# Intranasal vaccination

***Administration of vaccines by the intranasal route offers a number of benefits***

Courtesy of MedImmune

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In 2008, approximately $20 billion was spent on vaccines worldwide, $5.5 billion of that in developing countries, with a predicted annual growth rate of 9% overall and 15% in developing countries [1]. Countries that can afford it, such as the US, Germany, and Japan, pile up stocks of vaccines for vaccination campaigns to maintain essential services, to protect the vulnerable, and to limit the spread of infection in case of a pandemic outbreak. In addition, as globalization has increased, travel to areas with high risk for infection has also increased, making immunization against travel-related diseases another attractive market.

Intranasal vaccination, used successfully in veterinary medicine for years, has the potential to gain a reasonable share of the vaccination market within a few years. Intranasal delivery has a number of advantages over intramuscular and oral vaccines, particularly for special patient populations such as children and the elderly. Despite the introduction of fine hypodermic needles and prefilled syringes that make vaccine administration less painful and safer, patients and clinicians still associate injections with pain and with the possibility of an anaphylactic response. Needlestick injuries and disease transmission also pose significant threats.

## Influenza vaccines on the market

Only two intranasal influenza vaccines are currently on the market for human use, both containing live attenuated viruses and intended for the prevention of seasonal influenza. Microgen's seasonal vaccine, available exclusively in Russia, was first on the market and costs around 90 Rubles (~$3). MedImmune's FluMist, second on the market, has much better name recognition and wider availability. Neither of the two products has gained wide acceptance, though both made gains during the H1N1 pandemic in 2009. MedImmune sold 14 million doses of FluMist, at $15.25 per dose, in 2009, out of an estimated $3 billion seasonal influenza vaccine market [1].

## Vaccination costs

Dry powder preparations used in intranasal vaccines have the potential to hold down costs for vaccination programs, particularly in less developed countries, due to the ease of storage and transportation. The temperature sensitivity of most injectable vaccines means that they require cold-chain handling, which can account for 20% of the costs of vaccination. Injection requires a sterile liquid and a sterile syringe, while intranasal administration avoids the need for a sterile device.

Proper handling can prove challenging in Western countries, and the necessary infrastructure may not even be available in developing areas, leading to wastage of a large percentage of doses. Recent increases in the number of vaccines marketed, and

therefore the volume of doses, has also increased pressure on the cold chain.

Intranasal vaccines have another advantage in that the lower amount of antigen per shot necessary to elicit protective immune response represents another important cost-driving factor. For intramuscular vaccines, companies have developed new adjuvant systems that increase efficacy two to four times in order to minimize the amount of antigen needed. Intranasal vaccines naturally require 20 to 100 times less antigen than intramuscular vaccines because the nasal mucosa is very competent.

For example, one egg used to grow influenza antigen usually yields enough antigen for one injection. The same amount would provide a sufficient amount for up to 4 adjuvanted intramuscular doses (inactivated) or for 20 to 100 intranasal shots of live attenuated virus. Processing of each egg costs about $1.25. Although handling of live viruses for intranasal use costs slightly more due to more difficult handling and the need for higher bio-safety levels, cost savings can still reach 80-90% over intramuscular vaccines. MedImmune demonstrated this advantage recently when it made the first commercial pandemic H1N1 intranasal vaccine available weeks ahead of vaccines for injection.

Intranasal vaccines also require much less skill for safe administration and therefore may cost less than injections. While remaining egg proteins in intramuscular vaccines can cause an anaphylactic response and therefore require administration by a physician, intranasal administration causes a much milder, non-life-threatening response, making it suitable for administration by nurses, pharmacists, or perhaps even by patients themselves.

## Potential concerns with intranasal vaccines

Theoretically, intranasal vaccination should elicit better protection than intramuscular administration because it induces both mucosal protection at the site of infection and systemic immunity and may therefore provide protection against infections at other mucosal sites, as well as cross-protection against variant strains through mucosal antibody secretion. Recently, however, published data claim higher efficacy of intramuscular vaccines compared to the intranasal vaccine for the 2007–8 influenza season [1]. Other studies have raised concerns about the efficacy of intranasal vaccines following repeated administration [2], although successful use of an intranasal live attenuated flu vaccine in Russia for many years tends to refute this concern [3].

Concerns about the efficacy of intranasal vaccine administration generally fall into three areas:

1. Antigens may be unable to penetrate nasal mucosa in sufficient amounts to elicit an immune response

2. The vaccine's nasal dwelling time may be too short to get a reliable response

3. The activity of the vaccine may be hampered due to swirling, pressure, and shear forces during spray generation.

In addition, to gain wide acceptance, intranasal vaccines should avoid causing discomfort following administration due to an unpleasant smell, itching, nosebleed, or flu-like symptoms. The formulation also needs to be safe for ocular administration in case the vaccine is accidentally shot into the eyes. Developers can generally address all of these issues by adjusting the pharmaceutical formulation.

## Delivery of nasal vaccines

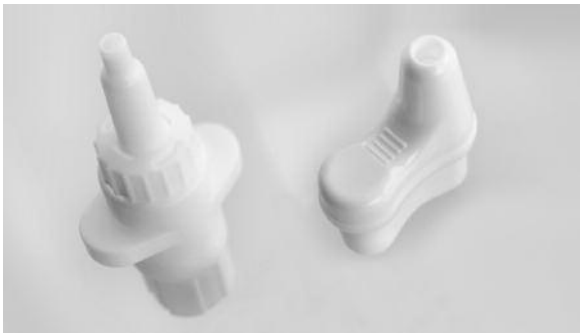
A variety of devices are available for delivery of both liquid and dry powder vaccines [Figs. 1 and 2]. Intranasal administration of a liquid vaccine requires

**Figure 1**

**Examples of spray pumps for liquid vaccine administration**

**Figure 2**

**Examples of devices for dry powder vaccine administration**



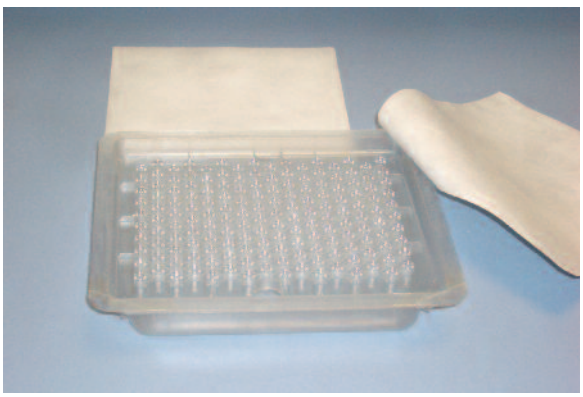
accurate delivery of a comparably low volume liquids, ideally 100 µl per nostril for adults but a smaller volume for children in order to avoid nasal dripping. For dry powder vaccines, devices generally need to deliver 20-50 mg per nostril, depending on the formulation characteristics. Some "single dose" devices may actually provide two doses, one for each nostril.

Administration to both nostrils seems to provide more confidence and will increase acceptance for the intranasal route, whether for liquid single dose, liquid multi-dose, or dry powder devices, because at any given time, one nasal cavity will be more open then the other due to differences in blood flow through the nasal mucosa. After approximately 30 to 60 minutes, the blood flow imbalance reverses, and the other nasal cavity opens further.

Single-dose devices offer the best protection for the vaccine, but require highly sophisticated filling technology due to the tiny volumes of vaccine formulation. To overcome this hurdle, device manufacturers are working intensively on a solution to adapt existing filling technology for pre-filled syringes for nasal single dose sprayers. This technology includes nested handling of glass vials in the water for injection (WFI) washing, as well as in the standardized filling and sealing processes for most commercial syringe filling lines [Fig. 3]. Nested vials reduce the required height of a storage tub, providing an additional advantage in the form of reduced transport costs.

**Figure 3**

**Nested glass vials for intranasal vaccines**



Multi-dose spray pumps provide a cost effective option for liquid vaccine administration, not only for developing countries but also for developed countries wanting to stockpile vaccines for use in the event of a pandemic or bioterrorism attack. Preservative-free pump systems, especially those systems with a tip seal to prevent drain-back of liquid into the nasal actuator, can prevent microbial contamination of the bottle content, and disposable sleeves or protection caps can effectively prevent contamination of the exterior of the pump, preventing transmission of disease from patient to patient.

For a multi-dose pump, the manufacturer fills the vaccine into a standard multi-dose bottle and seals it with a simple tear-off closure. The filled bottles, but not the pumps, must be transported within the cold chain. Just before the vaccination should start, the healthcare professional adminstering the vaccine removes the closure (Step 1) and snaps the pump on by hand (Step 2) [Fig. 4]. After 5-7 actuations to prime the pump, the system is ready to use. Disposable caps used between each patient prevent disease transmission, and no re-priming is required.

**Figure 4**

**Using a multi-dose spray pump for vaccine delivery**


## References

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