International Journal of Dermatology

Reminiscence

COVID-19 vaccination challenge: history lessons from a dermatologist's perspective

Diego Fernandez-Nieto, MD, Daniel Ortega-Quijano, MD, Juan Jimenez-Cauhe, MD, Patricia Burgos-Blasco, MD and Sonia Bea-Ardebol, MD, PhD

Dermatology Department, Ramon y Cajal University Hospital, Madrid, Spain

Correspondence
Sonia Bea-Ardebol, MD, PhD
Dermatology Department
Ramon y Cajal University Hospital
Carretera Colmenar Viejo km 9.100
28034 Madrid
Spain
Email: soniabeaardebol@gmail.com

Conflict of interest: None.

Funding source: None.

doi: 10.1111/ijd.15449

Dear Editor,

The Coronavirus Disease 2019 (COVID-19) pandemic has caused a major health crisis, deeply transforming health care systems worldwide. Closely related severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV) were the cause of two previous epidemics starting in 2002 and 2011, respectively. Even if almost two decades have passed, there are no approved vaccines nor specific antiviral treatments for these viruses.

SARS-CoV-2 clinical research has become a race against time. Several vaccination trials are underway, based on previous knowledge from SARS-CoV and MERS-CoV investigations.[1] Not only classical attenuated, inactivated, and protein subunit vaccines are under development but also modern DNA, mRNA, and recombinant viral vectored vaccines, which may enhance immune responses.[2] There is a complex relation between immunogenicity and safety concerns, that have previously hampered the development of SARS-CoV/MERS-CoV vaccines.[3]

In this constantly evolving globalized world, there are some lessons from prevaccination times which can be considered for modern-day challenges, including variolation administration routes and elicited immune responses. Like smallpox, COVID-19 can also induce vesicular "varicella-like" rashes.[4–6] However, the presence of viral particles has not been identified inside the vesicles, so a potential SARS-CoV-2 variolation appears unfeasible.[6]

Variolation, also known as inoculation, was the first method used to immunize an individual against smallpox. It induced a usually mild form of the disease with a rapid onset. Mortality rate was estimated to be 2–3% compared to 20–30% from an ordinary infection.[7] The earliest documented writing about variolation dates from 1549 in China. However, it is thought that this practice has been performed since ancient times in both China and India, as a mixture of medicine, magic, and religion with an oral transmission.

The Chinese implemented a method of nasal insufflation. Mild smallpox cases were selected as donors, whose dry scabs were ground into powder or mixed with a variety of herbs. This "pocky matter" was carried at body temperature for a month or exposed to hot steam before its use. It was then inoculated up the nose with a silver blowpipe.[7]

The nasal route for immunization is considered as a straightforward approach to induce potent immune responses, particularly at the lung mucosa.[8] Experimental SARS-CoV/MERS-CoV vaccines led to attractive correlates of protection, even higher than those achieved by parenteral vaccines.[9] This type of mucosal immunization has proven to induce specific SARS-CoV secretory IgA production in both the upper respiratory tract and lungs.[10] Major challenges for mucosal vaccines include the requirement of higher antigen doses, the need for effective and safe mucosal adjuvants, and the difficulties to elicit significant immune responses, as the default response is tolerance, especially toward soluble or subunit antigens. AdCOVID, an intranasal

adenovirus-vectored vaccine encoding the receptor binding domain (RBD) of the SARS-CoV-2 spike protein, has recently proven to elicit the induction of mucosal IgA serum neutralizing antibodies,[11] promoting both systemic and local mucosal immunity.

India is an alternative to China for the origin of variolation. The Indian subcutaneous method is very similar to the Ottoman technique, which was later transmitted to Europe in the 18th century by Lady Mary Wortley Montague, the wife of a British diplomat in Constantinople. It involved puncturing the skin in a small circle, usually on the upper arm, with a needle contaminated with scabs or pustules.

The skin is also an ideal target for immunization, because of its rich population of antigen-presenting cells, including dermal dendritic cells and mast cells, which favor the induction of a potent and durable adaptive immunity.[12] Compared to subcutaneous needle injections, intracutaneous delivery strategies, such as microneedle arrays (MNA), can elicit stronger and longer-lasting antigen-specific antibody responses. The production of MNA SARS-CoV-2 vaccines is currently underway.[8]

Although variolation has ceased, it has deeply influenced immunology and even modern-day society. "Pox parties", or in the present case, "COVID-19 parties", are social activities where people, especially children, are deliberately exposed to an infectious disease by a close contact with mildly symptomatic patients. These practices are highly discouraged in favor of vaccination, as they suppose a major public health concern with associated life-threatening complications and a risk of uncontrolled disease spreading.

The application of vaccination by Edward Jenner was safer for patients and their contacts than variolation, since it used material from cowpox (heterotypic vaccine). A hypothetical inoculation of the "common cold" HCoV-NL63 coronavirus would lead to mild symptoms and could also provide a cross-reactive immunity, like Jenner's vaccine. Even if the use of scabs from COVID-19 patients to inoculate them intranasally or transdermally is not feasible, the knowledge of variolation and its immunologic pathways is still the foundation for vaccine development. In the words of existentialist philosopher Søren Kierkegaard, *"Life can only be understood backwards, but it must be lived forwards"*.

References

1 Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020; **38**: 1–9. https://doi.org/10.12932/AP-200220-0772

2 Maruggi G, Zhang C, Li J, *et al*. mRNA as a transformative technology for vaccine development to control infectious diseases. *Mol Ther J Am Soc Gene Ther* 2019; **27**: 757–772. https://doi.org/10.1016/j.ymthe.2019.01.020

3 Caddy S. Developing a vaccine for covid-19. *BMJ* 2020; **369**: m1790. https://doi.org/10.1136/bmj.m1790

4 Galván Casas C, Català A, Carretero Hernández G, *et al*. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol* 2020; **183**: 71–77. https://doi.org/10.1111/bjd.19163

5 Marzano AV, Genovese G, Fabbrocini G, *et al*. Varicella-like exanthem as a specific COVID-19-associated skin manifestation: Multicenter case series of 22 patients. *J Am Acad Dermatol* 2020; **83**: 280–285. https://doi.org/10.1016/j.jaad.2020.04.044

6 Fernandez-Nieto D, Ortega-Quijano D, Jimenez-Cauhe J, *et al*. Clinical and histological characterization of vesicular COVID-19 rashes: a prospective study in a tertiary care hospital. *Clin Exp Dermatol* 2020; **45**: 872–875. https://doi.org/10.1111/ced.14277

7 Boylston A. The origins of inoculation. *J R Soc Med* 2012; **105**: 309–313. https://doi.org/10.1258/jrsm.2012.12k044

8 Marasini N, Kaminskas LM. Subunit-based mucosal vaccine delivery systems for pulmonary delivery - Are they feasible? *Drug Dev Ind Pharm* 2019; **45**: 882–894. https://doi.org/10.1080/03639045.2019.1583758

9 Lobaina MY. Nasal route for vaccine and drug delivery: features and current opportunities. *Int J Pharm* 2019; **572**: 118813. https://doi.org/10.1016/j.ijpharm.2019.118813

10 Lu B, Huang Y, Huang L, *et al*. Effect of mucosal and systemic immunization with virus-like particles of severe acute respiratory syndrome coronavirus in mice. *Immunology* 2010; **130**: 254–261. https://doi.org/10.1111/j.1365-2567.2010.03231.x

11 King RG, Silva-Sanchez A, Peel JN, *et al*. Single-dose intranasal administration of AdCOVID elicits systemic and mucosal immunity against SARS-CoV-2 in mice. *BioRxiv Prepr Serv Biol* 2020. [Epub ahead of print]. https://doi.org/10.1101/2020.10.10.331348

12 Kabashima K, Honda T, Ginhoux F, *et al*. The immunological anatomy of the skin. *Nat Rev Immunol* 2019; **19**: 19–30. https://doi.org/10.1038/s41577-018-0084-5