleotide substitutions in the 3' untranslated region (3'UTR) of the DENV genome altered the ability of the virus to suppress interferon induction.⁷ The reduced interferon expression during infection contributed, at least in part, to the ability of this strain of DENV to spread epidemically in Puerto Rico in 1994.⁷ Likewise, alterations in the 3'UTR sequence also could have contributed to another outbreak in Nicaragua in 2005.^{7,8} However, the science that links genetic mechanisms to epidemic transmission is still in its infancy and thus, not sufficiently mature to be incorporated into predictive models. Consequently, the fitness of circulating strains of DENV could be a major

confounding factor of the accuracy of current predictive models. It is thus plausible that emergence or introduction of an epidemiologically fit DENV could cause a major epidemic despite prediction of low dengue incidence based on climatic and other parameters considered in the model.

Mathematical models have exciting potential to be used as tools to predict disease incidence and guide or scale disease control measures accordingly. However, for mathematical models to be used in such a manner to safeguard our population's health, the quality of evidence for the use of such tools should meet the same rigour as prognostic biomarkers for case management. Until then, we believe that reduction of *Aedes* larval habitats regardless of the risk of epidemics, which is a strategy that has served Singapore well for decades,⁴ should continue to remain the emphasis of our dengue prevention programme. In that, there is no conundrum.

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