LETTERS

The effect of COVID-19 vaccine dosing regimens on the emergence of new variants depends on a range of factors.

Edited by **Jennifer Sills**

Partial immunity and SARS-CoV-2 mutations

In their Research Article, "Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes" (this issue, p. 363; published online 9 March), C. M. Saad-Roy *et al.* write that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine dosing regimens generating intermediate levels of immunity could accelerate the emergence of new variants that are capable of wholly or partially escaping immunity induced by prior infection or vaccination—immune-escape variants. Their argument assumes that such variants are most likely to arise through de novo mutation and selection in partially immune hosts (i.e., those people who have not mounted a strong immune response to infection or vaccination). However, for a pathogen like SARS-CoV-2 that typically transmits in the early stage of infection after relatively few cycles of replication (*1*), 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 viral population size within each vaccinated host (*2*, *3*). Furthermore, viral loads appear lower in infections 12 to 28 days after a single dose of vaccine than in unvaccinated individuals, which likely translates to decreased transmission by vaccinated individuals (*4*).

Because of limited opportunities for both mutation and selection within a host, the presence of immune-escape variants may be more important at the point of infection of immune individuals (*2*, *3*). 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 on 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 low probability of the confluence of mutation, selection, and transmission as well as the enormous public health benefits of widespread vaccination.

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COMPETING INTERESTS

W.P.H. was paid to provide expert witness testimony in a litigation matter related in part to the expected duration of the COVID-19 pandemic.

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Response

Hanage and Russell conjecture [see also (*1*)] that intermediate levels of immunity may sufficiently restrict within-host viral population size and thus limit adaptive mutations. The evolutionary model in our Research Article encompasses a wide range of scenarios, including the optimistic one Hanage and Russell propose (see scenario 1 in Fig. 4A of the Research Article). However, we also argued that uncertainties in immunodynamics, and in particular evolutionary dynamics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), dominate our ability to project key scenarios. We therefore produced generic models in an effort to encompass this variability while providing a useful framework for considering possible future outcomes.

We would also like to clarify that the calculations for evolutionary potential in our Research Article involve only infections after natural or vaccinal immunity has waned [i.e., I_S (secondary infection after waned natural immunity), I_{S1} (infection after waned one-dose vaccinal immunity), and I_{S2} (infection after waned two-dose vaccinal immunity), see Fig. 1]. Our accompanying interactive online application allows for the exploration of the effect of an even wider range of parameters on immunological and epidemiological outcomes.

We stress that the understanding of viral phylodynamics (the intersection of the epidemiological and evolutionary dynamics of pathogens) is still in its infancy, especially for novel pathogens like SARS-CoV-2. We therefore believe that exploring the resulting uncertainty is key. Understanding the dynamics of different classes of individuals experiencing infections after the waning of natural or vaccinal immunity will be crucial for teasing out drivers of viral immune escape (i.e., the ability of a virus to evolve to evade host immune factors); this is at the heart of our model. Along these lines, and as we highlight in the Research Article, an important area of future work will be to develop phylodynamic models with explicit within-host dynamics (*2*).

The other major source of uncertainties is in epidemiological outcomes. In their Letter, Hanage and Russell emphasize the likely epidemiological importance of widespread vaccine deployment. This echoes a conclusion of our Research Article, wherein we stress that short-term dose sparing deployment of a vaccine reduces infections and buys much time in public health planning. However, we also stressed the range of uncertainties that may modulate the longer-term outcomes of this strategy; in particular, less robust immunity could lead to more complex epidemiological and evolutionary outcomes.

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PAST AS PROLOGUE

A new frontier for mi familia

With sleek black hair, finely arched eyebrows, and deep brown eyes that sparkle, my feisty, 5-foot-tall *Abuelita* (grandmother) is my last link to my ancestors, who spoke a unique dialect of New Mexican Spanish. As the last generation of a disappearing New Mexican lineage, whose *güerita* (light-skinned) appearance belies my heritage, I feel a responsibility to carry on the stories and traditions of my family; yet I feel ill-equipped to do them justice. Every life decision I make carries the weight of the unspoken question: How do I move forward and remember who I am when my family roots are being erased?

The author's great-great-grandparents pose for a photo in Tecolote, New Mexico, in the early 20th century.

Immersed in the aromas of her homemade tortillas and red or green chile, Abuelita teaches me her native language in our effort to preserve my identity. Never a homeowner, Abuelita lives in a run-down studio apartment in the center of "the warzone," an impoverished area of Albuquerque adjacent to the heavily militarized Kirtland Air Force Base. "*No te preocupes, mi hijta*," she tells me, motioning to the SWAT vehicles that are a regular sight. "The more police, the safer the place!" Local research proves this to be untrue.

My childhood was filled with upheaval, and although school was always my refuge, I struggled to find where I belonged. My search came to an end with El Puente Research Fellowship, the Maximizing Access to Research Careers (MARC) scholars program, and the 2020 Society for Advancement of Chicanos/Hispanics and Native Americans in Science (SACNAS) conference. In these communities, I found diverse scientific research that could answer that ever-present question. I believe that solving the multifaceted issues facing my hometown, from mass incarceration to severe substance addiction, lies within biomedical health research. I hope one day to use scientific evidence to influence policy in these areas, giving families like mine a better chance of stability and allowing their stories to continue unbroken. Science is my pursuit of a new frontier for my family: one of identity, belonging, and community.

My Abuelita is a free spirit whose unflinching resistance to discrimination is often misunderstood as truculence. As I pursue science to move myself and my family history forward together, it is my hope that I will someday come close to her humble survivorship and the resilience of the frontier generations that came before me.

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PHOTO: RAVEN DELFINA OTERO-SYMPHONY

Science

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