Indirect benefits are a crucial consideration when evaluating SARS-CoV-2 vaccine candidates

To the Editor — Public-health interventions aimed at curbing the spread of the coronavirus SARS-CoV-2 have been limited to non-pharmaceutical interventions, including travel restrictions, isolation, contact tracing and quarantine, mask wearing and social distancing, with variable success worldwide. These interventions have been critical to slowing the spread of the virus, but given their substantial societal, economic and political costs, alternative long-term solutions are needed. A vaccine remains the most promising one. Thanks to tremendous worldwide research efforts, vaccine development is well underway, with more than 50 novel vaccine candidates already in clinical trials.

Clinical trials evaluate the safety and efficacy of vaccine candidates. Licensed vaccines must provide a direct protective benefit to the vaccinee. The endpoint for SARS-CoV-2 vaccine trials is the prevention of COVID-19 disease. In addition to directly protecting a proportion of vaccinated people, vaccination programs can also indirectly reduce infection risk to all susceptible people[1], either by reducing the number of infected people in the population or by rendering breakthrough cases less infectious. Vaccinated people who later become infected may have less viral shedding, fewer symptoms or faster recovery time, all of which could reduce the risk of transmission to an uninfected person.

Quantifying the indirect effects of vaccination on population-level outcomes such as disease incidence and mortality usually requires evaluation after a vaccine has been in use for some time[2]. However, mathematical modeling can help researchers bridge this gap and assess population-level effects in advance in order to gauge whether a vaccine should be further considered, even if the direct protective effects are lower than desired. For example, modeling of vaccine-allocation strategies for pandemic influenza showed that increases in vaccine efficacy against infection support increased prioritization of vaccinating people in age groups other than those at greatest risk of mortality[3]. With a similar model, we have demonstrated that a vaccine that modestly reduces the risk of clinical disease, but greatly decreases infectiousness, can be more beneficial at the population level than a vaccine that prevents most symptomatic SARS-CoV-2 infections, but does little to reduce onward transmission[4]. Strategic monitoring and targeted data collection during clinical trials, and perhaps challenge studies, can improve model parameterization by providing relevant information about the effect of vaccination on the potential for onward transmission. Specifically, susceptibility to symptomatic infection versus asymptomatic infection, peak viral load and degree of viral shedding, as well as infection duration, can all be measured. Independently, such data do not suffice to predict the indirect effects of vaccines at the population level, but they can be incorporated into epidemiological models that can forecast possible outcomes.

The main drawbacks to collecting such data are the increase in time and resources required and the challenge of frequently testing and monitoring large numbers of participants. These data might be more easily collected in challenge studies than in clinical trials: fewer participants are required, and since the challenge time is known and the inoculum dose is controlled, measurements can be taken more reliably and differences between study arms may be more readily apparent. But in the absence of an effective treatment for COVID-19, human challenge studies assessing vaccine efficacy remain unlikely to be approved for ethical reasons, although some argue that the benefits can outweigh the costs[5]. The risk of serious adverse effects or death following experimental infection is typically deemed unacceptable for a person who would not otherwise be exposed. Challenge studies in animal models offer an alternative, despite likely considerable differences between humans and non-human primates in viral dynamics and infection. Two vaccine challenge studies in rhesus macaques have already shown that SARS-CoV-2 vaccines can be moderately successful in preventing disease[6,7]. In one of these studies, the vaccine candidate AZD1222 reduced viral load, which can reduce transmission potential; however, the vaccine did not reduce nasal shedding or eliminate infectious virus in all animals, which suggests that the potential for transmission may not be entirely averted by vaccination[6].

We argue that in parallel to assessing the efficacy and safety of vaccine candidates for individual recipients, research aimed at gauging indirect benefits is a critical area of investigation. In assessing vaccine candidates, it should be recognized that a vaccine can have a moderate primary failure rate but nonetheless serve to reduce infectiousness and onward transmission. The indirect effects of SARS-CoV-2 vaccines may be particularly crucial given the severity profile of COVID-19. The risk of hospitalization and mortality increases substantially with age, but vaccination of older people is often less effective due to immunosenescence. Furthermore, because of indirect effects, overall morbidity and mortality can be reduced even when vaccination coverage is modest, if the right groups are targeted[8]. This is a crucial consideration, given that extensive coverage will be a challenge due to insufficient initial supply, delays in infrastructure delivery scale-up, and vaccine hesitancy. Therefore, indirect effects are critically important to consider when evaluating SARS-CoV-2 vaccine candidates and formulating strategies for their rollout. ❐

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References

1. Halloran, M. E. & Struchiner, C. J. *Epidemiology* **2**, 331–338 (1991).
2. Orenstein, W. A. et al. *Bull. World Health Organ.* **63**, 1055–1068 (1985).
3. Medlock, J. & Galvani, A. P. *Science* **325**, 1705–1708 (2009).
4. Gallagher, M. E. et al. *medRxiv* https://doi.org/10.1101/2020.08.07.20170456 (2020).

5. Eyal, N., Lipsitch, M. & Smith, P. G. *J. Infect. Dis.* **221**, 1752–1756 (2020).
6. van Doremalen, N. et al. *Nature* **586**, 578–582 (2020).
7. Yu, J. et al. *Science* **369**, 806–811 (2020).
8. Eichner, M., Schwehm, M., Eichner, L. & Gerlier, L. *BMC Infect. Dis.* **17**, 308 (2017).

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Competing interests
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