Expert Opinion

Alternative routes of influenza vaccine delivery

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The global emergence of virulent avian influenza and the concomitant raised threat of an influenza pandemic has increased interest in the development of improved influenza vaccines. Whereas conventional influenza vaccines are delivered by parenteral injection, an intranasal influenza vaccine has been marketed since 2003. Many other technologies are in development for intranasal, oral, epidermal and topical influenza vaccines. This editorial summarises the advances in clinical development of technologies for needle-free influenza vaccine delivery.

Keywords: epidermal, influenza, intranasal, oral, topical, vaccine

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1. Introduction

Although most vaccines are delivered by needle injection, several successful vaccines, including polio, typhoid, cholera, rotavirus and smallpox, are delivered by alternative routes. Conventional influenza vaccines are based on purified preparations of the influenza virus, delivered by needle injection. These vaccines elicit strain-specific serum neutralising antibodies and are generally efficacious and effective [1]. However, immunogenicity and effectiveness can be low in at-risk populations, notably in the elderly [2-5]. The goal of improved influenza vaccines is for increased immunogenicity and efficacy, as well as to increase patient acceptance [6,7]. One approach is delivering the vaccines by non-parenteral routes of administration, including intranasal, oral, topical and epidermal delivery. The physical and immunological mechanisms of immunisation by these routes have been recently reviewed [8].

Interest in developing needle-free influenza vaccines is motivated by several factors (reviewed in [8-10]). Conventional vaccines are designed to elicit circulating antibodies and are inefficient at eliciting antibodies in the respiratory tract. Vaccines that are delivered by mucosal routes can increase mucosal antibody responses, which may be important in blocking the virus at the site of primary infection and therefore improving efficacy. It is also expected that needle-free immunisation would increase vaccine acceptance. This may be a factor in the case of an influenza pandemic requiring rapid vaccination of a large population. Non-injected vaccines also benefit healthcare providers, avoiding risk of needle-stick injuries and sharps disposal. This is especially important with the movement of influenza vaccination procedures into community-based settings [11], and in developing countries where injection safety is a serious concern.

2. Intranasal influenza vaccines

In the last few years, two intranasal influenza vaccines have been approved for marketing. The first intranasal influenza vaccine (Nasalflu®; Berna Biotech) was based on an inactivated virosomal subunit adjuvanted by *Escherichia coli* heat-labile toxin (LT). Nasalflu was licensed in Switzerland for the 2000 – 2001 influenza season. Although the vaccine had been safe in clinical trials [12], Nasalflu was withdrawn from the market after 46 cases of Bell's palsy were reported in vaccine recipients [13]. These adverse events may be attributable to the LT mucosal adjuvant. In 2003, a live

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attenuated, cold-adapted intranasal vaccine-trivalent (CAIV-T; FluMist®, Medimmune Vaccines), was licensed in the US [14]. CAIV-T was shown to be safe, well tolerated and effective in adults and children [15,16]. CAIV-T is licensed for use in healthy persons aged 5 – 49 years; however, it is not indicated for the majority of populations for whom annual influenza vaccination is recommended. Studies are in progress with the goal of expanding the vaccine indications [17].

Lymphoid tissues in the upper respiratory tract are important immune inductive sites [10]. Intranasal vaccines are ideal for eliciting immune responses at the site of primary influenza infection, and the efficacy of CAIV-T is correlated with presence of influenza-specific nasal IgA antibodies [18]. For injected influenza vaccines, a serum haemagglutination-inhibition (HAI) titre of ≥ 1:40 is generally regarded as correlating with protection against influenza [19,20]. Although CAIV-T elicits lower serum HAI titres in adults than conventional injected influenza vaccines, nasal IgA antibody responses are significantly higher [1]. Despite differences in antibody responses, the efficacy of conventional and intranasal influenza vaccines against culture-positive influenza illness are similar [1].

Several other intranasal vaccines have been tested in clinical trials. Proteosomes are microparticles of purified proteins that serve as both a delivery system and adjuvant for mucosal vaccines. A proteosome vaccine (FluINsure; ID Biomedical) composed of inactivated influenza antigen non-covalently associated with outer membrane proteins of *Neisseria meningitides* [21,22], was well tolerated in healthy adults. The vaccine elicited ≥ 4-fold rise in serum HAI titres in 13 – 50% of subjects and nasal IgA responses in 13 – 83% of subjects, with the highest responses in subjects receiving a higher or second dose of the antigen.

A potentially safer detoxified mutant of LT (LTK-63) has been developed as a mucosal adjuvant and was evaluated in a Phase I intranasal influenza vaccine trial [23]. LTK-63 and trivalent inactivated influenza antigens were co-delivered intranasally using a bioadhesive formulation. Two doses of the adjuvanted intranasal vaccine elicited lower serum antibody titres but higher nasal IgA responses than one dose of the influenza vaccine delivered intramuscularly. Either two doses of the vaccine or a single higher dose of the antigen may be required for adequate immunogenicity of intranasal-inactivated influenza vaccines.

An alternative approach is expression of the major protective antigen of influenza, haemagglutinin (HA) in a viral vector with tropism for the respiratory tract. A replication-defective adenovirus expressing a single influenza HA gene was found to be safe and immunogenic in a Phase I trial [24]. A single intranasal vaccination elicited ≥ 4-fold elevation in HAI antibody titres in 67% of adult subjects, increasing to 83% following a second vaccination. Nasal IgA responses were not tested.

Other technologies for intranasal influenza vaccination are being tested in rodents, including DNA vaccines [25,26], formalin-inactivated virus [27], attenuated live virus [28], baculovirus virus-like particles, [29], retro-inverso peptide [30], and formulations of Iscomatrix® (CSL), virosome, lipid, nanoemulsion, powder, surf-clam adjuvant or chitin [31-37].

Additional testing is warranted to demonstrate the safety of intranasal vaccines in persons with asthma or other respiratory problems, as well as to the lack of CNS exposure to vaccine. For CAIV-T, safety studies also demonstrated the lack of transmission to unvaccinated contacts [38].

3. Oral influenza vaccines

Oral vaccination is attractive due to the simplicity of handling and use. Some currently marketed oral vaccines are based on live attenuated pathogens. A successful oral vaccine must address several challenges, including stability through the gastrointestinal tract, dilution and antigen contact with intestinal M cells. In comparison to parenteral injection, oral vaccination has generally required 100-fold more antigen to elicit 100-fold lower immune responses [39]. An enteric-coated inactivated influenza vaccine elicited nasal immune responses, but serum antibodies were not observed [40]. Given these challenges and the lability of the influenza HA, it is not surprising that few oral influenza vaccines have advanced to clinical testing.

4. Topical and epidermal influenza vaccines

The viable epidermis of the skin is laced with a network of antigen-presenting cells, the Langerhans cells, which form a line of defence against pathogens. Antigen presentation to the Langerhans cells leads to induction of both systemic and mucosal immune responses [41,42]. Skin delivery of vaccines is appealing from the perspective of patient acceptability and ease of administration. In theory, the skin should be easily accessible to vaccines. In practice, the outermost layer of the skin, the stratum corneum, acts as a protective barrier and simple topical application of a vaccine rarely yields an adequate immune response.

Several methods have been employed to facilitate topical delivery, including formulations that are based on topical adjuvants, permeability enhancers and colloidal carriers, and physical means of skin disruption such as abrasion, tape stripping or microporation to remove the stratum corneum (reviewed in [8]). In preclinical models, topical vaccines are generally inefficient, requiring high doses of antigen to elicit adequate immune responses. In addition, any disruption of the skin's protective barrier raises concerns for inadvertent introduction of pathogens. A replication-defective adenovirus vector expressing monovalent HA was immunogenic when applied to abdominal skin of healthy adults [24]. The skin was pretreated by shaving with a razor followed by 30 strokes with a toothbrush. Serum HAI antibodies were elicited following this immunisation procedure, but responses were higher when the same vaccine was delivered intranasally [24].

Powder- and particle-mediated systems have also been developed to deliver DNA and protein vaccines to the epidermis

(reviewed in [43]). The goal of particle-mediated DNA vaccination is to propel DNA-coated gold particles directly into the cytoplasm and nuclei of cells of the viable epidermis. A DNA vaccine encoding monovalent influenza HA was tested for safety and immunogenicity in a Phase I clinical trial [44]. Safety concerns included the potential for bleeding or persistent skin discolouration. A 4-fold increase in titres was elicited in 64 – 67% of subjects at doses of 2 – 4 µg DNA, and the seroprotection rate was 100% at the 4-µg dose. Serum HAI titres were lower and slightly delayed compared with antibody responses that were typically achieved with conventional vaccines.

A dense powder formulation has been developed for epidermal delivery of conventional influenza vaccine using an approach termed epidermal powder immunisation (reviewed in [43]). In Phase I, seroconversion rates were 75 – 100% against the three influenza strains in the vaccine [45]. These results are remarkable among the published literature for non-replicating needle-free influenza vaccines, in that immune responses were comparable between the intramuscular and needle-free vaccines at the same antigen dose level. Although mucosal immune responses were not tested in the clinical trial, influenza-specific secretory IgA was detected in animals immunised with adjuvanted influenza vaccines by epidermal powder immunisation [41].

5. Conclusion

At present, one needle-free influenza vaccine, intranasal CAIV-T, is marketed in the US. Early clinical results have been published for a handful of influenza vaccines delivered by intranasal, topical and epidermal routes. The scientific basis for intranasal influenza vaccination is stimulation of immune responses at the site of primary influenza virus replication, the upper respiratory tract, to modulate initial infection and disease. Interestingly, mucosal immune responses can also be elicited by epidermal immunisation. The clinical benefit of mucosal antibody has been difficult to assess, as the efficacy of CAIV-T and conventional injected vaccine are similar [1]. The immunogenicity of conventional influenza vaccination is measured by fold increase in serum HAI antibody titre following vaccination, seroconversion rate (≥ 4-fold increase or titre ≥ 1:40) and seroprotection rate (titre ≥ 1:40) [19]. Serum HAI antibody may not be the most appropriate immune correlate for vaccines delivered by alternative routes where cellular and/or mucosal immune responses contribute to protective efficacy [46]. In controlled human influenza challenge experiments, vaccine-induced influenza-specific serum antibody responses correlated to protection from experimental infection [20]. Where serum antibody responses were low, nasal antibody responses played a role in protection. Measurement of mucosal antibody responses is difficult to standardise, so it has not been possible to establish a protective antibody level. The development of alternative delivery routes is generating data to support establishment of alternative correlates of protective immunity, such as mucosal and/or cellular immune responses, and will necessitate development of robust validated assays for these parameters.

6. Expert opinion

Licensing of the CAIV-T intranasal influenza vaccine was an important step in demonstration of clinical feasibility and commercial viability of needle-free influenza vaccines. The efficacy of the intranasal vaccine is at least comparable to conventional vaccines. The next goal for alternative delivery technologies is to develop vaccines with superior efficacy. Although some persons have an aversion to needles, the key unmet need is not patient acceptance but rather improved efficacy in at-risk populations, particularly the elderly and those with chronic illnesses. Although it is perceived that most recipients of influenza vaccine would prefer a needle-free route such as intranasal, this is not always the case [47]. Influenza vaccine selection is price-sensitive, and third-party payers will not necessarily reimburse at a higher rate for a needle-free vaccine [48]. Improved efficacy will be required to drive pricing and broaden interest in alternative routes of vaccination. None of the needle-free approaches have demonstrated the ability to elicit serum HAI antibody titres that are superior to those elicited by conventional vaccines. In fact, the serum antibody titres are lower for most inactivated needle-free vaccines than when the same vaccine dose is given parenterally.

In contrast to serum antibody, intranasal or epidermal vaccines are more likely to elicit mucosal immune responses than injected vaccines. This local immunity may contribute not only to reduction in disease severity, but also to reduction in virus transmission. The next goal for influenza vaccine researchers will be the development of vaccine technologies that elicit both robust mucosal and systemic antibody responses. Alternative delivery routes that activate the mucosal immune system should also play an important role in achieving these goals. Achieving a greater breadth of immune responses, including cellular immunity as well as mucosal and systemic antibodies, should provide advantages in terms of ability to protect against drifted strains with less genetic similarity to the vaccine strain.

In the next few years, it is expected that additional intranasal vaccines, such as the proteosome vaccine, will progress to late stage clinical trials. New technologies for oral antigen delivery will be needed before a commercially viable oral influenza vaccine is feasible. Epidermal influenza DNA and protein vaccines are showing promise in early clinical testing. However, the epidermal vaccine technologies require the use of a device, in some cases a single use, disposable unit. In order to be commercially attractive, development of a multi-dose device may be required to reduce the cost per unit dose of vaccine, as well as distribution and storage requirements.

Both conventional influenza vaccines and CAIV-T are given as a single annual vaccination in adults, and two doses in previously unvaccinated children. New influenza vaccines should also be effective as a single dose. If an influenza pandemic

emerges, the population will be immunologically naive to the new influenza strain, and it is likely that two doses of vaccine would be required.

Renewed interest in improved influenza vaccine technologies that have been motivated by the avian influenza and risk of influenza pandemic has led to increased funding in the field and are likely to facilitate advancing the development of many influenza vaccine technologies. Needle-free approaches offer promise for addressing some of the unmet needs for improving efficacy and acceptance of influenza vaccines.

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