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Mucosal vaccine delivery: Current state and a pediatric perspective

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ABSTRACT

Most childhood infections occur via the mucosal surfaces, however, parenterally delivered vaccines are unable to induce protective immunity at these surfaces. In contrast, delivery of vaccines via the mucosal routes can allow antigens to interact with the mucosa-associated lymphoid tissue (MALT) to induce both mucosal and systemic immunity. The induced mucosal immunity can neutralize the pathogen on the mucosal surface before it can cause infection. In addition to reinforcing the defense at mucosal surfaces, mucosal vaccination is also expected to be needle-free, which can eliminate pain and the fear of vaccination. Thus, mucosal vaccination is highly appealing, especially for the pediatric population. However, vaccine delivery across mucosal surfaces is challenging because of the different barriers that naturally exist at the various mucosal surfaces to keep the pathogens out. There have been significant developments in delivery systems for mucosal vaccination. In this review we provide an introduction to the MALT, highlight barriers to vaccine delivery at different mucosal surfaces, discuss different approaches that have been investigated for vaccine delivery across mucosal surfaces, and conclude with an assessment of perspectives for mucosal vaccination in the context of the pediatric population.

1. Introduction — the need for mucosal vaccination

Majority of the pathogens invade via the mucosal surfaces such as those of the respiratory, reproductive and the gastrointestinal tracts. This is because these surfaces come in direct contact with the air, water, food, and the environment, and thus form an opportunistic portal for bacterial and viral infections. For example, infectious diseases resulted in the death of about 6.3 million children who were under the age of 5, worldwide in 2013, and the leading causes of death were pneumonia, diarrhea and malaria each contributing 14.9%, 9.2%, and 7.3%, respectively [1]. Sub-Saharan Africa contributed roughly half of these under-5 deaths, and southern Asia almost a third. The delivery of vaccines across mucosal surfaces has the potential to stimulate synthesis of pathogen-specific mucosal immune responses [2–4], but the conventional systemic delivery of vaccines against infectious diseases using a needle and syringe is unable to induce a strong mucosal immune response. Mucosal immune responses are important because the pathogen-specific antibodies that are stimulated by mucosal vaccination get secreted into the mucus where they can neutralize the pathogens even before they can cause infection. Thus, success in generating this first-line of defense on the mucosal surfaces will represent a major advance in vaccinology, and has the potential to improve childhood vaccinations and reduce mortality. Furthermore, delivery of vaccines to mucosal surfaces can also induce systemic immunity similar to that induced by the conventional needle and syringe based vaccination.

In addition to extending the body's immune protection to mucosal surfaces, mucosal vaccine delivery has other advantages. Importantly, mucosal vaccine delivery does not require needles and syringes, and is therefore inherently needle-free. Being needle-free, mucosal vaccinations can result in a pain free approach of vaccine delivery. Because pain from needle-injections and the ensuing fear is a significant challenge in pediatric vaccinations, mucosal vaccinations offer a very appealing alternative for the children and the parents alike [3]. Mucosal vaccines could also be self-administered, and therefore, could be provided in the comfort of one's home, which would also reduce the burden on the healthcare professionals. Being a needle-free delivery approach, mucosal vaccination should also be able to address another major problem associated with needle-based injections, i.e., of needle reuse. In the year 2000, an estimated 40% of the 16 billion injections administered worldwide were from reused needles, which led to an estimated 21 million, 2 million, and 260,000 new cases of hepatitis B, hepatitis C, and HIV infections, respectively [5]. While not all these injections were vaccine-related, mucosal vaccination can still help to reduce this burden. Furthermore, mucosal vaccination can also reduce incidents of needle-stick injuries among the health care workers, and reduce sharp waste.

Mucosal vaccination is however, challenging. The numerous natural defense mechanisms of the host at mucosal surfaces, such as the acid and enzyme-rich environment of the stomach, and the mucus layer that coats all mucosal surfaces, actually work against successful delivery of vaccines across these surfaces. In this review we provide a brief discussion of the mucosa-associated lymphoid tissue (MALT) to help familiarize the readers regarding the immune system that processes vaccine

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antigens upon mucosal delivery, different barriers to mucosal vaccine delivery, and the different approaches that have been investigated to deliver vaccines across different mucosal surfaces. Different adjuvants that have been investigated in the context of mucosal vaccination are also discussed. The review concludes with a perspective on pediatric mucosal vaccination. While the vaginal and rectal routes for mucosal vaccination are important, especially with respect to sexually transmitted diseases and for diseases that typically affect females, however, these routes of mucosal vaccination are not included in this review. This is because the vaginal route is only applicable to females, and the rectal route for vaccination has poor acceptability due to resistance against its use in some ethnic groups and cultures. As a result, these routes offer a more specialized vaccine development program. In this review, we have focused on more widely applicable mucosal vaccination routes.

2. Licensed mucosal vaccines approved for human use

Out of more than 25 diseases that have preventable vaccines, just five have mucosal vaccines, while the rest are delivered using needle and syringe. The diseases with mucosal vaccines are listed in Table 1. Out of the five, four are delivered via the oral route and one is delivered via the intranasal route. These five vaccines are discussed below especially with respect to safety considerations.

The cholera vaccine Dukoral® is a mixture of inactivated *Vibrio cholera* and cholera toxin B subunit (CTB). Presence of CTB allows the vaccine to provide short term protection against enterotoxigenic *Escherichia coli* (ETEC), however, to preserve CTB in the stomach's acidic environment the vaccine is mixed with a basic solution (sodium bicarbonate) just prior to oral uptake. The other two cholera vaccines do not contain CTB and thus can be ingested without mixing with sodium bicarbonate. Cholera vaccines are considered to be safe [6].

Mucosal influenza vaccine has been used in the Russian Federation for more than 50 years, and a variant of the formulation was first approved for use in the US in 2003. The vaccine is comprised of live attenuated influenza virus (LAIV), and is delivered by spraying as a mist in the nasal cavity. The virus is capable of replicating in the cooler environment of the nasal cavity, but not in the warmer temperature of the body in the deeper parts of the respiratory tract. This vaccine is not recommended for children under the age of 2 years due to increased risk of wheezing. The virus is known to shed from the nasal cavity of children after vaccination for up to 21 days (mean 7–8 days), however, this shed–virus has not been found to be of concern [7]. Asthma is also a contraindication for this vaccine.

Oral polio vaccine (OPV) is comprised of live attenuated polioviruses obtained by the passage of wild-type strains in non-human cells. These attenuated virus strains have significantly reduced neurovirulence and transmissibility. OPV is administered as two drops (about 0.1 ml) into the mouth. From a safety perspective, OPV is associated with rare vaccine-associated paralytic poliomyelitis (VAPP), and the emergence of vaccine derived polioviruses (VDPVs). VAPP occurrence rate is about 2–4 cases per million birth cohort per year. VDPVs can actually arise due to prolonged incubation and replication of the vaccine strain in a vaccinee, and could lead to transmission of the disease in the community [8].

Table 1
Mucosal vaccines licensed for human use.

Disease (example of licensed vaccine)	Delivery route	Live or Inactivated
Cholera (Dukoral®, Shanchol™, and mORC-Vax™)	Oral	Inactivated
Influenza (FluMist™)	Intranasal	Live attenuated
Poliomyelitis (Biopolio™ B1/3, and other oral polio vaccines — OPVs)	Oral	Live attenuated
Rotavirus (Rotarix® and RotaTeq®)	Oral	Live attenuated
Typhoid (Vivotif®)	Oral	Live attenuated

Rotavirus vaccine consists of human or human–bovine live attenuated rotavirus strains. The vaccine is administered orally. A previous rhesus rotavirus reassortant vaccine (RotaShield®) was found to have high (1:10,000) risk of intussusception, which is a serious and potentially lethal condition arising from intestinal invagination, leading to blockage, bleeding, vomiting, and pain. Even the Rotarix® and RotaTeq® vaccines have a risk of causing intussusception, however it is lower than that of RotaShield®, and the benefit of the two vaccines outweighs their risk [9]. As reported in the product inserts of Rotarix® and RotaTeq®, it has also been found that vaccine-rotavirus is shed from the vaccinee's stools, and can cause infection, especially in immunocompromised individuals or those on immunosuppressants.

The typhoid vaccine is comprised of attenuated strain *Salmonella typhi*. The formulation is comprised of an enteric-coated capsule that contains lyophilized bacteria. The vaccine is very well tolerated. Vaccine organisms are shed from vaccinees, however secondary infection has not been documented [10].

In general, the approved mucosal vaccines are not recommended for use in infants, except the rotavirus vaccine, which can be administered at the age of 6 weeks, and the oral polio vaccine, which can be given at birth. Other vaccines are recommended for humans above the age of 2 years. A typical reason for this age limit is the lack of safety data of the attenuated strains in infants. Live attenuated virus can replicate in mucosal epithelia at the site of delivery, and to create attenuated strains that are also safe for use in infants is often challenging. As seen from OPV, potential to regain virulence by the vaccine strain can be a safety hazard. Furthermore, choice of strain used to create the vaccine can have unforeseen effects as was seen in the case of rhesus rotavirus strain used in RotaShield®, which caused high incidence of intussusception. Clearly, the ability to use mucosal vaccines in infants is a high priority to help reduce childhood deaths, which are predominantly caused by pathogens associated with mucosal entry [1]. The use of non-viral vaccines can offer a safer alternative, however, delivery of non-viral vaccines is more challenging [2,11], because unlike attenuated viruses, they cannot simply infect the mucosal epithelial cells to produce an immune response.

3. The immunological defense at the mucosal surfaces and the mucosa-associated lymphoid tissue (malt)

To combat infection, mucosal surfaces are equipped with physical, chemical and immunological defense mechanisms [12]. In particular, mucosal tissues comprise of a highly compartmentalized and specialized immune system in the form of MALT. MALT helps to induce pathogen-specific immune responses, and in the secretion of immunoglobulin A (IgA) at mucosal surfaces to protect against infection [2,12]. IgA is the predominant immunoglobulin isotype in most mucosal secretions except the urogenital secretions in which IgG is found in a higher proportion. IgA can exist in monomeric or polymeric forms. IgA found in the serum is typically monomeric while that in the mucosal secretions is dimeric. IgA, which is secreted into the mucus is produced locally by the plasma cells at the mucosal surfaces. After release from the plasma cells, the dimeric form of IgA attaches to the polymeric immunoglobulin receptor (pIgR) located on the basolateral surface of mucosal epithelial cells, and is then transcytosed to the apical surface and secreted in to the mucus [13,14]. During transcytosis a portion of pIgR is cleaved while the remaining portion stays attached to IgA and is called the secretory component (SC). SC is a distinctive feature of mucosal secretory IgA (sIgA), and is not found in systemically circulating IgA (monomeric or polymeric). The protective role of sIgA is mediated by the binding of sIgA to the pathogen or toxin. Attachment of sIgA to the pathogen or toxin can either form a shell around it, preventing its interaction with the mucosal epithelial cells, or can form a partial barrier-shell, in which case the pathogen may bind to the epithelial cell surface but its uptake is inhibited. Multiple mechanisms including steric hindrance, agglutination, neutralization and mucus trapping are believed to be