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SARS-CoV-2 Vaccines: The Mucosal Immunity Imperative



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The incessant continuance of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is attributable, in part, to ongoing viral residence, replication, and mutation within the upper airways of not only unvaccinated but also vaccinated individuals. It is this exposed portal of viral entry that gives rise to breakthrough infections as well as to ongoing interpersonal transmission. None of this is unanticipated in that the current, parenterally administered SARS-CoV-2 vaccines engender effective humoral (IgG-dominated) immunity but only limited mucosal (secretory IgA-dominated) immunity.¹ A new generation of intranasal, mucosal immunity-inducing SARS-CoV-2 vaccines could potentially reverse this state of affairs. Early clinical trials to this very end are presently underway. It is also possible that all-out protection from SARS-CoV-2 will require the concurrent or sequential delivery of both parenteral and intranasal vaccines. In this *Perspective*, we review the potential benefit of mucosal immunity-inducing SARS-CoV-2 vaccines, explore recent developments in this arena, and discuss the potential impact thereof on the course of the ongoing pandemic.

The current parenterally administered SARS-CoV-2 vaccines are remarkable for their effectiveness in reducing the likelihood of hospitalization and in-hospital death. However, their capacity to prevent breakthrough infections remains limited, a deficiency that appears to be related to the limited mucosal immune (IgA) response elicited by the parenteral vaccines.² These realities are consistent with the observation that parenterally administered SARS-CoV-2 vaccines give rise to prominent increments in the circulating levels of IgG antibodies

against the SARS-CoV-2 receptor-binding domain (RBD) and spike protein (SP) while parallel increments in the circulating levels of IgM and IgA counterparts have proven far more modest.³ Although a modicum of SARS-CoV-2-specific IgA activity was detected in nasal and salivary secretions after the parenteral administration of the mRNA-BNT162b2 SARS-CoV-2 vaccine, it appears that the degree of local mucosal protection afforded by most parenterally administered SARS-CoV-2 vaccines does not rise to a level that is clinically relevant.⁴ The mRNA vaccines in current use are capable of producing a mucosal IgG response, but current evidence suggests that it is the IgA response that is required to prevent breakthrough infections and their related communal spread. It follows that vaccine-mediated all-out protection against SARS-CoV-2, one comprising both systemic IgG and mucosal IgA responses, has yet to materialize.

The limitations ascribed to the current parenterally administered SARS-CoV-2 vaccines are hardly novel. Similar challenges have plagued the parenterally administered vaccines for the prevention of pertussis, or whooping cough. Indeed, vaccines directed against *Bordetella pertussis*, not unlike their SARS-CoV-2 counterparts, failed to bring about mucosal immunity capable of preventing infection or communal transmission. Notably, both SARS-CoV-2 and *B. pertussis* are restricted to the respiratory tract. Dissemination of either pathogen beyond the airway epithelium is rarely encountered. It therefore stands to reason that durable protection of the airways from either *B. pertussis* or SARS-CoV-2 may well require intranasal, mucosal immunity-inducing vaccines. Recent developments appear consonant with this presumption. The intranasal

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administration of a live attenuated *B. pertussis* vaccine (BPZE1) to nonhuman primates proved strongly protective against a challenge by a highly virulent *B. pertussis* isolate.⁵ Moreover, early phase 2b clinical trials of intranasally administered BPZE1 gave rise to durable mucosal immunity.⁵ However, the consequent prevention of *B. pertussis* transmission and pertussis disease is less than certain. A similar situation pertains to the intranasal live attenuated influenza vaccine (brand name in the United States, FluMist Quadrivalent) that was first approved in 2003. The vaccine showed a significant loss of effectiveness between 2013 and 2016, leading the Centers for Disease Control and Prevention to suspend the recommendation for its use. The recommendation was reinstated for the 2018-2019 influenza season, when the reformulated vaccine was shown to be as effective as the parenterally administered vaccine. There are no data currently available to indicate that its ability to attenuate spread of the virus is superior to that of the parentally administered vaccine.

Evidence in support of the effectiveness of intranasal vaccination against SARS-CoV-2 has thus far been derived from studies in several animal species. Two recent reports indicate that intranasal administration of recombinant RBD of the SARS-CoV-2 SP to mice can elicit a robust mucosal immune response that persisted long term. In 1 case, the intranasal vaccine was administered as a booster after parenteral prevaccination.⁶ In the second case, administration was to unvaccinated mice.⁷ In both cases, effectiveness extended to neutralization of the Omicron variant. Particularly compelling are additional studies in hamsters that have found the ability of mucosal (intranasal or oral) vaccine administration to prevent animal-to-animal transmission.^{8,9} These findings are consistent with the established role of mucosal immunity in preventing viral entry and replication.¹

Whereas intranasally administered SARS-CoV-2 vaccines have the potential to reduce viral transmission, demonstration of such effectiveness will have to await the final

outcome of the ongoing clinical trials,¹⁰ a number of which are proceeding rapidly across several continents.¹⁰ The Center for Genetic Engineering and Biotechnology of Cuba is concluding clinical trials of an intranasal vaccine (CIBG-669) aimed at the SARS-CoV-2 RBD. Bharat Biotech International of India and the University of Hong Kong are advancing intranasal vaccines (BBV154 and DeINS1-nCoV-RBD LAIV) aimed at the SARS-CoV-2 RBD and SP, respectively. The University of Oxford (in collaboration with AstraZeneca) and Intravacc (Bilthoven, The Netherlands), for their part, are pursuing similarly targeted intranasal SARS-CoV-2 vaccines (ChAdOx1-S and CovOMV). US-based Altimmune, Meissa Vaccines, Codagenix, and Tetherex are heavily invested as well in the development of distinct intranasal SARS-CoV-2 vaccines (AdCOVID, MV-014-212, COVI-VAC, and SC-Ad6-1). In a departure from the aforementioned trials, the Laboratorio Avimex of Mexico and the Icahn School of Medicine at Mount Sinai are exploring the utility of dual parenteral and intranasal administration of SARS-CoV-2 vaccines (AVX/COVID-12 and NDV-HXP-S, respectively).

The above notwithstanding, consideration must also be given to the induction of mucosal immunity by parenterally administered SARS-CoV-2 vaccines. A compelling illustration of such functionality was afforded by Corbett et al¹¹ in the course of assessing the utility of the mRNA-1273 SARS-CoV-2 vaccine in nonhuman primates. The authors make note of the fact that “no viral replication was detectable in the nose” of any of the vaccinated animals in the wake of an upper airway challenge with SARS-CoV-2.¹² Similar results were previously reported for the mouse model, wherein parenterally administered mRNA-1273 was found to “protect against SARS-CoV-2 infection ... in the nose” as evident from the absence of any discernible immunopathologic changes.⁷ These reports stand out as apparent exceptions to an otherwise extensive body of observations wherein the parenteral vaccination route appears to have failed to engender mucosal immunity.¹ Taken together, these

observations lead one to conclude that mucosal immunity, as distinct from systemic immunity against SARS-CoV-2, represents a “neglected but critical aspect of SARS-CoV-2 infection.”¹

Indications are that mucosal immunity should be emphasized in the development of future SARS-CoV-2 vaccines. It follows that future vaccination efforts could well focus on intranasal SARS-CoV-2 vaccines as an effective stand-alone approach or as an adjunct to their parenteral counterparts. Should intranasal vaccination prove effective in the absence of parenteral vaccination, the process of needle-free immunization could be carried out by lay personnel. Ideally suited for children, intranasal vaccines are bound to be welcome by the public at large as well. The same could be said for the developing world, wherein the logistic challenges of distribution and administration of parenterally administered vaccines have been difficult to surmount. Polio, after all, was all but eradicated worldwide courtesy of markedly simplified oral rather than parenteral vaccine administration. Whereas comparable predictions for the SARS-CoV-2 pandemic may be premature, a renewed focus on mucosal immunity appears paramount. It is in this context that intranasal vaccines could well fill a void heretofore unattended to.

CONCLUSION

The SARS-CoV-2 parenteral vaccines currently in use, although highly effective at preventing hospitalization, severe disease, and death, are limited in their ability to prevent breakthrough infections and disease transmission. This is likely a consequence of their relative inability to induce mucosal immunity. This limitation of the parenteral vaccines can best be overcome by the development and implementation of an effective intranasal vaccine, one that could serve as either a stand-alone vaccine or an adjunct to parenteral vaccination.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

Abbreviations and Acronyms: RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SP, spike protein

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