SARS-CoV-2 incidence and vaccine escape

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An Editorial[1] earlier this year described the potential for the evolution of SARS-CoV-2 variants that render vaccines less effective (vaccine escape), assisted by waning immunity following vaccination. This raises a crucial question: how can COVID-19 exit strategies be planned while limiting the vaccine escape risk?

A key component of any plausible strategy towards the permanent removal of non-pharmaceutical interventions (NPIs) is ensuring low case numbers in the short to medium term using NPIs and vaccination. Assuming a fixed vaccine escape mutation probability per infection (p), the risk of a vaccine escape variant arising in a specified time period is $1-(1-p)^N$, where N represents the number of cases in that period. Crucially, this expression indicates that the vaccine escape risk is sensitive to background incidence; the risk of an escape variant appearing within a fixed time is an increasing function of incidence (figure). Reducing cases is not only beneficial for decreasing the pressure on health-care systems, but also for lowering the vaccine escape risk.

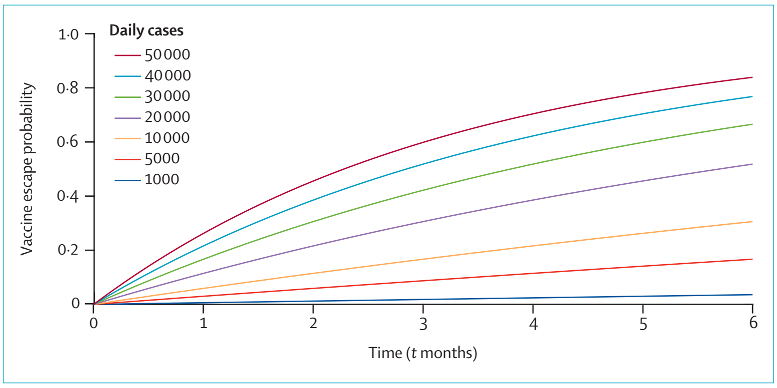

***Figure:* Risk that at least one vaccine escape variant arises in a time period of length *t*, for different daily numbers of cases**
The per-infection probability of vaccine escape is $p = 2 \times 10^{-7}$ (for details, see the appendix).

See Online for appendix

Of course, there are fundamental differences between using NPIs and vaccines to lower incidence. When considering vaccines that do not prevent transmission entirely, there is an interplay between reduced cases at the population-level and the potential for selection for vaccine escape variants in infected vaccinated hosts.[2–4] A related question is whether it is most beneficial to vaccinate many individuals using single vaccine doses or fewer individuals twice. Dose-sparing strategies could in theory lead to selection for vaccine escape variants.[5] However, evidence suggests tentatively that the net vaccine escape risk is lower when more hosts are vaccinated with single doses than when fewer hosts are vaccinated twice due to reduced cases.[2]

Despite its simplicity, our quantitative illustration demonstrates that strategies for mitigating the vaccine escape risk should be explored. Reducing case numbers locally should be only one element of these strategies. Travel restrictions to reduce the risk of importing novel variants should be considered. We recognise that assessing the escape variant emergence risk not only requires the variant to arise via mutation as considered here, but also to grow to appreciable frequencies. This is a stochastic process, depending on the availability of hosts to infect and the escape variant's fitness. A reduction in cases leads to both a reduction in the risk of escape variants appearing and a reduction in their subsequent establishment via transmission in the population. Acquisition of additional mutations that are beneficial for the virus is also more likely to be suppressed if incidence is reduced.

In summary, high SARS-CoV-2 incidence rates act to increase the vaccine escape risk. Maintaining low case numbers using NPIs and vaccines is crucial at this time.

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**Robin N Thompson, Edward M Hill, Julia R Gog*
robin.n.thompson@warwick.ac.uk

Mathematics Institute (RNT, EMH), Zeeman Institute for Systems Biology and Infectious Disease Epidemiology Research (RNT, EMH), and School of Life Sciences (EMH), University of Warwick, Coventry, UK; Department of Applied Mathematics and Theoretical Physics, University of Cambridge, Cambridge, UK (JRG)

1 The Lancet Infectious Diseases. An exceptional vaccination policy in exceptional circumstances. *Lancet Infect Dis* 2021; **21:** 149.

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