Expert Opinion

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Noninvasive delivery technologies: respiratory delivery of vaccines

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This paper reviews the developments in noninvasive methods of drug delivery, with a focus on the delivery of vaccines via the respiratory tract. Recent results indicate that the respiratory system, and the nasal mucosa in particular, provide a valuable target site for immunisation against respiratory and mucosal pathogens. Vaccine delivery via the nasal and pulmonary routes each present distinct sets of performance requirements. Current delivery systems in development for both routes are reviewed herein. The storage and respiratory delivery of drugs and vaccines in powder form has been shown to provide improved stability and extended retention time in the respiratory mucosa. These features, in addition to the noninvasive nature of respiratory delivery, can provide benefits to public health vaccination campaigns, facilitating mass vaccination without the high cost of maintaining cold-chain storage.

Keywords: aerosol, cold chain, dry powder, immunisation, mucosal, nasal, pulmonary, stability, vaccine

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1. Introduction

The rapid rise in the number of large molecule biopharmaceuticals in development, which are generally not suited to delivery via the gastrointestinal tract, has led to an increased interest in alternative delivery technologies. The pharmaceutical industry continues to look at nontraditional drug delivery routes as a means to improve patient compliance and overall market acceptance of products [1].

The field of noninvasive drug delivery is broad, encompassing a number of different routes of delivery, including buccal, sublingual, nasal, pulmonary, and transcutaneous and transdermal routes. A range of different technologies is being applied to deliver drugs and vaccines via these routes. Transcutaneous and transdermal delivery technologies involve methods of breaching the skin barrier using means other than the standard needle and syringe typically employed for parenteral delivery. Significant advances have recently been made in the fields of electroporation and jet injector technologies [2,3], as well as in microneedle and microabrasion technologies for the delivery of medicaments into the shallow skin [2]. In general, skin-based delivery of drugs at high dose requires some degree of mechanical disruption of the skin. Thus, despite the relatively low bioavailabilities achieved with mucosal (i.e., buccal, sublingual, nasal and pulmonary) delivery of proteins, there continues to be a high level of research activity devoted to these approaches, as they represent truly noninvasive delivery modes [1]. Sublingual and buccal delivery technologies have been reviewed elsewhere [4,5] and will not be covered in the present review, which will focus on needle-free delivery of vaccines via the respiratory tract.

The vaccine industry is expected to experience rapid growth over the next several years [6-8]. The majority of vaccines are still envisioned as parenteral products, but many clinical and preclinical studies have been initiated to explore the advantages of mucosal delivery; both for the noninvasive feature of these delivery modes and the

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potential for achieving improved patient outcomes through mucosal immunisation. This paper will briefly review recent developments in noninvasive respiratory vaccine delivery technologies and highlight recent developments in the author's own laboratories in the area of delivery of vaccines in dry powder form to the respiratory mucosa.

2. Respiratory vaccine delivery

The respiratory tract provides a route for the delivery of vaccines and drugs without requiring the use of needles. In addition, many human diseases involve the entry of pathogens into the body via the respiratory or mucosal systems, including influenza, measles and respiratory syncytial virus, to name a few. Recent research in mucosal immunisation indicates that nasal and pulmonary delivery of vaccines can offer the advantage of inducing both local and systemic immunity [9]. Interestingly, nasal delivery of antigens can also illicit immune responses at distant mucosal surfaces [9,10].

Delivery of drugs or vaccines to the deep lung is more challenging than delivery to the nasal mucosa for a number of reasons. First, deep lung delivery requires the production of aerosol particles in the 0.5 – 3 µm range [1,11], which is technically difficult for any drug but especially for sensitive biopharmaceuticals, which may be degraded by shear or at the air–water interface. For intranasal delivery, on the other hand, particles of > 50 µm are generally required [12]. Second, reproducible deep lung delivery requires control of patient breathing, whereas intranasal delivery can be achieved without such control, as inertial impaction is the primary mechanism of particle deposition [11,13].

2.1 Intranasal delivery

Intranasal delivery is already well established for many drugs intended for treatment of local disorders, such as rhinitis and sinusitis, as well as for nasal congestion or other symptoms of nasal infection [6,12]. However, the intranasal route for delivery of systemic drugs has recently been widely studied. Because of the potential for rapid systemic drug uptake in the bloodstream, intranasal delivery of drug classes such as sedatives, analgesics and anaesthetic medications have been evaluated extensively. Many branded and generic products exist for the treatment of migraine and acute pain [12,14,15]. Triptans and ergotamine derivatives, for control of migraine, are two of the most widely used classes of nasally delivered drugs [16]. Other marketed nasal products include calcitonin, fentanyl and desmopressin. So far, successful intranasal drug delivery has generally been limited to low molecular weight drugs and low dose ranges [1].

The vast majority of nasal delivery devices are designed for the administration of liquid formulations of steroidal anti-inflammatory drugs, histamine H_1 blockers, antiseptics, antibiotics and vaso-constricting active ingredients. Droppers, pipettes and squeeze bottles have been used for many years to deliver drugs to the nasal cavity to treat clinical conditions such as rhinitis and sinusitis. Concerns about the safety and dose accuracy of these delivery devices have limited their use to drugs characterised by a wide pharmacodynamic dose window and large maximum tolerable dose [17]. Other drugs requiring more precise delivery employ mechanical pumps and sprayers delivering a more controlled range of particle sizes over well-defined regions of the nasal mucosa [12,17]. A limited number of devices for intranasal delivery of powders have also been developed [11,14,17]. Companies currently developing intranasal delivery devices for powders include Direct Haler, OptiNose, BD, Bespak and Pfeiffer, and specific information on these devices may be found on the companies' websites. Powder formulations can offer advantages of improved drug stability, and certain powder formulations have demonstrated increased residence time in the nasal cavity compared with liquids, which may translate into higher bioavailability and therapeutic benefits [18].

A prototype device for delivery of a lyophilised cake has been described that offers the advantage that a powder can be metered as a liquid and lyophilised directly in the device [14]. The primary limitation of such an approach is the poor control of particle size obtained by direct aerosolisation of such a lyophilised cake. Bi-dose powder devices have also been described, although published performance data for such devices is limited [17]. A new device allowing the delivery of unit doses of vaccine powder into the lung or nasal cavity is described in Section 2.2 [19].

Although nasal delivery of therapeutic proteins has shown limited success so far [1], studies on the delivery of vaccines via the nasal route has shown promise for a number of respiratory pathogens. In addition, the demonstration in humans that nasal immunisation can illicit immune responses at genital mucosal locations indicates the potential for nasal immunisation against sexually transmitted diseases [10,20,21]. Intranasal vaccination has been investigated for HIV, hepatitis B, measles, anthrax, plague, diphtheria, pertusis, tetanus, bacterial meningitis, respiratory syncytial virus, rotavirus and other diseases [22,23].

As described above, numerous devices for nasal administration of drugs have been developed, but many of these have been designed as multi-use devices and are not suitable for vaccine delivery due to cost and device complexity, and to the fact that such devices are not designed for use in an immunisation setting, where the potential for disease transmission from one patient to another favours single-use devices. The ideal delivery system for use in mass vaccination campaigns should combine the attributes of improved vaccine efficacy, vaccine formulation stability, ease of use in clinical and field settings, portability, unfailing safety (before, during and after use) and flexibility for use with any vaccine in any setting. Although alternate needle-free approaches to mass vaccination, such as patches, jet injectors and oral delivery systems, have been proposed, only a small number of oral and intranasal vaccines have yet demonstrated in commercial form the ability to provide efficacious immunisation in safe, reliable and easy-to-use formats [9].

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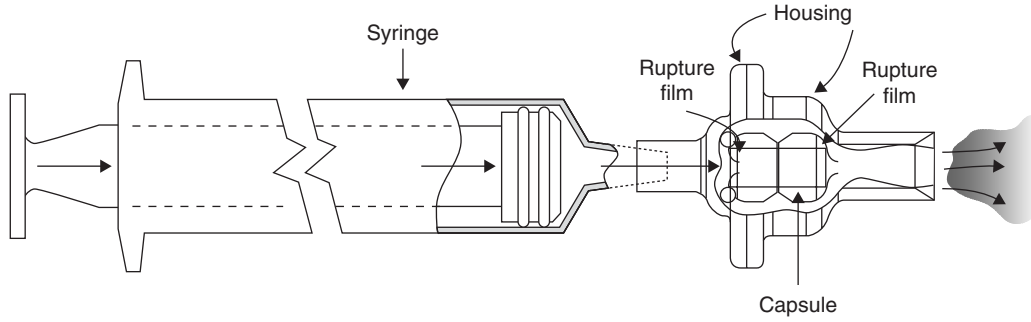

Figure 1. Prototype device for delivery of dry powders. The capsule housing is suitable for attachment to a Luer tip syringe. The two halves of the housing can be assembled so as to hold the plastic vaccine capsule in a central void. The plastic vaccine capsule incorporates pressure-activated rupture films inline with the longitudinal axis of the syringe [19].

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There are two areas in which new vaccine delivery systems are urgently needed; developing world vaccination and biodefense. For the purposes of mass vaccination in these settings, it will be necessary to vaccinate large numbers of people very rapidly. Delivery devices that require little to no advance training will greatly accelerate the vaccine administration process and will reduce the burden on highly skilled medical practitioners. In addition, increasing ease of use may enable vaccines to be administered at numerous decentralised locations rather than at large, centralised vaccination centres that represent potential targets for terrorist attack and could facilitate the spread of a bioweapon or other infectious agent.

2.2 Pulmonary delivery

Devices for pulmonary delivery of liquids and powders have been described in the literature [11,13,24,25]. Extensive work has been carried out to demonstrate in humans the feasibility of using certain portable devices and associated liquid or powder formulations for postprandial delivery of insulin [26-29]. Pulmonary delivery of protein therapeutics seems to be more promising than intranasal delivery, in large part due to the fact that the lung has a much larger area for deposition, thus allowing larger doses to be administered. The surface area of the human nasal cavity is estimated to be 150 cm^2 versus 140 m^2 for the alveolar surface [11,12]. In addition, higher bioavailability of therapeutic proteins can generally be achieved with pulmonary versus intranasal delivery, without the need for penetration enhancers [1].

In contrast, relatively little work has been published on the pulmonary delivery of vaccines. Devices in development for deep lung delivery of proteins are often too complex to be used in mass vaccine settings, both from cost and ease of use standpoints. In addition, delivery of vaccine to the respiratory tract of young children is especially challenging due to the need to gain reliable access to the respiratory system without the ability to train the patient to inhale in a controlled manner [30].

So far, the most extensive evaluations of pulmonary vaccine delivery in humans have been carried out with live attenuated measles vaccines [24,31,32]. Whereas both intranasal and pulmonary delivery have proven effective in eliciting protective immune responses against measles, certain intranasal studies showed lower immune responses; a result that may be attributable either to the presence of pathological conditions of the upper respiratory tract or to the various methods of intranasal delivery employed in these studies, including nonoptimal nasal delivery devices [31].

Because of the difficulty of training young children to breathe in the controlled manner needed for deep lung deposition, the dry powder inhalers currently on the market are generally prescribed for use only in patients of 4 years of age or older. The inability to reliably control the inspiration of infants and small children means that the devices used in such patients should be capable of achieving a high level of independence of powder aerosolisation and dispersion on patient inspiratory flow rate and volume [13,15,33]. For such use, a device employing a mechanism for active dispersion of liquid or powder is highly desirable.

3. Devices for intranasal or pulmonary delivery of dry powders

Research in the author's laboratory has focused on the delivery of stable dry powder vaccine to the lung or nasal cavity via a simple active dispersion mechanism. This is achieved with a single-use, unit-dose, disposable delivery device that disperses an active dry powder medicament for respiratory delivery via either the nose or mouth. Effective delivery is achieved without priming steps or other extensive user preparation prior to use [19]. An illustration of the powder delivery device is shown in Figure 1. The device consists of a powder-filled capsule contained within a plastic housing unit. The housing can be adapted to allow attachment to a standard disposable syringe via a Luer fit. The patient or care-giver depresses the syringe plunger, pushing air through the device, and causing the rupturable films to burst. This creates a powder plume that exits the device through a diffuser. Prototypes of this delivery device have been tested in animal models. In addition, *in vitro*

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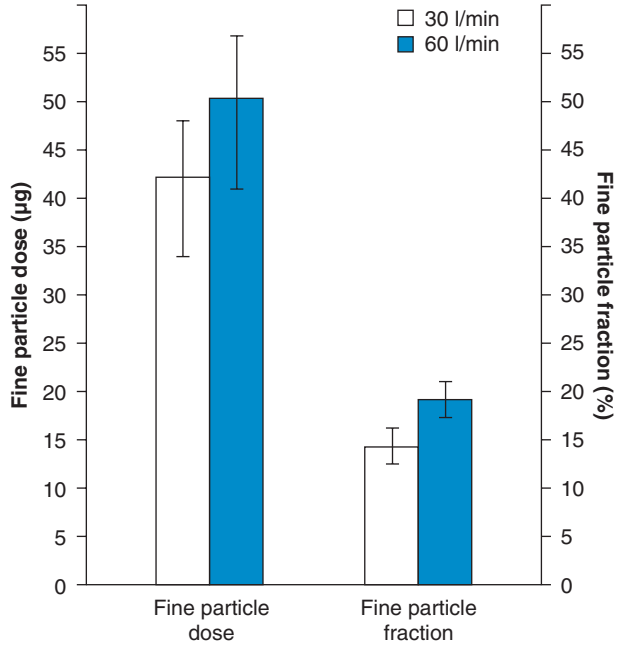

Figure 2. Comparison of fine particle dose (left) and fine particle fraction (right) of a milled albuterol/lactose blend, as measured by cascade impaction, using the prototype dry powder device at 400 µg and flow rates of 30 and 60 l/min. Reprinted from FORD B, SULLIVAN VJ, BHUTA WILLS A: Comparative analysis of BD's novel active powder delivery device with commercial products. *Proceedings of Respiratory Drug Delivery VIII*, Tucson, AZ, USA (2002) 367-370 [34], with permission from Virginia Commonwealth University.

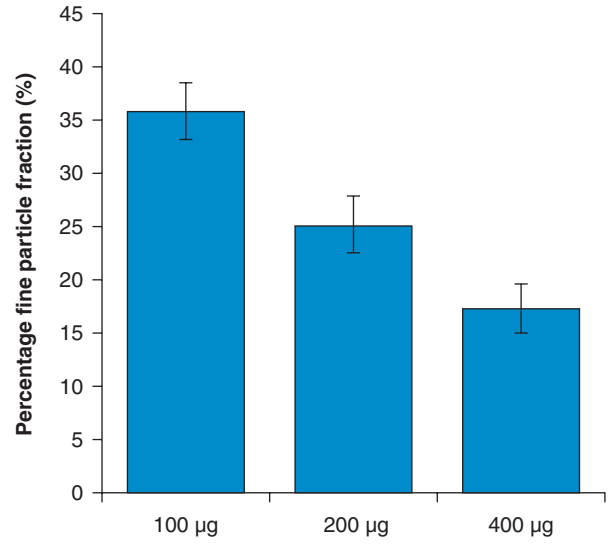

Figure 3. Fine particle fraction results for different dose levels at 60 l/min. Reprinted from FORD B, SULLIVAN VJ, BHUTA WILLS A: Comparative analysis of BD's novel active powder delivery device with commercial products. *Proceedings of Respiratory Drug Delivery VIII*, Tucson, AZ, USA (2002) 367-370 [34], with permission from Virginia Commonwealth University.

testing, via cascade impaction, was employed to demonstrate the feasibility of pulmonary delivery with the device [34].

A dry powder albuterol formulation was used as a model powder for cascade impaction studies. For a given particle size distribution, a dry powder vaccine or other large molecule drug would be expected to perform similarly in the device, provided particle density and interparticle adhesion properties were similar. In the cascade impaction study, the fine particle dose (FPD) [13], defined as the sum of albuterol with aerodynamic diameters < 4.5 µm divided by the number of doses discharged from the device, was measured for the prototype dry powder delivery device shown in Figure 1. The device was tested at constant flow rates of 30 and 60 l/min. Results are shown in Figure 2. The device showed an average FPD of 50.1 µg at 60 l/min; comparable to or better than a range of other powder and liquid inhalation devices tested at these conditions (data not shown) [34]. In addition, there was little change in FPD going from 60 to 30 l/min. Figure 2 also shows a comparison of fine particle fraction (FPF) at 30 and 60 l/min, where FPF is defined as the fraction of emitted dose with aerodynamic diameters < 4.5 µm [13]. As with FPD, little change in FPF is seen over the range of flow rates tested. The consistency of powder dispersion performance over this flow rate range is likely to be a consequence of the pressure-activated powder dispersion mechanism of the device.

It was found that FPF for the dry powder device depends on dose loading (Figure 3). Generally as the dose decreases, the FPF increases. This demonstrates the efficiency of the device, where a smaller amount of drug can achieve a greater FPF. Note that the dose level used in Figure 2 for flow rate comparisons was that giving the lowest FPF and FPD results (i.e., 400-µg dose).

Overall, the device performed as a highly efficient delivery system, showing little dependence of aerosol performance on flow rate over the flow rate range tested.

Although the device described above is suitable for pulmonary delivery of a fine powder, powders of larger particle size, suitable for intranasal delivery, have also been used in conjunction with this system for intranasal delivery of vaccines. Studies employing a candidate dry powder influenza vaccine based on whole inactivated influenza virus, with a powder median volume diameter of 37 µm, were carried out in rats and demonstrated immune responses comparable to those achieved with intramuscular or intranasal delivery of liquids [19] (Figures 4 and 5). For these studies, the delivery end of the device was fitted with exit diffusers that were finely tapered to fit the nasal cavity of either rats or rabbits.

Positive nasal IgA responses were only seen after nasal administration, regardless of formulation (Figure 5). No detectable IgA responses were observed in the intramuscular injection group or in the intranasal dry powder control

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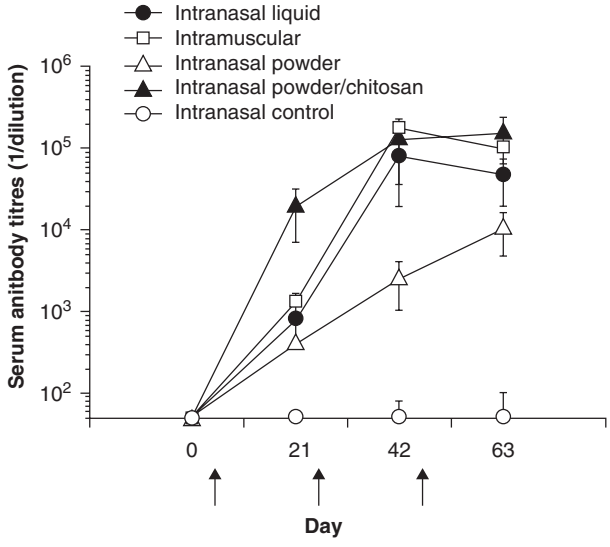

Figure 4. Serum anti-influenza total antibody titres following intranasal powder immunisations. Arrows indicate time points for each of the three immunisations. Milled trehalose was used as a negative control [19].

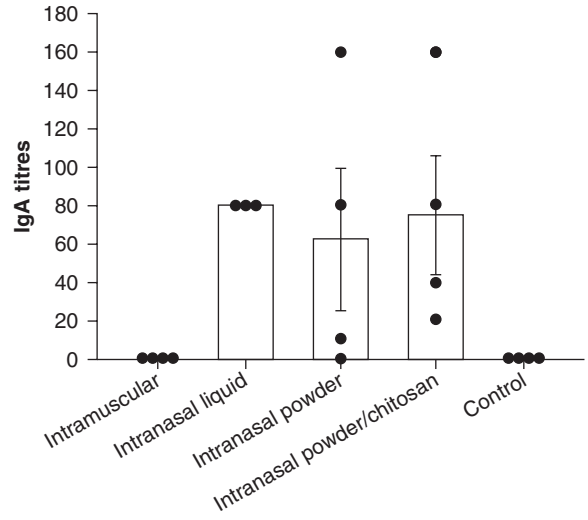

Figure 5. Nasal anti-influenza IgA antibody titres following intranasal antigen powder immunisation. IgA titres of individual rats are indicated by closed symbols. [19].

group, which received only inert powder excipient and no vaccine. The average IgA titres of intranasal powder groups were equivalent to the intranasal liquid group, although somewhat higher variability is seen in the intranasal powder group. This variability may be the result of higher variation in delivered powder dose due to the small size of the rat nasal cavity.

To determine whether or not lung deposition of powders occurred with the delivery method used in this study, the author's formulated luciferase plasmid powder of similar particle size as the influenza powder vaccine. The luciferase plasmid powder was administered intranasally to rats. Lung and nasal tissue was assayed for the presence of luciferase. No luciferase was found in the lung, indicating that intranasal, not lung deposition, was achieved (data not shown). The results show that the powder formulation and delivery system employed provides an immune response at least as potent as conventional liquid formulations.

In further studies conducted in rabbits, a dry powder anthrax vaccine was delivered with the same type of device as was used in the influenza study described above [35]. The exit diffuser of the device was adapted to fit the rabbit nasal cavity, but the storage capsule and actuation mechanism was the same. A powder formulation of recombinant protective antigen (rPA) vaccine was evaluated for protective efficacy as an intranasally administered vaccine, as compared with liquid formulations administered intranasally, intramuscularly, or topically. rPA vaccine was formulated either as a liquid or as freeze-dried (FD) or spray-freeze dried (SFD) powders. The SFD process results in vaccine particles of very high porosity, which are rapidly reconstituted when deposited onto the nasal mucosa. FD powders were prepared by lyophillisation followed by ball milling to achieve an appropriate particle size for intranasal administration. Vaccine powders prepared by the FD method used in this study had mean diameters of ~ 50 µm, as measured by laser diffraction, whereas SFD powder formulations had mean diameters of ~ 70 µm. For intramuscular administration, rabbits were immunised with rPA alone or in combination with cytosine phosphoryl guanine (CpG)-containing oligonucleotides or adsorbed onto aluminum hydroxide gel (Alhydrogel®, Superfos Biosector) as adjuvant. All intranasal formulations included CpG-containing oligonucleotides. Powder formulations were prepared with or without the mucoadhesive chitosan. Rabbits were immunised three times with 50 µg of rPA either alone or with adjuvant. At the completion of the three-dose series, the strongest overall toxin neutralising antibody titres were observed following intramuscular administration (Figure 6). Titres were similar across all of the groups immunised via the intranasal route. Topical administration resulted in no measurable toxin neutralising antibody.

Rabbits were aerosol challenged with ~ 100 times the median lethal dose of anthrax spores (Ames strain) 6 weeks after the last dose of vaccine. Among the intranasal groups, better protection (83 – 100%) was observed in rabbits immunised with powder formulations as compared with liquid, where 67% (4/6) of immunised animals survived (Figure 6). Neither the method of powder formulation (SFD or FD) nor the mucoadhesive chitosan seemed to have a major impact on survivability in this study.

The results demonstrated for the first time that intranasal delivery of a stable powder form of anthrax vaccine based on rPA provided 100% protection against lethal inhalational

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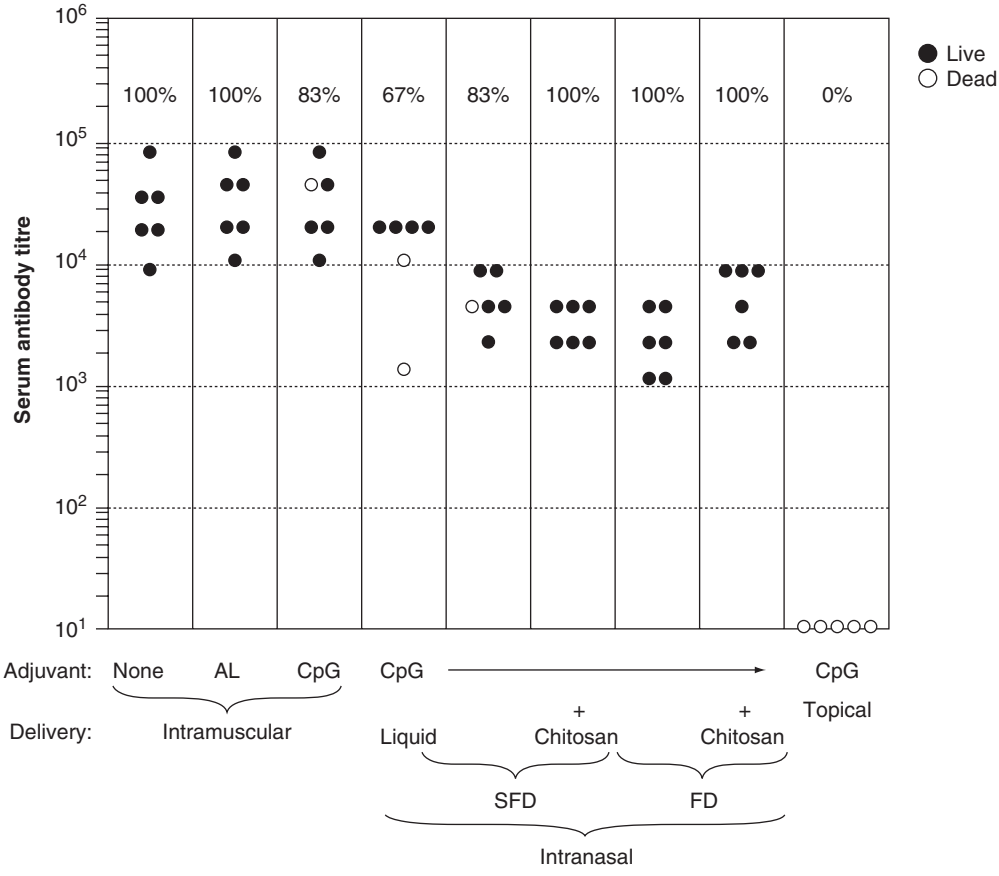

Figure 6. Neutralising antibody titres and survival following aerosol challenge with *Bacillus anthracis*. See text for descriptions of the formulations used. Reprinted with permission from MIKSZTA JA, SULLIVAN VJ, DEAN C *et al.*: Cutaneous or mucosal delivery of anthrax vaccine provides complete protection against inhalational anthrax. *J. Infect. Dis.* (2005) **191**:278-288 [35].
AL: Alhydrogel; CpG: Cytosine phosphoryl guanine; FD: Freeze dried; SFD: Spray-freeze dried.

challenge with anthrax [35]. The powder form of rPA was also more stable than a conventional liquid.

These studies show the potential for effective, noninvasive intranasal vaccine delivery via an easy to use, single-use, disposable device and vaccine in a stable powder form.

4. Conclusions

The results of testing a dry powder intranasal vaccine and nasal delivery device in rats shows that this system is capable of providing a safe and effective alternative to current influenza vaccines. The powder vaccine also showed high stability, potentially allowing mass distribution without the high cost of maintaining cold-chain storage. Similarly, intranasal vaccination with a dry powder anthrax vaccine based on rPA showed good stability and delivered 100% protection against inhalational anthrax challenge in a rabbit model.

These results, along with a large body of preclinical data on intranasal immunisation with vaccines against a wide range of pathogens, indicate the potential for effective vaccination via the mucosal route.

The success of mass vaccination campaigns depends in part on effective supply chain management for vaccine distribution. A prefilled intranasal delivery device with room temperature stable vaccine formulations will contribute substantially to reducing this logistical burden. It is hoped that further clinical evaluation of such vaccines and delivery systems will be undertaken in the near future to exploit the advantages of vaccine stability and noninvasive delivery.

5. Expert opinion

The nasopharangeal region contains a high density of immune competent cells, most notably in Waldayer's ring, and is a logical target site for immunisation against respiratory and mucosal pathogens. Portability, ease of use, and potential for enhanced local mucosal and systemic immune responses are major advantages to respiratory vaccine delivery. The introduction of Flumist™ (MedImmune, Inc.), the first intranasally delivered vaccine product for the US market, opens the way for increasing the use of inhalation delivery for vaccination.

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Although there are currently no marketed, dry powder, intranasal delivery devices, the advantages of such systems (i.e., portability, vaccine stability), particularly for use in mass immunisation settings, are expected to outweigh the added device complexity of these systems in comparison to liquid intranasal delivery devices. The currently marketed Flumist influenza vaccine is in liquid form and requires refrigeration for storage and distribution. Recent studies in animal models have shown that dry powder forms of vaccines can be effectively administered to the nasal cavity [19,35], or by pulmonary delivery [24,32]. Dry forms of vaccines can provide the advantage of enhanced stability. Elimination of cold-chain costs could provide a major benefit in public health vaccination campaigns by improving portability and reducing the logistic burden and cost of vaccine administration [24,36]. In addition, powder forms of vaccine may provide more intimate and longer term contact of vaccine with the respiratory mucosa. Microparticle vaccine formulations, which are designed for enhanced uptake and improved immune response [37,38], are potentially better suited to dry powder administration as these formulations may otherwise require reconstitution and resuspension of formulation prior to delivery, a cumbersome and expensive delivery system compared with direct powder administration.

The complexities of pulmonary vaccine delivery noted above, especially for children or uncooperative patients, or subjects suffering from pulmonary disease, indicates that intranasal delivery should be the primary route of choice for inhalation delivery unless data are available that suggests pulmonary delivery provides higher efficacy.

Several preclinical studies indicate the feasibility of intranasal immunisation for a range of respiratory pathogens, and efficacy in the clinic has also been demonstrated for intranasal influenza immunisation. The clinical literature also indicates that efficacious immune responses against measles are achievable via either nasal or pulmonary routes. As a direct head-to-head comparison of nasal versus pulmonary immunisation against measles has not yet been carried out, the optimal target tissue for respiratory measles immunisation remains unknown. In considering whether to deliver a dry powder aerosol to target the nasal cavity or the pulmonary tract, several device and medical-related issues should be considered, as discussed below.

Efficient pulmonary immunisation requires the coordination of actuation with patient inspiration. This is difficult to design into a single-use disposable device, and it is not easily accomplished through training in young patients, especially given the time constraints of mass immunisation. In addition, mechanisms to activate a device on inspiration are not likely to be consistent with the needs of mass vaccination campaigns (e.g., low cost, ease of use, disposability). Thus, the first key element making a substantial differentiation between nasal versus pulmonary immunisation methods is the absence of any requirement for coordination of the subject's inhalation when spraying into the nostril. In the absence of air movement during powder spraying, powder dispersion will not occur in the airway beyond the cavum in the direction of the lung airways. As a consequence of the fact that nasal deposition occurs primarily by inertial impaction, nasal delivery is applicable even in infants. The requirement of a subject's coordination of device actuation and air inhalation, and the dependence of deposition site on breathing are the major drawbacks of both active and passive dry powder inhalers (DPIs) targeting the pulmonary system. As a result, current pulmonary DPI devices are not prescribed for use in children below the age of 4. In addition, paediatric use of DPIs for children above the age of 4 still requires a certain level of parent and subject education, which significantly limits their applicability to mass immunisation even for older children. In comparison, nasal delivery is comparatively easy to use for preventive vaccine delivery in children.

One of the main concerns regarding intranasal immunisation with either liquid or dry powder is the potential for upper respiratory diseases to prevent effective immunisation in some patients. Rhinitis is a very frequent pathological condition affecting the nasal cavity; the incidence in children is estimated to be in the range of 40% of the population with peak incidence during the winter period. Two main types of rhinitis have to be considered: infectious rhinitis and allergic rhinitis. Infectious rhinitis induces local inflammation, with abundant and thick mucous serous fluid blocking the nasal passage due to mucosal oedema and pus. Superimposed viral and bacterial infections are usually the leading root causes. The nasal cavity obstruction impacts mostly the rear part of the nasal passage, involving the superior and medium turbinates. With this condition, part of the vestibular area remains normal. Powder deposition in the vestibular area and most of the anterior part of the lower turbinate remains possible. Wiping the nose before powder spraying is highly recommended. Infectious rhinitis is not expected to be a major concern for powder delivery in the nose, as the targeted M cells are numerous throughout the nasal epithelium. Finally, mucociliary clearance in the case of active rhinitis with nasal passage blockage is usually reduced, which tends to increase the residence time of deposited particles.

Allergic rhinitis is probably the most critical concern for intranasal immunisation because, in addition to mucosal inflammation, a large increase in mucosal fluid floods the nasal passage with a dramatic increase in particle clearance from the nasal cavity surfaces in both the direct vestibular area and cavum. In such a pathological condition, any powder deposition will be quickly washed out from the nasal cavity, potentially interfering with effective immunisation by limiting the residence time of the vaccine in the nasal cavity.

The presence of respiratory disease is also a concern for pulmonary immunisation. Bronchitis due to superimposed bacterial infection in the lower airway, and allergic asthma are as

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frequent as rhinitis. In developing countries, 20 – 30% of children experience allergic diseases and among these children at least 20% are affected by asthma or chronic cough. Lower airway pathological disease can be expected to be at roughly the same level of concern as rhinitis in terms of incidence. The major difference is that ongoing bronchitis or asthma attack will contraindicate vaccine delivery, but infectious rhinitis probably would not unless significant systemic symptoms are involved.

The FDA approval of Flumist provides a regulatory background that can be expected to help significantly in the preclinical and clinical development strategies for further intranasal vaccine products. In contrast, there are currently no licensed pulmonary vaccine products.

For the reasons cited above, nasal immunisation is expected to be more broadly applicable than pulmonary immunisation for respiratory pathogens, and possibly for sexually transmitted pathogens as well. Both intranasal and pulmonary routes of vaccine delivery have shown promise, and the route of preference for a particular vaccine will ultimately depend on their relative clinical efficacy as well as the relative practicality of the delivery systems.

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. BROWN L: Commercial challenges of protein drug delivery. *Expert Opin. Drug Deliv.* (2005) 2(1):29-42.
2. KERSTEN G, HIRSCHBERG H: Antigen delivery systems. *Expert Rev. Vaccines* (2004) 3(4):453-462.
3. PRAUSNITZ MR: Overcoming skin's barrier: the search for effective and user-friendly drug delivery. *Diabetes Technol. Ther.* (2001) 3(2):233-236.
4. SENEL S, KREMER M, NAGY K, SQUIER C: Delivery of bioactive peptides and proteins across oral (buccal) mucosa. *Curr. Pharm. Biotechnol.* (2001) 2(2):175-186.
5. HARRIS D, ROBINSON JR: Drug delivery via the mucous membranes of the oral cavity. *J. Pharm. Sci.* (1992) 81(1):1-10.
6. DEVILLERS G: Exploring a pharmaceutical market niche and trends: nasal spray drug delivery. *Drug Delivery Technology* (2003) 3(3):38-41.
7. MARTINEAU B: Stats. Sticking with growth. Vaccine market continues to rise. *Mater. Manag. Health Care* (2004) 13(11):42.
8. GRECO M: Key drivers behind the development of global vaccine market. *Vaccine* (2001) 19(13-14):1606-1610.
9. HOLMGREN J, CZERKINSKY C: Mucosal immunity and vaccines. *Nat. Med.* (2005) 11(4 Suppl.):S45-S53.
10. KOZLOWSKI PA, CU-UVIN S, NEUTRA MR, FLANIGAN TP: Comparison of the oral, rectal, and vaginal immunization routes for induction of antibodies in rectal and genital tract secretions of women. *Infect. Immun.* (1997) 65(4):1387-1394.
    - • Achievement of remote mucosal immune responses via nasal and other immunisation routes in humans.
11. MARTONEN T, YANG Y: *Inhalation Aerosols: Physical and Biological Basis for Therapy*. AJ Hickey (Ed.), Marcel Dekker, New York, NY, USA (1996).
    - •• Primer on pulmonary delivery technologies.
12. NEWMAN SP, PITCAIRN GR, DALBY RN: Drug delivery to the nasal cavity: *in vitro* and *in vivo* assessment. *Crit. Rev. Ther. Drug Carrier Syst.* (2004) 21(1):21-66.
    - •• Thorough review of nasal delivery, with an emphasis on imaging techniques used in deposition studies.
13. ZANEN P, LAUBE B: *Drug Delivery to the Lung*. H Bisgaard, C O'Callaghan, G Smaldone (Eds), Marcel Dekker, New York, NY, USA (2002).
14. KUBLIK H, VIDGREN MT: Nasal delivery systems and their effect on deposition and absorption. *Adv. Drug Deliv. Rev.* (1998) 29(1-2):157-177.
    - •• Extensive review of nasal delivery systems.
15. RANADE VV: Inhalation therapy: new delivery systems. *Am. J. Ther.* (2001) 8(5):367-381.
16. DAHLOF CG: Non-oral formulation of triptans and their use in acute migraine. *Curr. Pain Headache Rep.* (2005) 9(3):206-212.
17. BOMMER R: Latest advances in nasal drug-delivery technology. *Med. Device Technol.* (1999) 10(4):22-28.
18. SOANE RJ, HINCHCLIFFE M, DAVIS SS, ILLUM L: Clearance characteristics of chitosan based formulations in the sheep nasal cavity. *Int. J. Pharm.* (2001) 217(1-2):183-191.
    - • Demonstrates the use of chitosan microparticles for achieving increased nasal residence times.
19. HUANG J, GARMISE RJ, CROWDER TM *et al.*: A novel dry powder influenza vaccine and intranasal delivery technology: induction of systemic and mucosal immune responses in rats. *Vaccine* (2004) 23(6):794-801.
    - • Demonstration of a nasal powder influenza vaccine delivery system providing an improved vaccine stability.
20. RUDIN A, JOHANSSON EL, BERGQUIST C, HOLMGREN J: Differential kinetics and distribution of antibodies in serum and nasal and vaginal secretions after nasal and oral vaccination of humans. *Infect. Immun.* (1998) 66(7):3390-3396.
21. BERGQUIST C, JOHANSSON EL, LAGERGARD T, HOLMGREN J, RUDIN A: Intranasal vaccination of humans with recombinant cholera toxin B subunit induces systemic and local antibody responses in the upper respiratory track and the vagina. *Infect. Immun.* (1997) 65(7):2676-2684.
22. DAVIS SS: Nasal vaccines. *Adv. Drug Deliv. Rev.* (2001) 51(1-3):21-42.
    - • Thorough review of nasal vaccine delivery.
23. BOYAKA PN, TAFARO A, FISCHER R, LEPPLA SH, FUJIHASHI K, MCGHEE JR: Effective mucosal immunity to anthrax: neutralizing antibodies and Th cell responses following nasal immunization with protective antigen. *J. Immunol.* (2003) 170(11):5636-5643.

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24. LICALSI C, CHRISTENSEN T, BENNET JV, PHILLIPS E, WITHAM C: Dry powder inhalation as a potential delivery method for vaccines. *Vaccine* (1999) 17(13-14):1796-1803.
25. PEART J, CLARK MJ: New developments in dry powder inhaler technology. *Am. Pharm. Rev.* (2001) 4(3):37-45.
26. OWENS DR, ZINMAN B, BOLLI G: Alternative routes of insulin delivery. *Diabet. Med.* (2003) 20(11):886-898.
27. PATTON JS, BUKAR JG, NAGARAJAN S: Inhaled insulin. *Adv. Drug Deliv. Rev.* (1999) 35(2-3):235-247.
28. PATTON JS, BUKAR JG, ELDON MA: Clinical pharmacokinetics and pharmacodynamics of inhaled insulin. *Clin. Pharmacokinet.* (2004) 43(12):781-801.
29. SKYLER JS, CEFALU WT, KOURIDES IA, LANDSCHULZ WH *et al.*: Efficacy of inhaled human insulin in Type 1 diagetes mellitus: a randomised proof-of-concept study. *Lancet* (2001) 357(9253):331-335.
30. ALPAR HO, SOMAVARAPU S, ATUAH KN, BRAMWELL VW: Biodegradable mucoadhesive particulates for nasal and pulmonary antigen and DNA delivery. *Adv. Drug Deliv. Rev.* (2005) 57(3):411-430.
31. CUTTS FT, CLEMENTS CJ, BENNETT JV: Alternative routes of measles immunization: a review. *Biologicals* (1997) 25(3):323-338.

•• Review of alternate-route clinical measles immunisation data.

32. LICALSI C, MANIACI MJ, CHRISTENSEN T, PHILLIPS E, WARD GH, WITHAM C: A powder formulation of measles vaccine for aerosol delivery. *Vaccine* (2001) 19(17-19):2629-2636.
33. *Pharmaceutical Inhalation Aerosol Technology (2nd Edition)*. AJ Hickey (Ed.), Marcel Dekker, New York, NY, USA:(2003).
34. FORD B, SULLIVAN VJ, BHUTA WILLS A: Comparative analysis of BD's novel active powder delivery device with commercial products. *Proceedings of Respiratory Drug Delivery VIII*, Tucson, AZ, USA (2002):367-370.
35. MIKSZTA JA, SULLIVAN VJ, DEAN C *et al.*: Cutaneous or mucosal delivery of anthrax vaccine provides complete protection against inhalational anthrax. *J. Infect. Dis.* (2005) 191:278-288.

• First demonstration of the efficacy of nasal powder anthrax immunisation in the rabbit challenge model.

36. ILLUM L, JABBAL-GILL I, HINCHCLIFFE M, FISHER AN, DAVIS SS: Chitosan as a novel masal delivery system for vaccines. *Adv. Drug Deliv. Rev.* (2001) 51(1-3):81-96.
37. O'HAGAN DT, MACKICHAN ML, SINGH M: Recent developments in adjuvants for vaccines against infectious diseases. *Biomol. Eng.* (2001) 18(3):69-85.
38. O'HAGAN DT, VALIANTE NM: Recent advances in the sicovery and delivery of vaccine adjuvants. *Nat. Rev. Drug Discov.* (2003) 2(9):727-735.

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