

Saad-Roy *et al.* write that SARS-CoV-2 vaccine dosing regimens generating intermediate levels of immunity could accelerate the emergence of new immune-escape variants. However, their argument assumes such variants are most likely to arise through *de novo* mutation and selection in partially immune hosts. For a pathogen like SARS-CoV-2 that typically transmits in the acute phase after relatively few cycles of replication, there is little opportunity for adaptive mutants to be generated and rise to a frequency that makes onward transmission likely. Simultaneously, there is good reason to think that intermediate levels of immunity should both reduce the probability of infection and limit the supply of adaptive mutations by restricting the within-host viral population size (1,2). Furthermore, viral loads appear lower in infections 12-28 days following a single dose of vaccine than in unvaccinated individuals, which likely translates to decreased transmission by vaccinated individuals (3).

Because of limited opportunities for within-host mutation *and* selection, the presence of immune-escape variants may be more important at the point of infection of immune individuals (1,2). If so, what matters is the standing diversity of such variants in the population as a whole. Reducing numbers of infections through vaccination should then reduce opportunities for such diversity to be generated, transmitted and selected. In short, vaccination is likely to make evolution slower and this benefit may be realized by initially optimizing breadth of vaccine coverage, rather than strength of immunity.

We do not advocate for delayed dosing strategies without further clinical evidence, and it is important to consider the issues raised by Saad-Roy *et al.*, which will depend upon the properties of the vaccines involved. However, anxiety about the potential of vaccination to increase the emergence rate of immune-escape variants should be tempered by the observations above and the enormous public health benefits of widespread vaccination.

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## References

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