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

Molly E. Gallagher[1*], Andrew J. Sieben[2], Kristin N. Nelson[3], Alicia N. M. Kraay[3], Walter A. Orenstein[4], Ben Lopman[3], Andreas Handel[5], Katia Koelle[1;6]

1. Department of Biology, Emory University, Atlanta, GA, USA. 2. School of Medicine, Emory University, Atlanta, GA, USA
3. Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA
4. Emory Vaccine Center, School of Medicine, Emory University, Atlanta, GA, USA
5. Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, GA, USA
6. Emory-UGA Center of Excellence of Influenza Research and Surveillance (CEIRS), Atlanta GA, USA
*Corresponding author e-mail: mgallagher@emory.edu

Public health interventions aimed at curbing the spread of SARS-CoV-2 have been limited to non-pharmaceutical interventions, including travel restrictions, isolation and quarantine, contact tracing, mask wearing, and social distancing, with variable success worldwide. These interventions have been critical to slowing viral spread, but given their substantial societal, economic, and political costs, 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 prevention of symptomatic COVID-19 disease. In addition to directly protecting vaccinated individuals, vaccination programs can also indirectly reduce infection risk among the unvaccinated [1], either by reducing the number of infected individuals in the population or by rendering breakthrough cases less infectious. Vaccinated individuals who later become infected may have reduced viral shedding, symptoms, or time to recovery, all of which could reduce the risk of transmission to an uninfected individual. 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 us to bridge these gaps 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, when the seasonal influenza vaccine is less effective than usual, it can still provide substantial community-level benefits [3]. This scenario is not perfectly comparable to a novel virus like SARS-CoV-2: influenza is endemic, with high levels of pre-existing immunity in the population. With a similar model we demonstrate that in a naïve population, a vaccine that modestly reduces infection risk, but greatly decreases infectiousness, can be more beneficial at the population level than a vaccine that prevents most symptomatic 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 design and parameterization. Susceptibility to symptomatic vs. asymptomatic infection, as determined by frequent testing, peak viral load and degree of viral shedding, severity of symptoms, and infection duration can all be measured and incorporated into mechanistic models. Together, these data and models can better inform our understanding of transmission potential and population-level effects.

The main drawbacks to this approach are the increase in time and resources required and the challenge of frequently testing and monitoring large numbers of participants. Challenge studies may be more feasible: fewer participants are required, and they can be completed faster, as there is no need to wait for incidental exposures to the virus. But in the absence of an effective treatment for COVID-19, human challenge studies of vaccines 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 to an individual who would not otherwise be exposed. Challenge studies in animal models offer an alternative, despite likely significant differences in viral dynamics and infection between humans and non-human primates. Two vaccine challenge studies in rhesus macaques were moderately successful in preventing disease and showed no evidence of antibody-dependent enhancement following vaccination [6, 7]. But despite reducing viral load, the vaccine candidate AZD1222 did not reduce nasal shedding or eliminate infectious virus in all vaccinated animals, suggesting the transmission potential from infected vaccinated individuals could remain high [6].

In parallel to assessing the efficacy and safety of vaccine candidates for individual recipients, we argue that research aimed at gauging indirect benefits is a critical area of investigation. In assessing vaccine candidates, we should recognize that a vaccine can have a moderate primary failure rate but serve to reduce infectiousness and onward transmission nonetheless. 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 significantly with age, but vaccination of older individuals 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 low initial supply, delays in infrastructure scale-up, and vaccine hesitancy. The vast majority of the global population remains susceptible to the virus and we are likely well below the herd immunity threshold. Therefore the indirect effects of vaccine candidates are critically important to consider when evaluating SARS-CoV-2 vaccine candidates and formulating strategies for their roll-out.

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