Microbial antigen in human milk: a natural vaccine?

Lieke W. J. van den Elsen1,2, Tobias R. Kollmann2 and Valerie Verhasselt1,2✉

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Infants are at high risk for infectious diseases, which account for over one third of deaths in children under 5 years of age. Improving the effectiveness of vaccines, which have limited success in the first weeks of life, is important for better protection of this vulnerable population. One overlooked avenue to help achieve long-term protection from infectious disease is newborn immunization through breast milk. Here we bring forward a new paradigm where imbibing microbial antigen-containing milk is akin to the process of vaccination, which captures the act of vaccine delivery. Bioactive agents in milk have potential to function as adjuvants, enhancing the infant’s immune response against an antigen. The infant’s immune response to the human milk containing microbial antigens with adjuvant molecules is the equivalent of immunization, resulting in less susceptibility to disease.

Human milk is known to be the most potent way to prevent respiratory and gastro-intestinal infections. This major impact is attributed to its high content in a wide array of anti-infective compounds such as maternal antibodies, lactoferrin and human milk oligosaccharides. These factors provide invaluable help for compounds such as maternal antibodies, lactoferrin and human milk oligosaccharides. These factors provide invaluable help for the developing immune system and can kill pathogens, inhibit their proliferation or prevent invasion of the mucosa of the developing immune system and can kill pathogens, inhibit their proliferation or prevent invasion of the mucosa.

HOW CAN ANTIGEN IN BREAST MILK EFFECTIVELY VACCINATE CHILDREN?

A few studies shed light on the possible ways breast milk vaccination may work and provide the optimal route to activate the newborn’s immune system (Fig. 1).

The very low amounts of antigens in human milk may fit the specific requirements for activation of the developing immune system. Neonates mount an efficient cytotoxic immune response to a viral dose 10,000 times lower than an adult, while higher doses are unable to activate an appropriate immune response. The levels of Plasmodium falciparum antigen histidine-rich protein 2 and hepatitis B e antigen are 10-100-fold lower, and hepatitis B surface antigens are 30,000 times lower in human milk than in serum. These low levels may be an important cue for the developing immune system of the neonate.

Exogenous proteins in human milk are pre-digested within the mammary gland. This process might be key for the generation of immunogenic peptides. As the newborn has only limited digestive abilities, predigesting pathogen-specific proteins in breast milk may be important for the newborn to generate a long-lasting and protective response.

The presence of both maternal pathogen-specific antibodies and pathogens in breast milk highly suggests the presence of pathogen antigen-immune complexes. Antigen-IgG antibody immune complexes improve the transport of pathogen across the gut barrier using the neonatal Fc receptor and enhance the stimulation of effector immune responses by antigen-presenting cells.

Antigen-presenting cells present in milk might play a role in the induction of a pathogen-specific immune response. Interestingly, the proportion of leucocytes in human milk increases upon maternal infection, which may increase pathogen-derived antigen presentation by milk antigen-presenting cells. Human milk extracellular vesicles also express major histocompatibility...
complex molecules, which could contribute to the induction of antigen-specific immune responses in breastfed infants. Finally, microbes and microbial antigens in breast milk are surrounded by thousands of immune modulatory factors. The breast milk milieu contains molecules including antibodies and enzymes that can alter, weaken or reduce the viability of microbes present in the milk. This could lead to the generation of live attenuated pathogens that are fit to immunize the infant without infecting them. Among the bioactive compounds in breast milk are also potential strong adjuvants such as cytokines, the milk microbiota, soluble CD14 and Toll-like receptors. The complex and dynamic composition of breast milk may have specifically been selected for and adapted to the newborn’s situation, in order to effectively promote immune defence upon microbial antigen transfer in the milk.

CONCLUSION
Rather than merely a potential vehicle for transmission of disease, breast milk likely acts as a route that activates the neonatal immune system to mount a protective, long-lasting response. Very few studies have considered that pathogens and their antigens in human milk may immunise offspring. Further research is required to conclusively establish whether and how human milk from infected or vaccinated mothers can immunise their offspring. Studies demonstrating active immunization of newborns through breastfeeding have important implications for maternal and child vaccination protocols. The knowledge can be used to develop infant-tailored, mucosal vaccines with an appropriate dose, adjuvant and form of the antigen for the developing immune system to react. In addition, maternal interventions to improve active immunization of newborns through breast milk, a physiological and needle-free route, are also in need of investigation. This includes improving antigen transfer into human milk and assessing storage and treatment conditions of expressed milk.

With most preventable deaths in under 5 years old children due to infections and in the light of the current COVID-19 pandemic, stimulation of immunity to antigens from pathogens through breastfeeding makes for an invaluable field to explore.

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ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Valerie Verhasselt.

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