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## Intranasal SARS-CoV-2 Vaccines: Indispensable and Inevitable



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Their extraordinary efficacy notwithstanding, the parenterally administered mRNA vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have proven incapable of preventing breakthrough infections in otherwise fully vaccinated subjects.<sup>1</sup> Interpersonal transmission of SARS-CoV-2 through respiratory droplets and aerosols by fully vaccinated subjects has also proven resistant to vaccine-induced immunity.<sup>1</sup> These relative shortcomings of the parenterally administered mRNA vaccines are hardly unanticipated because upper airway protection against SARS-CoV-2 replication and shedding requires local mucosal rather than systemic humoral immunity.<sup>2</sup> Mucosal protection would entail a secretory IgA antibody response replete with tissue-resident CD4<sup>+</sup> helper T cells and CD8<sup>+</sup> cytotoxic T lymphocytes.<sup>2</sup> Intranasal SARS-CoV-2 vaccines offer the potential to produce such a response, thereby preventing breakthrough infections, diminishing person-to-person transmission, and reducing ongoing viral multiplication and mutation.<sup>3–5</sup> In this article, the authors review the import of mucosal immunity, explore current intranasal SARS-CoV-2 vaccine candidates, and discuss the significance of added upper airway protection to the moderation of the coronavirus disease 2019 (COVID-19) pandemic.

The introduction of intramuscular mRNA vaccines against SARS-CoV-2 in record time will go down in the annals of medicine and public health as one of the greatest medical achievements of all time. Although they have been critical in restraining the impact of COVID-19, the mRNA vaccines against SARS-CoV-2 have a number of relative shortcomings. Among their drawbacks is their waning effectiveness, which necessitates booster programs.<sup>1</sup> Other drawbacks include the persistence of breakthrough infections and of ongoing person-to-person transmission through respiratory droplets.<sup>1</sup> These latter observations indicate the absence of adaptive mucosal immunity in the nasopharyngeal region in otherwise fully vaccinated subjects.<sup>2</sup> Addressing these limitations by the development and deployment of

intranasal SARS-CoV-2 vaccine should be viewed as an imperative. Preliminary experimental evidence in support of the feasibility of such an undertaking is in hand.<sup>3–5</sup>

The mucosal immune system is by some measures the most prominent component of the immune apparatus.<sup>2</sup> The quantity of secretory IgA antibodies that is produced by the mucosal immune system far exceeds that of all the other immunoglobulin isotypes combined.<sup>2</sup> The IgA antibody class stands out further by dint of its resistance to proteases, which renders it uniquely suited to function in mucosal secretions.<sup>2</sup> Although heavily reliant on the tonsils and the adenoids (i.e., Waldeyer's ring), the mucosal immune system of the upper respiratory tract encompasses the entire nasopharynx.<sup>2</sup> Intranasal vaccination against SARS-CoV-2 could thus add a local mucosal immune dimension to the containment of the virus at its principal site of entry. It is in this site that secretory IgA antibodies along with tissue-resident CD4<sup>+</sup> helper T cells and CD8<sup>+</sup> cytotoxic T lymphocytes stand to arrest potential incursions of SARS-CoV-2.<sup>2,3</sup>

At the time of this writing, intranasal vaccines approved for clinical use remain a rarity. A sole, live, attenuated, intranasal influenza vaccine (FluMist Quadrivalent) in the form of a nasal spray is currently available and approved for use in healthy nonpregnant subjects aged  $\geq 50$  years. An intranasal SARS-CoV-2 vaccine of Cuban origin was afforded emergency authorization in Cuba, Venezuela, and Vietnam.<sup>3</sup> In addition, a total of 11 intranasal SARS-CoV-2 vaccine candidates are presently the subject of early clinical trials.<sup>6</sup> Seven of

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these intranasal vaccine candidates deploy live attenuated influenza virus, parainfluenza virus, respiratory syncytial virus, Newcastle disease virus, or an adenovirus as their lead vector.<sup>6</sup> Two other intranasal vaccine candidates deploy simian adenovirus vectors heretofore unencountered by humans.<sup>6</sup> Yet, another intranasal vaccine candidate is making use of the adenovirus type 5 vector.<sup>6</sup> A candidate vaccine developed at the Gamely Research Institute of the Russian Federation utilizes a combined vector approach. The COVI-VAC vaccine, developed by Codagenix, Inc., is unique in its use of a live, attenuated SARS-CoV-2 virus. The other vaccines utilize either the SARS-CoV-2 spike host receptor protein or its receptor-binding domain.<sup>6</sup> Both antigens have been shown in preclinical studies to generate long-lived virus-neutralizing antibodies in the respiratory tract of nonhuman primates.<sup>7</sup> Whether or not use will be made of any of the earlier-mentioned intranasal SARS-CoV-2 vaccine candidates on a large population scale remains to be seen. Glaringly absent from the earlier-mentioned listing of intranasal SARS-CoV-2 vaccine candidates are intranasal mRNA vaccines against SARS-CoV-2. Preclinical evidence in support of the feasibility of an intranasal mRNA vaccine (against tuberculosis) was first reported more than a decade ago.<sup>8</sup>

Herd immunity is a state of collective immunity wherein interpersonal infectivity is at a nadir.<sup>9</sup> It is at this point that SARS-CoV-2-positive subjects infect <1 other susceptible individual.<sup>9</sup> Achieving this desired equilibrium in a large, open, globally connected, yet-to-be fully immunized society is beset by ongoing vaccine hesitancy on the part of SARS-CoV-2 naïve as well as recovered individuals.<sup>9</sup> The exercise of populist expediency by policymakers stands in the way as well.<sup>9</sup> Additional obstacles to the attainment of herd immunity include the long and highly infectious incubation period of SARS-CoV-2, the emergence of novel SARS-CoV-2 variants, and the waning of immunity of SARS-CoV-2 vaccines and natural infection.<sup>9</sup> One area in which a modicum of progress toward herd immunity could be made is in the prevention of breakthrough infections and of interpersonal transmission in otherwise fully vaccinated subjects.<sup>1</sup> It is here that user-friendly (needle-free) intranasal SARS-CoV-2 vaccines could enhance mucosal immunity and thus reduce COVID-19 morbidity and mortality.

At present, it seems unlikely that SARS-CoV-2 will be eradicated. Instead, breakthrough infections and person-to-person transmission are likely to result in a state of cohabitation with the virus. Although their efficacy is far from certain, intranasal SARS-CoV-2 vaccines offer the potential to markedly ameliorate this state of affairs. Relevant authorities worldwide, led by the WHO, would do well to pool their resources to accelerate the clinical trials of intranasal vaccine candidates. Failure to do so stands to prolong the pandemic and delay its potential transition to an endemic phase. Inaction is not an option.

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