Cite as: Topol and Iwasaki, *Sci. Immunol.* 10.1126/sciimmunol.add9947 (2022).

CORONAVIRUS

Operation Nasal Vaccine—Lightning speed to counter COVID-19

Eric J. Topol[1*] and Akiko Iwasaki[2, 3*]

[1]Scripps Research, La Jolla, CA [2]Department of Immunobiology, Yale University School of Medicine, New Haven CT [3]Howard Hughes Medical Institute, Chevy Chase, MD

***Corresponding author. Email: etopol@scripps.edu (E.J.T.); akiko.iwasaki@yale.edu (A.I.)**

Just 10 months after the initial genome sequencing of the SARS-CoV-2 virus, two mRNA vaccines were demonstrated to provide 95% efficacy against symptomatic infections via randomized, placebo-controlled trials of more than 74,000 participants (*1*). That unprecedented success was, in part, fueled by the $10 billion governmental investment in Operation Warp Speed (OWS) in March 2020 to accelerate the development, manufacturing, and distribution of COVID-19-19 vaccines. We urgently need such an accelerated initiative now for nasal vaccines.

During the first year of the pandemic, meaningful evolution of the virus was slow-paced, without any functional consequences, but since that time we have seen a succession of important variants of concern, with increasing transmissibility and immune evasion, culminating in the Omicron lineages. With that, there has been a dramatic falloff in the capacity for vaccinations and booster shots to block infections and transmission (*2*). A major unmet clinical need has arisen to block the transmission chain, prevent the frequent breakthrough infections, and achieve high levels of durable protection against severe disease, no less prevent post-acute sequelae of SARS-CoV-2 infection (PASC, Long COVID-19).

That has spotlighted the possibility of nasal vaccines, with their allure for achieving mucosal immunity, complementing, and likely bolstering the circulating immunity achieved via intramuscular shots. A new report by Tang and colleagues (*3*) sheds considerable light on the shortcomings of mRNA vaccines for not achieving respiratory mucosal immunity against Omicron in people, while also showing how well this can be accomplished with a nasal vaccine in mice.

Beyond the conventional parameters of circulating antibodies, B and T cell immunity in the blood, this elegant study assessed bronchoalveolar lavage (BAL) fluid immunity to specifically characterize the lower respiratory mucosa, tissue-resident memory B and T cells that are part and parcel of protection. In the human part of the study, 19 vaccinated participants were compared with 10 who had convalesced from COVID-19 and 5 who were unvaccinated. Notably, the mean age of the participants was 70 years and similar for the three groups. The vaccinated group, despite having comparable circulating neutralizing antibodies against D614G, delta, and omicron variants, had significantly lower neutralizing titers against all variants in the BAL compared to the convalescent group. Moreover, the vaccinated group had substantially fewer BAL tissue-resident spike-specific memory CD4 T, CD8 T, and RBD-specific memory B cells than the group with prior COVID-19. These observations are an important addition to other studies that have reported superior mucosal (saliva) antibodies in those with prior COVID-19 than vaccinated individuals (*4*) and the establishment of tissue-resident T cells for up to 6 months after infection (*5*).

In the mouse model experiments, a booster dose consisting of intramuscular mRNA, intranasal recombinant spike trimer protein plus cGAMP adjuvant (a STING agonist) or intranasal adenovirus-vector encoding the ancestral spike (AD5-S) was administered to mice previously vaccinated with 2 doses of intramuscular mRNA vaccine shots. Only weak neutralizing antibodies were induced in the BAL by intramuscular shots and nasal spike trimer + cGAMP, in contrast to very high levels when AD5-S was administered nasally. This was true against both the ancestral strain and the Omicron BA.1.1 lineage. Supporting the mucosal immunity achieved via intranasal delivery there were marked increases in the BAL of S-1 and RBD-specific IgA levels and tissue-resident T cell immunity after nasal booster with recombinant spike or AD5-S. Similar findings of elevated mucosal IgA and tissue-resident memory cells were reported after an unadjuvanted recombinant spike protein nasal booster strategy following mRNA prime (*6*).

These are noteworthy and timely findings at a point in the pandemic with substantial attrition in the ability of current vaccines to reduce infections and transmission. The variant-chasing strategy of an Omicron BA.1 specific or multivalent vaccine, which took more than 7 months to develop and validate after BA.1 was found to be spreading in South Africa, is not likely to provide a remedy for this problem. Even BA.5 specific vaccines that may be available by the end of 2022 will likely be obsolete by that time, outcompeted by new variants. Beyond that fundamental concern, the new findings by Tang and colleagues, strongly point to the defect of relying on intramuscular shots alone—they do not provide tissue-level mucosal immunity. The only path to achieve this will be via

nasal or orally administered vaccines.

Fortunately, there are at least 12 nasal vaccines that are in clinical development and four have reached Phase 3 randomized, placebo-controlled trials (*4*): 3 are viral vector (Bharat Biotech, Codagenix and Beijing Wantal Biological), using a recombinant spike protein or receptor-binding domain or a live, attenuated virus; a 4th is a protein subunit vaccine (Razi Vaccine and Serum Research Institute). Of these, Codagenix has announced positive results via a press release (*7*) of a strong cellular immune and mucosal antibody response versus Omicron BA.2 and that this vaccine will be incorporated in the World Health Organization multicenter clinical trial network. While only in Phase 1 currently, the Astra Zeneca vaccine (ChADOx1/AZD1222) was assessed in macaques and hamsters, inducing a robust mucosal response to the D614G variant with a better humoral response via intranasal delivery than intramuscular (*8*).

The potential for broad sarbecovirus protection via intranasal nonadjuvanted spike subunit protein vaccination after a varying interval (days to months) following clinically approved intramuscular mRNA vaccine shots, what has been called "prime and spike," showed proof of concept in the mouse model eliciting strong protective mucosal immunity via CD8+ and CD4+, memory T cells, memory B cells and IgA that significantly lowered viral load in the upper and lower airways, and prevented disease and death from a lethal SARS-CoV-2 challenge (*6*).

Despite these encouraging data, we fully recognize the challenges of validating a clinically effective and safe nasal vaccine for which there has been limited success in the past. FluMist, reformulated in 2018, is the only intranasal vaccine approved by the Food and Drug Administration. While it is now quadrivalent and has efficacy comparable to flu shots (which is moderate at best), the approval population is limited (for example, not for age 50 years and older, and excludes immunocompromised and pregnant people). But in many ways influenza represents a different and more formidable challenge than SARS-CoV-2, with the hypermutating feature of its hemagglutinin head and immune evasion propensity of its stem. Recall that COVID-19 vaccines had an initial efficacy of 95% against symptomatic infections and severe disease, a level never approximated by flu shots. The gradient of high efficacy of the nirmatrelvir/ritonavir (Paxlovid) to SARS-CoV-2 to relatively low efficacy of oseltamivir (Tamiflu) for influenza is noteworthy. These are indicators that point to SARS-CoV-2's higher vulnerability for both prevention of infections and success of therapy if we act on time.

The early and striking success of the initial COVID-19 vaccines led many to believe that this shot strategy would ultimately achieve global containment. Had the virus not evolved to its current strains, that might have been possible. But now we have a global surge of Omicron BA.5 that is occurring, in large part, because of our inability to block infections and transmission. Even a pan-sarbecovirus or pan-β-coronavirus vaccine, which we fully support should be pursued, will be unlikely, as a shot, to achieve a high and durable level of mucosal immunity. At the same time the totality of the evidence for nasal vaccines, reinforced by the findings of Tang *et al.*, supports this path to patch up our "leaky" vaccines. Despite the lack of any governmental support for intranasal vaccines, there has been steady but substantive progress with multiple candidates in late-stage clinical trials. The likelihood that at least one of these nasal vaccine programs will be successful is high, but the lack of an OWS-like push means there will be substantial delays in manufacturing at scale, regulatory approval, and distribution.

As the virus continues its accelerated ability to evade our immune response and increase its transmissibility, we urgently need to achieve population-wide respiratory mucosal immunity. The objective of breaking the chain of transmission at the individual and population level will put us in a far better position to achieve containment of the virus, no less reducing the toll of sickness and long COVID-19. The prospect of achieving this with nasal vaccines is high, but will only be possible with dedicated funding, priority, and breaking down of any regulatory hurdles. While we have waited far too long to take such initiative, a new operation at lightning speed could help us get ahead of the virus and build on the initial success of COVID-19 vaccines.

REFERENCES AND NOTES

1. E. J. Topol, Messenger RNA vaccines against SARS-CoV-2. *Cell* **184**, 1401 (2021). doi:10.1016/j.cell.2020.12.039 Medline
2. R. Link-Gelles, M. E. Levy, M. Gaglani, S. A. Irving, M. Stockwell, K. Dascomb, M. B. DeSilva, S. E. Reese, I.-C. Liao, T. C. Ong, S. J. Grannis, C. McEvoy, P. Patel, N. P. Klein, E. Hartmann, E. Stenehjem, K. Natarajan, A. L. Naleway, K. Murthy, S. Rao, B. E. Dixon, A. B. Kharbanda, A. Akinseye, M. Dickerson, N. Lewis, N. Grisel, J. Han, M. A. Barron, W. F. Fadel, M. M. Dunne, K. Goddard, J. Arndorfer, D. Konatham, N. R. Valvi, J. C. Currey, B. Fireman, C. Raiyani, O. Zerbo, C. Sloan-Aagard, S. W. Ball, M. G. Thompson, M. W. Tenforde, Effectiveness of 2, 3, and 4 COVID-19 mRNA Vaccine Doses Among Immunocompetent Adults During Periods when SARS-CoV-2 Omicron BA.1 and BA.2/BA.2.12.1 Sublineages Predominated — VISION Network, 10 States, December 2021–June 2022. *MMWR Morb. Mortal. Wkly. Rep.* **71**, (2022). doi:10.15585/mmwr.mm7129e1
3. J. Tang, C. Zeng, T. M. Cox, C. Li, Y. M. Son, I. S. Cheon, Y. Wu, S. Behl, J. J. Taylor, R. Chakraborty, A. J. Johnson, D. N. Schiavo, J. P. Utz, J. S. Reisenauer, D. E. Midthun, J. J. Mullon, E. S. Edell, M. G. Alameh, L. Borish, W. G. Teague, M. H. Kaplan, D. Weissman, R. Kern, H. Hu, R. Vassallo, S.-L. Liu, J. Sun, Respiratory mucosal immunity against SARS-CoV-2 following mRNA vaccination. *Sci. Immunol.* eadd4853 (2022). doi:10.1126/sciimmunol.add4853
4. S. Sheikh-Mohamed *et al*., *Mucosal Immunol.* (2022).
5. M. M. Poon, K. Rybinka, Y. Kato, *Sci. Immunol.* (2021).
6. T. Mao *et al*., bioRxiv 2022; https://www.biorxiv.org/content/10.1101/2022.01.24.477597v1
7. Codagenix press release, https://codagenix.com/codagenix-intranasal-COVID-19-vaccine-shows-potent-cellular-immune-response-against-conserved-viral-proteins-indicating-potential-for-immunogenicity-against-omicron-and-future-variants-in-phase-1-dat/
8. N. van Doremalen, J. N. Purushotham, J. E. Schulz, M. G. Holbrook, T. Bushmaker, A. Carmody, J. R. Port, C. K. Yinda, A. Okumura, G. Saturday, F. Amanat, F. Krammer, P. W. Hanley, B. J. Smith, J. Lovaglio, S. L. Anzick, K. Barbian, C.

Martens, S. C. Gilbert, T. Lambe, V. J. Munster, Intranasal ChAdOx1 nCoV-19/AZD1222 vaccination reduces viral shedding after SARS-CoV-2 D614G challenge in preclinical models. *Sci. Transl. Med.* **13**, eabh0755 (2021). doi:10.1126/scitranslmed.abh0755 Medline

Conflicts of interest: EJT does not have any conflicts to disclose. AI is a cofounder of RIGImmune and Xanadu Bio, is a consultant for 4BIO, BlueWillow Biologics, Healthspan Technologies, Revelar Biotherapeutics, Paratus Sciences, RIGImmune and Xanadu Bio, and is listed as an inventor on patent applications relating to intranasal SARS-CoV-2 vaccines.

Published First Release 21 July 2022
10.1126/sciimmunol.add9947

Science Immunology

Operation Nasal Vaccine—Lightning speed to counter COVID-19

Eric J. TopolAkiko Iwasaki

Sci. Immunol., **Ahead of Print** • DOI: 10.1126/sciimmunol.add9947

Science Immunology (ISSN) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science Immunology* is a registered trademark of AAAS.