OPEN ACCESS

PERSPECTIVE

The Innovation

Advocating mucosal immunization: A global need in a viewpoint from China

Diana Boraschi,[1,2,3,4,11,*] Rita Carsetti,[5,11] Ling Chen,[6,7,11] Aldo Tagliabue,[1,8,11] Anthony T. Tan,[9,11] and Bin Wang[10,11]

[1]Shenzhen Institutes of Advanced Technology, Shenzhen 518055, China

[2]Shenzhen University of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China

[3]Institute of Biomolecular Chemistry, National Research Council, 80078 Pozzuoli, Italy

[4]Anton Dohrn Zoological Station, 80122 Napoli, Italy

[5]Immunology Research Area, B Lymphocyte Research Unit, Bambino Gesù Children's Hospital IRCCS, 00165 Roma, Italy

[6]State Key Laboratory of Respiratory Diseases, Guangzhou National Laboratory, Guangzhou 510530, China

[7]Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou 510530, China

[8]Institute of Biomedical Technologies, National Research Council, 20054 Segrate, Italy

[9]Emerging Infectious Diseases Programme, Duke-NUS Medical School, Singapore 169857, Singapore

[10]School of Basic Medical Sciences, Fudan University, Shanghai 200032, China

[11]These authors contributed equally

*Correspondence: diana.boraschi@gmail.com

Received: January 12, 2025; Accepted: May 12, 2025; Published Online: May 16, 2025; https://doi.org/10.1016/j.xinn.2025.100951

Citation: Boraschi D., Carsetti R., Chen L., et al., (2025). Advocating mucosal immunization: A global need in a viewpoint from China. The Innovation **6(10)**, 100951.

Human mucosal immunization is expected to afford protection against infection and reduce transmission by generating anti-infective immunity at the mucosal entry site of viruses and bacteria. Nasal or oral administration has the advantage of being needle free and self-administered, thereby improving compliance and coverage of large populations. In China, the experience of COVID-19 has promoted substantial efforts in the development of nasal vaccinations in the general health protection strategy. The hurdles we are facing in the development of mucosal vaccines, however, come from the still limited knowledge of the mechanisms controlling mucosal immunity in different anatomical locations and in response to different pathogens/vaccines. Identifying and filling the knowledge gaps in order to develop effective and safe mucosal immunization strategies requires global collaboration, not only at the scientific level but, most importantly, by engaging public and private health organizations, governments, and regulatory authorities. We have highlighted here some of the crucial issues in mucosal immunization and provided suggestions for the way forward toward a global preparedness effort to prevent infectious diseases and ensure vaccine equity.

INTRODUCTION: WHY DO WE NEED MUCOSAL VACCINES?

Vaccination is an effective tool for preventing infectious diseases and is also becoming particularly important because of new health emergencies caused by antimicrobial resistance and pandemic infections.

The first immunization practice in the world was by a mucosal route, the old and widely used variolation in China, dating back over 1,000 years, performed by blowing powdered smallpox scabs into the nostrils. The vaccines currently on the market are, however, almost all injectable and are based on the activation of systemic immunity. The application of new technologies (mRNA and adenoviral vectors) was fast forwarded by the global pandemic emergency of SARS-CoV-2. Vaccines were generated worldwide using both new and conventional technologies (e.g., inactivated and protein subunit vaccines) and rapidly approved for emergency use by regulatory authorities. All first-generation COVID-19 vaccines were administered via intramuscular injection and were effective against severe disease, but none were effective in preventing infection and transmission. Thus, the World Health Organization (WHO) established a new target product profile for COVID-19 vaccines that included the desirability of mucosal vaccines able to block infection and transmission.

Mucosal immunization has the advantage of easy administration, even self-administration at home. Avoiding the use of needles also increases acceptance and decreases vaccine hesitancy. The WHO, the Gates Foundation, and the Program for Appropriate Technology in Health (PATH) are all pushing for the development of mucosal immunization strategies that can be applied in a rapid fashion to a large population in the effort for preparedness and use in less developed countries. In China, about 50 companies have vaccines on the market, and several of them have started the development of mucosal vaccines. China needs to protect a very large population distributed across different geographical and economic/social contexts, and mucosal vaccines may become the preferred goal for domestic vaccination programs. Problems and difficulties in developing highly effective and fully safe mucosal vaccines and immunization protocols come from the fact that immunologists are still engaged in attaining a better understanding of the peculiarities of mucosal immunity (Figure 1).[1]

The following is the personal view of a small group of international immunologists and vaccinologists with first-hand knowledge of the Chinese vaccine scenario. All of us vouch for a collaboration beyond borders to rapidly fill the current gaps in our basic knowledge of mucosal immunity and enable us to design effective and safe mucosal vaccines. This will help to not only solve country-specific hurdles in large-scale vaccination coverage but also efficiently tackle the global need for life-saving vaccines and epidemic preparedness and reach vaccine equity. Since solving the scientific hurdles is just the first step, we strongly call for an active and global engagement of governments, regulatory authorities, funding agencies, and companies in the effort toward protecting human health at a global level.

STATE OF THE ART

Only a few of the vaccines currently on the market are delivered via mucosal routes, including the only nasal vaccine based on a live-attenuated influenza virus (e.g., FluMist), and a number of oral vaccines, for rotavirus (e.g., RotaTeq and Rotarix), cholera (e.g., Dukoral, Shanchol, and Vaxchora), and the oral polio vaccine based on live-attenuated poliovirus that is still used in some developing countries.[1] These mucosal vaccines have provided huge benefits to people in both developed and developing countries. The fact that only a few mucosal vaccines are currently licensed is most likely due to our limited knowledge of mucosal immunity, which acts and is controlled in peculiar ways. Hereafter, some of the most important issues that we need to address are listed.

Mucosal surfaces are functional barriers that should not be damaged

Mucosae are the interface between our body and the external environment and represent an active barrier constantly faced with microbes. In addition to mechanical and chemical barriers (mucus, surfactant, and antimicrobial peptides), the mucosal tissues include a large number of immune cells that ensure tissue protection. To maintain their functions (respiration and nutrient adsorption), mucosae must establish a virtuous balance with the external environment. Thus, the mucosal immune system adopts a number of tolerance-like mechanisms that prevent constant inflammation in the presence of microbiota and other conventional external agents.[1] The main challenge in mucosal immunization is

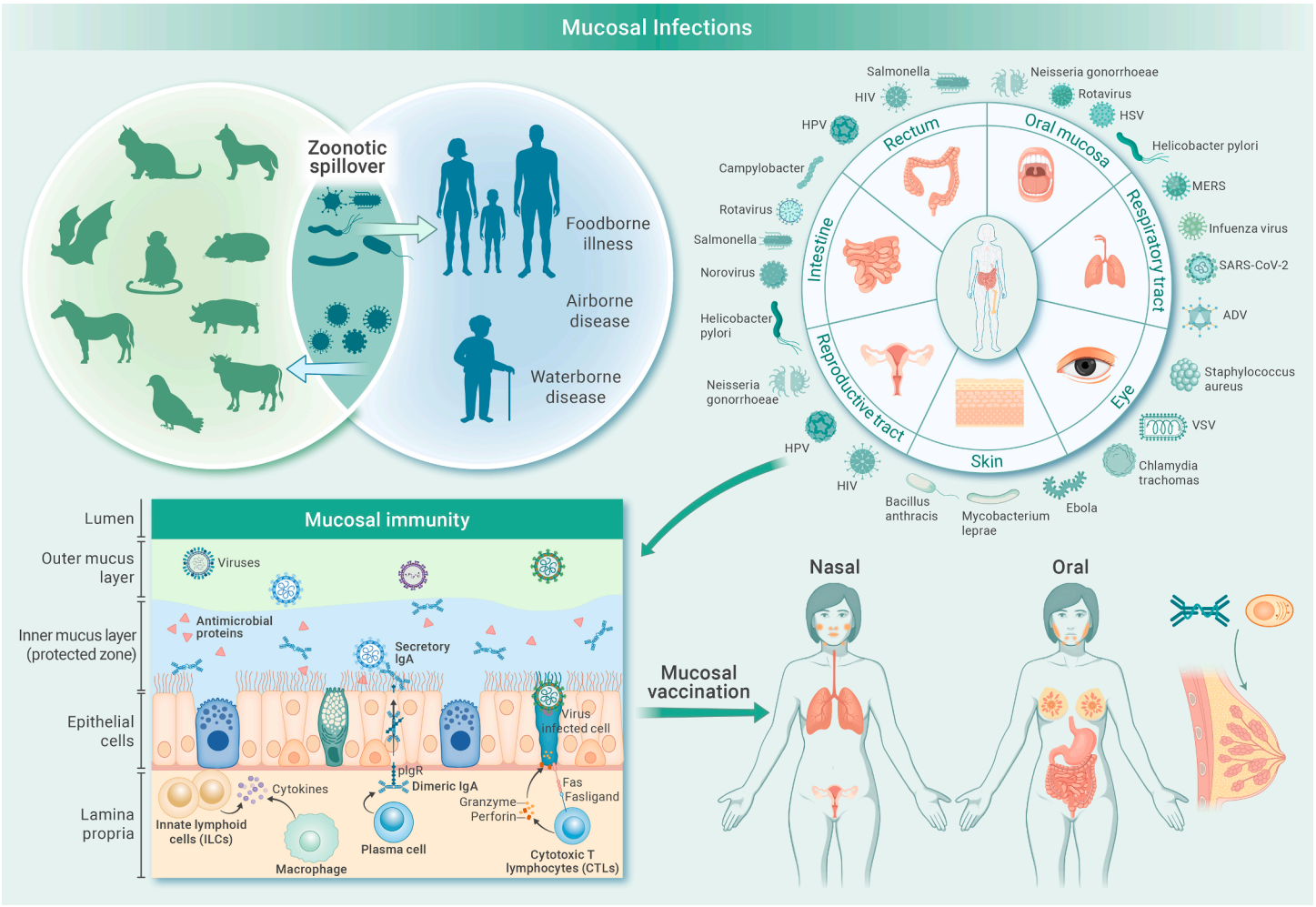

Figure 1. Mucosal infections and mucosal immunization Mucosal infections in human beings are caused by several different pathogens, many of which can come from zoonotic spillover and cross-infection, promoted by close interactions with domestic, feral, and livestock animals (top left). Different mucosal and barrier tissues in the human body are selectively targeted by different viral and bacterial pathogens (top right). Mucosal immunity has specific mechanisms that are active at the interface with the external environment, mainly encompassing secretory IgA and antimicrobial peptides in the inner mucus layer at the epithelial surface, in addition to innate and adaptive immune mechanisms in the lamina propria (bottom left). Mucosal vaccination drives long-term protection by triggering the local immune mechanisms at the mucosal barriers: nasal vaccination generates protective immunity in the upper and lower respiratory tracts, including IgA in the salivary and nasal secretions, as well as in the genital-vaginal tract; oral immunization triggers immunity in salivary glands and the entire gastrointestinal tract and in the mammary glands, in which sIgA is produced that acts as passive immunization for babies during breastfeeding (bottom right). ADV, adenovirus; HIV, human immunodeficiency virus; HPV, human papilloma virus; HSV, herpes simplex virus; MERS, Middle East respiratory syndrome virus; pIgR, polymeric immunoglobulin receptor; VSV, vesicular stomatitis virus.

bypassing the barrier/tolerance and initiating a protective immune reaction while at the same time avoiding disrupting the mucosal defensive and trophic functions.

Mucosal immunity differs from systemic immunity

Conventional intramuscular vaccines elicit systemic adaptive immune responses, with antibodies and memory B and T cells in the circulation. Protection mediated by systemic immunity, however, does not prevent infection at mucosal sites.[2] Immunity at the mucosal level is key for blocking respiratory infections at their entry site, thereby maintaining respiratory functions and preventing the diffusion of the pathogens to adjacent tissues like the olfactory epithelium and brain. Recent characterization of immunity in the human nasal cavity has illustrated the unique composition of immune cells in this compartment.[2] In this tract, ciliated epithelial cells and mucus represent the first barrier that, in the case of infection, activates innate immune/inflammatory pathways.[3] However, despite accumulating information, the mechanisms by which an adaptive immune response and memory are triggered and maintained at the mucosal level are still largely understudied.

Mucosa-associated immune mechanisms are anatomically different

In each mucosal tract, the components of the immune barriers differ in the distribution of antibody isotypes (secretory immunoglobulin A [IgA] vs. IgG) and T cells, in addition to the different mucosal tissue architecture and function. Effective immunization in the different mucosal tracts requires knowing the local immunological characteristics, anatomy, physiological functions, and microenvironmental conditions (e.g., composition and velocity of the flux, associated microbiota, influence of the tissue-specific autonomous nervous system, etc.). However, mucosal immune compartmentalization and cross-talk are still poorly understood.

sIgA is the most important antibody isotype in mucosae

IgA is the predominant antibody isotype present at mucosal surfaces.[4] Secretory IgA (sIgA) is a dimer composed of two IgA antibodies linked by a joining chain. It is produced locally and transported through epithelial cells via the polymeric Ig receptor before being released at the mucosal surface. Due to its dimeric structure, sIgA possesses four antigen-binding sites, which enhance its avidity compared to monomeric antibodies, allowing it to bind a broad range of antigens. This unique feature plays a crucial role in preventing infections caused by both known and emerging pathogens.[4,5] Mucosal sIgA can be 1–2 orders of magnitude more effective than systemic IgG and IgA in neutralizing pathogens and blocking infection at the apical surface of the mucosa.[5] Additionally, because of its transport mechanism, sIgA can neutralize intracellular pathogens within mucosal epithelial cells. This capacity allows IgA to target non-surface and non-structural viral components, potentially inhibiting viral replication in the early stages of infection.

Protective mucosal immunity varies by pathogen

Protective mucosal immunity exploits different mechanisms depending on the infective agent. For rapidly infective agents such as respiratory viruses, high levels of pre-existing sIgA are crucial to neutralize them quickly at the mucosal surfaces and prevent infection, while classical cytotoxic T cells clear the virus-infected cells that escaped antibody neutralization. Persistent protective immunity (e.g., consistently high antibody levels) is also necessary to protect against rapidly toxic bacteria such as *Bordetella pertussis*, whereas for many other pathogens the establishment of systemic immune memory is often sufficient, and less energetically costly, for optimal protection.

Mucosal immunization must consider the specific tissue context

An effective mucosal immunization strategy must be considered in the context of the specific tissue in which it takes place. Mucosal immunization can "prime" epithelial cells and fibroblasts,[6] in addition to innate and adaptive immune cells, and consequently induce a multifactorial defensive reaction and memory. The influence of the tissue microenvironment, e.g., cellular, molecular, mechanical, and chemical cues, can shape the generation of both protective immunity and immunological memory. Particular attention should be paid to the potent tissue-specific control of immune responses performed by the autonomous nervous system.[7]

Mucosal immunization may induce immune memory with broad spectrum

Inducing a protective response against a broad range of pathogens is one of the key elements for improving vaccine efficacy. As previously mentioned, the enhanced avidity of dimeric and polymeric sIgA allows for binding antigens more effectively than monomeric IgG and IgA, although the affinity for individual epitopes may be relatively low. This mechanism promotes the cross-recognition of new pathogens and broadens the protective efficacy of sIgA. To increase cross-protection, mucosal vaccines can also take advantage of the abundant presence in the mucosal tissues of innate immune cells, which can be primed and activated by the vaccine. Several cases have been reported of vaccination against respiratory infections inducing protection against other antigenically unrelated respiratory pathogens, thereby suggesting the establishment of a non-specific broadly protective innate immune memory.[8]

Mucosal immunization may generate a durable protective immune response

Depending on the pathogen, mucosal immunization strategies aim at attaining durable protective immunity (i.e., constantly high immunity, such as mucosal sIgA levels) or generating long-term adaptive and innate immune memory (i.e., long-lasting capacity to mount a more rapid and efficient response to new infections). In both cases, attaining durable protection implies a thorough design of immunization protocols: type and dose of vaccine and adjuvant, number of administrations, delivery systems and platforms, and administration routes and schedules, all tailored based on the characteristics of the pathogen and the type of desired response (protective immunity vs. long-lasting memory).

Live-attenuated vaccines must balance the immune responses and side effects

Live-attenuated vaccines are the best platform for obtaining a strong and long-lasting immune memory since they reproduce the original infectious agent in its shape, composition, and cross-talk with mucosal professional and non-professional immune cells. The safety risks of live-attenuated vaccines can be eliminated by engineering vaccine microorganisms with mutated/suicidal genes that limit replication, as in the case of the oral Ty21a typhoid vaccine. Viral vector vaccines represent a good alternative, as they at least partially establish the bidirectional host-pathogen interaction required for attaining efficient immunization.

Developing safe adjuvants is critical for controlling side effects and efficacy of subunit mucosal vaccines

Avoiding inflammatory side effects requires deeper knowledge of the immune mechanisms at the mucosal surface. A localized inflammatory reaction is at the basis of effective immunization, but it should be controlled in order to avoid tissue damage. The use of mucus-penetrating/muco-adhesive platforms and mucosal adjuvants must consider the risk posed by breaching protective barriers and inducing inflammation in particular mucosal locations, as in the case of Bell's palsy caused by the nasal LT adjuvant. Adjuvants based on molecules displayed by the pathogenic agents, as for instance bacterial flagellin or microbial oligonucleotides, can provide adequate non-specific stimulation for amplifying the adaptive immune response and generating long-lasting protective innate memory.

Mucosal correlates of protection are different from those for parenteral vaccines

Correlates of protection are still a major unsolved problem for all vaccines. Also, those for mucosal immunization may substantially differ from those currently used for parenteral vaccines, such as, for instance, the neutralizing antibody titer in blood. Different correlates may predict different levels of protection, e.g., protection from infection severity and death vs. block of infection and transmission. In addition, correlates of protection may vary depending on the pathogen and the vaccine. A key correlate of protection in the case of respiratory viruses is the nasal level of sIgA.[5] A "protective threshold" for sIgA against infection can be established to predict the risk of infection following natural infection or nasal vaccination.

THE WAY FORWARD

Although this is the opinion of a small group of scientists working in China, it is shared by colleagues across the world and becomes a global opinion advocating for intense collaboration without borders. We have identified the following urgent issues to be addressed.

Advocating more intense studies on mucosal immunity

This is the stepping stone for the design of knowledge-based, effective, durable, and safer mucosal immunization strategies. More intense research implies strong financial support from governments and funding agencies, in view of the importance of fundamental studies for the implementation of broader health protection policies.

Implementing global partnerships

Studies on mucosal immunization should rely on collaboration across countries and between academic and industrial partners. Collaboration should be strongly encouraged, as it will lead to faster results with a more efficient use of resources by reducing duplicative efforts.

Prioritizing human studies

Mice are not humans. Human challenge studies are an invaluable tool for reliably assessing vaccine efficacy and delivery strategies, as recently demonstrated for new intranasal pertussis vaccines.[9] Although some regulatory hurdles and ethical concerns still need to be solved, human challenge studies would advance vaccine development without the need for clinical trials as well as facilitate the identification of predictive correlates of protection.

Optimizing mucosal vaccination strategies for women of child-bearing age to protect mother and child

Vaccination must be strongly recommended for women planning a pregnancy and during pregnancy. Maternal immunity protects the newborn from infection through the transplacental passage of IgG antibodies and the transfer of IgA and IgG via colostrum and breast milk, a process known as passive immunization. In the future, mucosal vaccines could not only protect the mother from infection but also enhance the protective function of breastfeeding. The role of breastfeeding may be even more critical than previously understood, as antigen and immune complexes in breast milk can stimulate the neonatal immune response at mucosal sites, potentially acting as a true mucosal vaccine.[10]

Support from regulatory authorities to accelerate approval

Regulators license vaccines based on their actual performance in clinical trials. In order to align the approval criteria with the rapid developments in knowledge and technologies, it would be necessary to accelerate the amending and updating of standards and regulations for the evaluation of the safety and efficacy of mucosal vaccines. A substantial step forward would be the acceptance of human challenge studies for vaccine licensing.

Aiming at One Health

The effort toward human mucosal vaccines must include a global effort for limiting the spillover of infections from animal reservoirs. Vaccinating/monitoring domestic animals and reducing contact with feral animals may help to limit the spillover. It is notable that many of the veterinary vaccines used for domestic and farm animals are mucosal vaccines.

CONCLUSION

By advocating for mucosal immunization as a strategy for blocking infection and transmission, including the respiratory infectious disease X of the future, we want to underline the reasons for recommending it, i.e., their efficacy in blocking infection and transmission and the possibility of rapidly vaccinating large populations in a fast and easy way. To obtain knowledge-based, effective, and fully safe mucosal vaccines, we have identified several of the conceptual and scientific gaps that we must fill. Eventually, we want to vouch for a supranational, multilevel cooperation effort that engages not only scientists but, most importantly, governments, funding agencies, and regulatory authorities. We aim to contribute to the United Nations' Sustainable Development Goals "good health and well-being" and "partnership for the goals" and, as a consequence of improving health and human life conditions, the final SDG, "peace, justice and strong institutions."

FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Gates Foundation (INV-059115) and the Alliance of International Science Organizations (ANSO-CR-KP-2022-01) and was partly supported by the National Natural Science Foundation of China (92469301). The funding sources had no role in the preparation of this manuscript. We are especially thankful to Lance Rodewald of the Chinese Center for Disease Control and Prevention, who offered his expertise in revising and implementing the concepts put forward in our manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Tsai, C.J.Y., Loh, J.M.S., Fujihashi, K. et al. (2023). Mucosal vaccination: onward and upward. *Expert Rev. Vaccines* **22**:885–899. DOI:https://doi.org/10.1080/14760584.2023.2268724.
2. Lim, J.M.E., Tan, A.T., Le Bert, N. et al. (2022). SARS-CoV-2 breakthrough infection in vaccinees induces virus-specific nasal-resident CD8+ and CD4+ T cells of broad specificity. *J. Exp. Med.* **219**:e20220780. DOI:https://doi.org/10.1084/jem.20220780.
3. Parker, D. and Prince, A. (2011). Innate immunity in the respiratory epithelium. *Am. J. Respir. Cell Mol. Biol.* **45**:189–201. DOI:https://doi.org/10.1165/rcmb.2011-0011RT.
4. Macpherson, A.J., McCoy, K.D., Johansen, F.E. et al. (2008). The immune geography of IgA induction and function. *Mucosal Immunol.* **1**:11–22. DOI:https://doi.org/10.1038/mi.2007.6.
5. Chen, S., Zhang, Z., Wang, Q. et al. (2024). Intranasal adenovirus-vectored Omicron vaccine induced nasal immunoglobulin A has superior neutralizing potency than serum antibodies. *Signal Transduct. Targeted Ther.* **9**:190. DOI:https://doi.org/10.1038/s41392-024-01906-0.
6. Yang, J. and Yan, H. (2021). Mucosal epithelial cells: the initial sentinels and responders controlling and regulating immune responses to viral infections. *Cell. Mol. Immunol.* **18**:1628–1630. DOI:https://doi.org/10.1038/s41423-021-00650-7.
7. Schiller, M., Ben-Shaanan, T.L. and Rolls, A. (2021). Neuronal regulation of immunity: Why, how and where? *Nat. Rev. Immunol.* **21**:20–36. DOI:https://doi.org/10.1038/s41577-020-0387-1.
8. Aaby, P., Netea, M.G. and Benn, C.S. (2023). Beneficial non-specific effects of live vaccines against COVID-19 and other unrelated infections. *Lancet Infect. Dis.* **23**:e34–e42. DOI:https://doi.org/10.1016/S1473-3099(22)00498-4.
9. de Graaf, H., Ibrahim, M., Hill, A.R. et al. (2020). Controlled human infection with *Bordetella pertussis* induces asymptomatic immunizing colonization. *Clin. Infect. Dis.* **71**:403–411. DOI:https://doi.org/10.1093/cid/ciz840.
10. van den Elsen, L.W.J., Kollmann, T.R. and Verhasselt, V. (2022). Microbial antigen in human milk: A natural vaccine? *Mucosal Immunol.* **15**:1058–1059. DOI:https://doi.org/10.1038/s41385-022-00561-4.