Nasally delivered SARS-CoV2 vaccine shows future promise

In *The Lancet Respiratory Medicine*, Fengcai Zhu and colleagues report the efficacy of a novel mucosal vaccine, as 23-55% dependent on vaccination status, as measured by protection against PCR-confirmed symptomatic SARS-CoV2 infection. The vaccine is a replication deficient H1N1 influenza virus vector carrying the RNA sequence for an ancestral SARS-CoV2 receptor-binding domain (RBD) that was delivered by intranasal inhalation via an atomiser spray.

Conducting an efficacy trial two years after the start of the pandemic presents several challenges. The numbers of previously exposed participants (either previously undiagnosed or asymptomatic SARS-CoV2 infection) will be greater. The lateral flow antibody test used, will be of limited use due to the reported reduced sensitivity for responses against newer SARS-CoV2 variants. Its sensitivity will be further compromised by the natural waning of antibody response post-infection.

It is difficult to compare directly the efficacy of protection of this vaccine against the efficacy of established intramuscular vaccines tested originally in naïve individuals, not only because of a change in serostatus of the target population, but also a change in circulating variant – in this case, the predominant circulating variant was the more transmissible Omicron variant. Increased pre-existing immunity to SARS-CoV2, either via viral exposure or vaccination, and insufficient trial size will have contributed in tandem to the fact that there were insufficient numbers of severe SARS-CoV2 infection to judge efficacy against severe disease.

The results of the trial failed to reach the pre-specified criterion for success (>30% efficacy against symptomatic infection). However, the level of protection offered by this vaccine appears broadly similar to the levels of protection afforded by intramuscular booster vaccination programmes, as reported by population efficacy studies during the Omicron era (1). Within the context of a population that has had greater exposure to SARS-CoV2 and with the majority of infections being due to the Omicron variant, this suggests that this mucosal vaccine might be comparable in effect to intramuscular booster vaccination.

This influenza virus vectored vaccine shares some similarities with another SARS-CoV2 mucosally delivered vaccine in development – Ad5 nCoV, an aerosolised orally inhaled replication-deficient adenovirus type-5 vectored vaccine encoding the SARS-CoV-2 spike protein (2–4). Both these vaccine candidates are vectored by replication deficient viral backbones, but there are some notable differences in design, delivery and immunogenicity. This influenza virus vectored vaccine uses the sequence for RBD as the immunogen. The adenovirus mucosal vaccine, in comparison, along with the most commonly used and successful intramuscular vaccines, use the sequence for whole spike protein. There is also a difference in the mucosal delivery system. This influenza virus vectored vaccine is administered to the nasal mucosa using an atomiser spray, whereas the adenovirus vectored vaccine is delivered by aersolised inhalation, which presumably has more chance of reaching the mucosa of the lower respiratory tract.

The immunological differences are perhaps even more dramatic (Zhu et al., 2022) . The aerosolised adenovirus vaccine induces a robust systemic neutralising humoral and cellular response as well as a significant mucosal secretory IgA response, although this mucosal response appears relatively short-lived. In comparison, the influenza virus-vectored vaccine described in this edition of the Lancet Respiratory Medicine has a much more modest rate of both seroconversion and ‘mucoconversion’ – a concept that may need further refining as this field of mucosal vaccinology develops.

One may argue, that the measured immune response is irrelevant in the context of demonstrated efficacy (albeit a relatively low level of efficacy with the caveats mentioned above). However, the story may not be so straightforward for future pathogens. It is still unclear what immune mechanism offers protection from severe SARS-CoV2 disease. Future mucosal vaccine candidates might offer protection against symptomatic infection, but a potential concern is whether vaccines that produce limited detectable systemic immune responses also provide protection against severe disease and death. If protection against symptomatic disease wanes over time, is the vaccine recipient left open to the possibility of severe illness once their immunity wanes to such a level that they can develop clinical illness?

There is a lot of anticipation surrounding the development of mucosally delivered vaccines and their potential impact. It is clear that intramuscular SARS-CoV2 vaccines can reduce transmission in the short term (6) and it is an attractive thought that a vaccine delivered at the portal of infectious entry, might have greater potential at transmission blocking. Currently, however, evidence for this is lacking, and this study does not add significantly to the hope that mucosal vaccination might, in the future, be better than intramuscular vaccination.

In the absence of clear protection against severe disease in a seronegative population, the results of this trial need to be taken cautiously. There is precedent that a mucosally delivered vaccine, such as the live-attenuated influenza vaccine can be just as efficacious as intramuscular vaccines at preventing illness in children (7), but it is not clear that this benefit is realised across all age groups (8). Mucosal vaccines might be a more acceptable needle-free alternative, especially to those who are needle-phobic, and they have the potential to facilitate rapid deployment in a future pandemic setting. However, ultimately, our understanding of mucosal immunity and how to augment it through immunisation remains with many deficits and further work is required to better understand the mucosal immune response both to infection and vaccination.

The author declared no conflicts of interest

1. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. New England Journal of Medicine [Internet]. 2022 Apr 21 [cited 2023 Oct 12];386(16):1532–46. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2119451
2. Li JX, Hou LH, Gou JB, Yin ZD, Wu SP, Wang FZ, et al. Safety, immunogenicity and protection of heterologous boost with an aerosolised Ad5-nCoV after two-dose inactivated COVID-19 vaccines in adults: a multicentre, open-label phase 3 trial. Lancet Infect Dis [Internet]. 2023 Oct 1 [cited 2023 Oct 10];23(10):1143–52. Available from: http://www.thelancet.com/article/S147330992300350X/fulltext
3. Li JX, Wu SP, Guo XL, Tang R, Huang BY, Chen XQ, et al. Safety and immunogenicity of heterologous boost immunisation with an orally administered aerosolised Ad5-nCoV after two-dose priming with an inactivated SARS-CoV-2 vaccine in Chinese adults: a randomised, open-label, single-centre trial. Lancet Respir Med. 2022 Aug 1;10(8):739–48.
4. Wu S, Huang J, Zhang Z, Wu J, Zhang J, Hu H, et al. Safety, tolerability, and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults: preliminary report of an open-label and randomised phase 1 clinical trial. Lancet Infect Dis. 2021 Dec 1;21(12):1654–64.
5. Zhu F, Zhuang C, Chu K, Zhang L, Zhao H, Huang S, et al. Safety and immunogenicity of a live-attenuated influenza virus vector-based intranasal SARS-CoV-2 vaccine in adults: randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Respir Med [Internet]. 2022 Aug 1 [cited 2023 Oct 10];10(8):749–60. Available from: http://www.thelancet.com/article/S221326002200131X/fulltext

6. Eyre DW, Taylor D, Purver M, Chapman D, Fowler T, Pouwels KB, et al. Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants. New England Journal of Medicine [Internet]. 2022 Feb 24 [cited 2023 Jan 22];386(8):744–56. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa2116597
7. Belshe RB, Edwards KM, Vesikari T, Black S V., Walker RE, Hultquist M, et al. Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children. New England Journal of Medicine [Internet]. 2007 Feb 15 [cited 2023 Oct 12];356(7):685–96. Available from: https://www.nejm.org/doi/10.1056/NEJMoa065368
8. Monto AS, Ohmit SE, Petrie JG, Johnson E, Truscon R, Teich E, et al. Comparative Efficacy of Inactivated and Live Attenuated Influenza Vaccines. New England Journal of Medicine [Internet]. 2009 Sep 24 [cited 2023 Oct 12];361(13):1260–7. Available from: https://www.nejm.org/doi/10.1056/NEJMoa0808652