

## Vaccination for COVID-19: benchmarks in Public Health and virus transmission

Vaccines are arguably one of the most important disease prevention strategies in public health and are one of the pillars of our response to the ongoing crisis that is COVID-19. It is perhaps clichéd to say that “vaccines save lives”, but they do, and that is what they are designed to do. Whether they also prevent transmission is a more complex question, but one that has risen to the forefront of the COVID-19 response.

In this context, it is worth taking a step back and assessing other vaccines that impact public health, and their successes and limitations. Vaccines fall into two basic classes, often referred to as “killed” or “live-attenuated”<sup>1</sup>. For COVID-19, all the current vaccines and vaccine candidates fall—for safety reasons—into the “killed” category, generally as “subunit” or “vectored” vaccines; the risk of a live-attenuated virus (by reversion to virulence, or by recombination with a “live” virus) is deemed unacceptable. Traditional killed vaccines may be limited from an immunological perspective, but the new technologies of mRNA delivery or adenovirus-vectoring have yielded great benefits for vaccine efficacy in the case of COVID-19<sup>2</sup>.

The last major public health crisis where the impact of vaccines was indisputable was for poliomyelitis. In 1955, the inactivated (killed) poliovirus vaccine (IPV) developed by Salk was introduced, to be followed in 1961 by the Sabin live-attenuated oral poliovirus vaccine (OPV)<sup>3</sup>. The switch was in large part due to the higher efficacy of OPV vs. IPV; while IPV reduced central nervous system disease and paralysis it quickly became apparent that it did not prevent transmission. Because of this limitation, OPV became the backbone of the global polio eradication campaign. However, OPV carries the very rare risk of reversion to virulence, and once polio was effectively eliminated in many countries childhood immunization reverted back to the safer IPV; i.e. safety outdid efficacy as reducing transmission was deemed unimportant in these communities<sup>4</sup>.

A similar scenario applies to influenza—the “flu shot”. The backbone of current immunization schemes is a killed virus, that is “split” to form the subunit vaccine in widespread use<sup>5</sup>. The “flu shot” is designed to save lives, and it does, but unlike the live attenuated influenza vaccine “FluMist”, whether the subunit flu shot prevents spread in the wider community is less clear<sup>1</sup>. This is a

critical factor in how we currently approach vaccination for COVID-19. Based on current data all the available COVID-19 “subunit” vaccines will save lives, but they may well not prevent person-to-person transmission and spread in the community, and so strict adherence to other pillars of transmission reduction; i.e., masks and social distancing remain essential. Even if the evidence does eventually show a reduction in virus transmission, this reduction will only kick in after an individual’s immune system can respond and a booster is given; i.e., several months after the initial shot.

Eradication of a disease requires complete elimination of transmission. To date, smallpox is the only human disease that has been eradicated, through use of a live vaccine<sup>6</sup>. The initial stages of that eradication campaign bear striking parallels to the current state of COVID-19, with vaccine shortages playing a huge role early on. The ultimate success of smallpox eradication is attributed to a coordinated global compliance effort, although it took significant time to reach populations around the world<sup>1</sup>. While eradication of COVID-19 is not a goal, the rapid development of vaccines will play a major role in containing the current pandemic.

While there is much to celebrate with the warp speed timeline of COVID-19 vaccine development, now is not the time to let our guard down<sup>7,8</sup>. The vast majority of the population is not vaccinated, and manufacturing, distribution and acceptance remains a serious challenge even in Western countries. It should also be remembered that clinical trials can only go so far in terms of the diversity of the population that can be recruited and the timescale over which data can be collected. The real figures will only come from real-world vaccination. Countries such as Israel that have led the way in population-level immunization will be key to this<sup>9</sup>, but even there the critical data will only arrive after a frustratingly long period, and efficacy may well be derailed if viral variants emerge that circumvent the immunological pressure from the population that widespread vaccination will undoubtedly bring. Until that time, public trust and understanding, and strict adherence to mask-wearing and social distancing need to remain cornerstones of the COVID-19 response.

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