The nasal delivery of vaccines has recently emerged as an attractive alternative to injection. Nasal vaccination has the advantage that it elicits both local and systemic immune responses. The mucosal immune response is rapid and nasal vaccines may also induce protection in distant mucosal sites. Correct formulation and adequate distribution to the nasal mucosa are, however, essential for efficacy and safety. The complexity of nasal geometry represents a major challenge for efficient intranasal vaccination, and current delivery devices may prove inadequate in meeting future safety and reliability requirements.

**INTRANASAL DELIVERY OF VACCINES**

The vast majority of disease-causing bacteria, viruses and parasites reach our bodies through the mucosal surfaces. It is only natural, therefore, that most of the immune system is either located in, or in direct contact with, mucosal membranes so providing a ‘first line defence’ system against harmful microorganisms.

The nose filters the air we inhale. Airborne particles and microorganisms are trapped in the nasal secretions and presented to the nasal immune system. If protective mechanisms in the nasal mucus are inadequate, the microorganisms may invade the mucosal lining and cause a local infection, or penetrate deeper to cause more widespread disease. When microorganisms bypass this first line of defence, systemic immune systems will be activated.

Vaccination is a method of stimulating resistance to specific diseases using attenuated live microorganisms, dead microorganisms, or parts of microorganisms not able to induce disease. Vaccination against infectious diseases is regarded as the most cost-effective public health intervention. Currently, most vaccines are given by injection.

Injected vaccines stimulate the systemic immune response, but do not provide mucosal immune protection. Mucosal vaccines, on the other hand, elicit not only good local immune protection, but also a systemic response similar to that of injection. There are also indications that nasal vaccination can lead to immune protection in other distant mucosal organs, such as the urogenital tract and intestines.

Oral vaccination has been considered for mucosal vaccination, but it has proven difficult to obtain a good immune response, probably because of degradation and dilution in the stomach and intestines.

Recently nasal vaccination has emerged as an attractive alternative. The potential advantages, as well as the challenges involved in developing this route of delivery, are outlined in Table 1 on page 25 (adapted from CD Partidos – see review articles).

**FORMULATION ISSUES AND ADJUVANTS**

The physical properties of a vaccine can greatly influence its performance. Nasal vaccines must be specifically formulated and optimised to achieve a good immune response and at the same time prevent local irritation and other potential adverse effects. Several strategies have been developed to improve efficiency and safety. These include the use of adjuvants (1) and improved delivery systems targeting the specific cells or regions of the nasal mucosal surfaces important in eliciting the immune response.

Adjuvants appear to be required for enhancing the immune response of nasal vaccines. Toxins from the bacteria *Vibrio cholerae* and *Escherichia coli*, both of which cause severe diarrhoea, are potent mucosal adjuvants, but exactly how these toxins exert their adjuvant effect is still unclear. There are also safety concerns when administered nasally, although considerable effort has been devoted to reducing their toxicity for use in humans. The use of live attenuated cold adapted viral vaccines has been advocated as an alternative because of their ability to produce a stronger immune response more closely mimicking a natural infection. For some vaccines a combination of intranasal administration and injection may be preferable for optimal protection, especially when an inactivated vaccine is used. This can be achieved by giving an initial injection ‘priming’ the immune response, followed by one or more nasal vaccinations to ‘boost’ the response.
Nasally administered substances, including toxins and attenuated microorganisms, may penetrate to the brain through the olfactory region. Such direct nose-to-brain transport may be advantageous for certain vaccines and drugs targeting neurological diseases, but raises concern about potential adverse effects when the brain is not the target organ. There is, therefore, a great need to develop new adjuvants that are safe for human use and enhance the immune responses to nasal vaccine antigens. A variety of alternative adjuvant strategies are currently being investigated, including liposomes, chitosans, microspheres and bacteria-derived particles. One example is a promising new nasal adjuvant developed by the Swedish company Eurocine based on a combination of naturally occurring lipids without toxic effects.

THE NASAL IMMUNE SYSTEM
Humans and other mammals have evolved organised lymphatic tissue structures capable of facilitating the mucosal immune response in the airways. In the upper airways these structures include the palatine tonsils and other lymphoepithelial structures of Waldeyer’s pharyngeal ring, such as the adenoids in humans. Recent studies, in addition, have shown that the human nasal mucosa is extremely rich in specialised cells capable of inducing the local immune response. To obtain an enhanced immune response, a nasal vaccine should target these widely distributed specialised mucosal cells, as well as the structures in Waldeyer’s ring, particularly the adenoid (see Figure 1). Another important advantage of the mucosal immune response is that it occurs very rapidly. Vaccination by injection takes a week or more to obtain a good response, while mucosal/nasal vaccination takes only a few hours. This difference may prove crucial in rapidly spreading epidemics.

CHALLENGING NASAL GEOMETRY
Despite easy access, the narrow and complex geometry of the nose represents an important challenge for the reliable and efficient delivery of vaccines and drugs to the mucosal surfaces. The nasal valve is the narrowest segment of the respiratory tract, accounting for up to 80 per cent of nasal resistance and almost half of total respiratory resistance. Numerous studies have shown that traditional spray pumps deliver the dose primarily to the anterior segment of the nasal passage. This anterior area is lined with skin, which is neither the target for therapies against mucosal pathologies (allergy and common cold), nor the target for drugs and vaccines intended for systemic absorption (see Figure 1).

The skin in the anterior region of the nose does not have cilia – tiny threads which transport deposited particles toward the mucosa and other immunological structures. Nasal mucociliary clearance is a fundamental defence mechanism. A blanket of secretions moves towards the posterior of the nose at a speed of approximately one centimetre per minute. This is somewhat slower in the upper parts of the nasal passages. Particles larger than five to 10µm are trapped in this blanket and are eventually presented to the immunological cells and structures in the nose and mouth before being swallowed. The time available for contact between the vaccine or drug particles is limited – emphasising the importance of an optimal balance between the formulation of a nasal drug or vaccine and the delivery method. Several approaches can be employed to enhance absorption, including the use of adjuvants, absorption enhancers, and substances increasing the viscosity or slowing of mucociliary activity. Nevertheless, even with a perfect formulation it becomes essential to obtain a reliable and optimal distribution of the drug or vaccine to a large part of the nasal mucosal surface, whilst at the same time limiting the depositions outside the target sites.

NASAL CYCLE AND NASAL DISEASE
The naturally occurring nasal cycle, present in 80 per cent of humans, causes alternating reciprocal congestion and decongestion of the two nasal passages every three to eight hours. Overall nasal resistance and dimensions remain relatively stable. Other factors such as posture, emotions and physical exercise also influence nasal potency. Septal deviations, nasal polyps and intranasal disease can all cause obstruction and alter nasal aerodynamics. It is therefore rational to deliver vaccine to both nasal passages. Although drug absorption seems little affected by infections and inflammation, it is not known whether the immune response to nasal vaccines is altered by these conditions.

LIMITATIONS OF CURRENT NASAL DELIVERY DEVICES
Currently, nasal drugs and vaccines are typically delivered by pipette or mechanical metered-dose spray pump. So far multi-dose spray pumps dominate the market for nasal delivery, but unit-dose or duo-dose nasal sprays have been introduced for certain drugs and vaccines. The spray pumps for nasal delivery typically produce a mean particle size (MPS) of 50µm, where the fraction of particles <10µm is approximately five per cent. Traditional spray pump technology cannot provide MPS much less than 30µm. A mist with a MPS less than 30-40µm, in addition, is likely to include a higher fraction of small particles (<10µm) than the five per cent recommended by FDA guidelines.

The triangular shaped valve area located two to three centimetres into the nose limits the fraction of particles able to penetrate further (see Figure 1). The particles leaving a traditional spray pump have a high velocity, causing the larger particles, in particular, to be shot against and deposited anterior to, or in the nasal valve region. The relatively wide plume angle...
of the mist leaving the nozzle may also contribute to anterior impingement of particles.

A considerable fraction of the dose deposited in this anterior region may eventually be wiped away or be blown out of the nose without entering deeper regions. In addition, the fraction that is transported towards the posterior seems to be mainly cleared along the floor of the nose, limiting the exposure to the mucosal surface and some of the structures of the Waldeyer’s ring (see Figure 1 on page 23).

**FUTURE NASAL DELIVERY CONCEPTS**

Inhalation of a nebulised aerosol containing particles with a MPS of 6µm, which move more slowly, could improve the distribution to the upper and posterior regions of the nasal passage. However, up to half the inhaled dose may bypass the nose and enter the lungs, questioning the suitability of this type of nasal inhalation for targeted nasal delivery. Several companies have proposed alternative delivery technologies, which can provide a more uniform particle size distribution, and possibly improve the nasal deposition pattern. Some of these approaches include the introduction of more complex dispersion systems requiring electrical power or other potentially expensive technologies.

Novel new nasal delivery technology suitable for both liquid and powder vaccines is currently being developed. This novel concept combines knowledge of both functional nasal anatomy and aerodynamics. Ongoing studies have shown that the targeted distribution to the mucosa and lymphatic structures in the nose can be significantly enhanced.

**MASS VACCINATION**

One third of all deaths occurring globally are due to infectious diseases. Mortality is highest in developing countries, but morbidity is also considerable in the industrialised world. Injection of vaccines is not only traumatic for the individual, but also of great concern for the medical community due to reuse of syringes and accidents caused by syringes. The annual costs for unsafe handling of syringes leading to contamination and transmission of infectious diseases, apart from deaths, is estimated at US $540 million.

Another important concern to the World Health Organization (WHO) is the need for inexpensive refrigeration for the handling of most of the currently used vaccines. The WHO is encouraging the development of mucosal and dry-powder vaccines but to become a viable and attractive alternative to injection, the price of a new delivery system must be competitive and highly cost-effective. Unit-dose and duo-dose devices for nasal delivery are likely to be too expensive and unsuitable for extensive public vaccination programmes. In an effort to fill this void, a system based on a new concept, but specifically adapted for cost-effective mass-vaccination is being developed.

**CONCLUSIONS**

The nasal delivery of vaccines is an attractive option. This route of delivery avoids the discomfort and hazards associated with injection and provides improved local immune protection and cross protection in distant mucosal sites. It is important however to improve distribution to the nasal mucosa, while at the same time limiting deposition outside the target sites. Achieving this balance is essential in improving the reproducibility, safety, clinical efficacy and patient compliance of nasally delivered vaccines and potent drugs.

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**Reference**

(1) *An adjuvant is a substance administered along with a vaccine antigen to enhance the immune response stimulated by the vaccine*

**Suggested Review Articles**


Carlotti P, Unit-Dose Nasal Sprays – Systemic Delivery Through the Nose, Pharmaceutical Manufacturing and Packing Sourcer, pp 70-71, Summer 2002


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**Table 1: Intranasal Vaccination**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Challenges</th>
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<tbody>
<tr>
<td>Easily accessible mucosal organ</td>
<td>Narrow nasal entrance</td>
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<tr>
<td>Highly vascularised mucosa</td>
<td>Complex geometry with narrow passages</td>
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<tr>
<td>Large surface available for absorption</td>
<td>Variable dosing with traditional delivery methods</td>
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<tr>
<td>Both mucosal and systemic immune responses</td>
<td>Mucociliary clearance and nasal cycle</td>
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<tr>
<td>Protection at distant mucosal sites</td>
<td>Reformulation of vaccines required</td>
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<tr>
<td>Suitable for mass-vaccination</td>
<td>Adjuvant required for good immune response</td>
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<tr>
<td>Needle-free vaccination</td>
<td>Influences of nasal inflammation and obstruction</td>
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<td>Faster onset of strong immune response</td>
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