

# COVID-19 vaccine efficacy in a rapidly changing landscape

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The COVID-19 pandemic has presented new challenges to healthcare infrastructure, virology, vaccinology research, and implementation science. Misinformation concerning vaccines and non-pharmacologic measures to mitigate the spread of COVID-19 has made the study of vaccine efficacy extremely important for both transparency and accountability. The vaccines for COVID-19 were developed with urgency but without compromise of any safety or regulatory measures. They are undoubtedly the most efficacious means of disease mitigation we currently have available. As of this writing, 11.7 billion doses have been given worldwide, with 578 million in the USA alone.<sup>1</sup>

Unfortunately, due to the nature of the coronavirus, new variants continue to emerge. When dealing with a rapidly changing pathogen, it is essential to continuously review and update the known data, as manuscripts become outdated as soon as the first draft is written. In this issue of *Journal of Investigative Medicine*, Hirsh *et al*<sup>2</sup> reviewed the breakthrough COVID-19 infections in vaccination but emphasize the overwhelming effectiveness of the vaccines overall. The article cites the known efficacy of the mRNA vaccines as 95% against symptomatic infection in initial studies. Even with the advent of newer variants and their increased immune evasion, severe infections, hospitalization, and death are still much more common in the unvaccinated compared with the vaccinated population; however, this effect is diminished in the vaccinated cohort who are immunocompromised or more elderly. During the Delta and subsequent Omicron surges, this predominance of severe disease among the unvaccinated was repeatedly illustrated by the published illustrations from numerous hospitals showing the disproportionate number of unvaccinated patients admitted to the COVID-19 wards, critical care units, and on the ventilators.<sup>3</sup> The other benefits of vaccination, such as reduction in detectable viral load and reduction in contagious period, are more difficult to measure on a population-wide level.

Even as we write, the current variants of concern in the USA now include BA.2, which is quickly being outcompeted by BA.2.12.1.<sup>4</sup> Meanwhile, the WHO is tracking the rapid spread of BA.4 and BA.5 internationally, as well as its recent arrival in the USA.<sup>5</sup> With each

variant, the performance of the vaccination or native immunity is again called into question. Ongoing studies report that vaccine efficacy against the Omicron variant is maintained against severe disease, although to a lesser extent for symptomatic disease and infection among both mRNA and inactivated vaccines. However, these benefits are highly dependent on receipt of booster doses as well as time from vaccination.<sup>6</sup> There remains no consensus on the frequency or number of booster doses that will ultimately be required as these new variants appear. Recent data also suggest that fourth vaccine doses in the general population again offer improved protection against infection and severe disease compared with three doses.<sup>7</sup>

The issue of the waning immunity of the population, especially at the extremes of age, and the issue of vaccine availability to the very young or the disadvantaged continue to require further investigation and appropriate action. The United Nations estimates that only 1% of COVID-19 vaccines administered worldwide have been in developing countries.<sup>8</sup> This has far-reaching repercussions; the generation of variants, like in the mutation of the well-known pandemic virus, HIV, is directly related to the amount of uncontrolled viral replication that is allowed. More unvaccinated cohorts will allow the virus to replicate freely and increase the odds of forming new and potentially more virulent variants. This makes the issues of expanding availability and eligibility for vaccination of paramount importance. Humanity has been fortunate with maintained vaccine efficacy; although as a result, the other non-pharmacologic interventions to prevent COVID-19 spread have been dropped as the public perception of risk has decreased. This only increases the need for continued timely, quality, peer-reviewed data on which to base future public health decision-making. Whether there may yet be a variant which escapes the vaccine's curated antibodies and adversely impacts that risk calculation—only time will tell.

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