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Effect of Vaccine Administration Modality on Immunogenicity and Efficacy

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Summary

The many factors impacting the efficacy of a vaccine can be broadly divided into three categories: (1) features of the vaccine itself, including immunogen design, vaccine type, formulation, adjuvant, and dosing; (2) individual variations among vaccine recipients; and (3) vaccine administration-related parameters. While much literature exists related to vaccines, and recently systems biology has started to dissect the impact of individual subject variation on vaccine efficacy, few studies have focused on the role of vaccine administration-related parameters on vaccine efficacy. Parenteral and mucosal vaccinations are traditional approaches for licensed vaccines; novel vaccine delivery approaches, including needless injection and adjuvant formulations, are being developed to further improve vaccine safety and efficacy. This review provides a brief summary of vaccine administration-related factors, including vaccination approach, delivery route, and method of administration, to gain a better understanding of their potential impact on the safety and immunogenicity of candidate vaccines.

Keywords

vaccine; vaccination; vaccine delivery; administration; immunogenicity; efficacy

Introduction

Since Edward Jenner's use of material from cowpox pustules to provide protection against smallpox in 1796[1], modern vaccination has played a significant role in protection against

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infectious disease in the human population. Based on the Advisory Committee for Immunization Practices (ACIP) Vaccine Recommendations, vaccines are currently recommended to prevent 22 infectious diseases in humans in the United States (US) (http://www.cdc.gov/vaccines/hcp/aciprecs/index.html). These recommended vaccines include those previously recommended by the US Center for Disease Control and Prevention(CDC) to prevent 17 infectious diseases in children, adolescents, and adults[2]. Successful vaccination depends on many factors that can impact vaccine efficacy. These factors can be broadly divided into three categories:(1) features of the vaccine itself, including immunogen design, vaccine type, formulation, adjuvant use, and dosing; (2) individual variations among vaccine recipients, such as gender, age, developmental stage, nutrition status, and preexisting immune conditions; and (3) vaccine administration-related parameters, including vaccination approach, delivery route, and method of administration, number of immunizations, immunization site, and intervals between administrations. While a large volume of literature exists related to the design of vaccines[3–12], and more recently, systems biology research has started to dissect the impact of individual subject variation on vaccine efficacy[13–15], few studies have focused on the role of vaccine administration-related parameters on vaccine efficacy.

Based on historical knowledge and recent literature, this review summarizes the following vaccine administration-related factors and their potential influence on vaccine immunogenicity and efficacy: vaccination strategy, route of vaccine delivery, site of inoculation, vaccine delivery tools, and alternative vaccine delivery approaches. Use of such knowledge will allow for the development of optimal vaccination strategies as part of a critical pathway to maximize the efficacy of candidate vaccines in both preclinical and clinical studies.

1. Vaccination strategies

The vaccination strategy can greatly influence the immunogenicity, efficacy, and safety of a vaccine. For any specific vaccine product, vaccine immunogenicity and efficacy can be dramatically affected by the vaccination strategy used, including number of and interval between immunizations, and use of prime/boost regimens and vaccine modulators.

It has been generally accepted that a proper vaccination schedule requires a minimal number of doses and an optimal interval between immunizations. Most currently licensed vaccines are administered either by intramuscular or subcutaneous needle injection, and require multiple doses to elicit an adequate antibody response with an interval variation between 4 weeks and 6 months. Due to the complexity of different types of vaccines, there is no standard universal formula that can be used to determine an appropriate vaccination strategy. However, it is important to understand the impact of vaccine administration parameters on immunogenicity and efficacy.

1.1 The number of and interval between immunizations—Among the 22 vaccines recommended by the ACIP, 20 of them (with the exclusion of herpes zoster and pneumococcal 13-valent conjugates), require one or more booster vaccinations in order to reach desired protection levels (http://www.cdc.gov/vaccines/schedules/)[2]. Vaccine

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immunogenicity and efficacy can be increased upon repeat vaccinations as demonstrated in different populations, including the vaccination of young adults with inactivated influenza A/H5N1 vaccine[16] and infants with pneumococcal conjugate vaccines[17]. Vaccine immunogenicity and efficacy may also be affected by several booster-related variables, including the number of and interval between immunizations and the type of booster used. The minimum number of immunizations needed to generate adequate protection often depends on vaccine type and dosing, as well as the age and health status of the vaccinee. For example, one dose of non-adjuvanted inactivated A/H1N1 vaccine consisting of 15 μg of hemagglutinin (HA) was adequate to elicit protective antibody responses against influenza, as determined by the FDA Center for Biologics Evaluation and Research (CBER), three weeks after administration in 9-17 year-old healthy subjects; however, younger children, aged 3-7 years, required two immunizations of the same vaccine to achieve protective titers[18]. For certain patients with a low vaccine response, such as patients on hemodialysis, more immunizations may be needed in order to achieve seroconversion. In these patients, four or more vaccine doses may be needed to achieve seroconversion against hepatitis B virus (HBV) surface antigen (HBsAg)[19, 20].

Variation in intervals between primary and booster immunizations may lead to different levels and qualities of immune responses, depending on the vaccine. Many clinical studies demonstrated that a longer interval between two immunizations may help achieve better immune responses, such as 6 months versus 21 days for the H5N1 vaccine in adults[21], 2 months versus 1 month for the pneumococcal conjugate vaccine in infants[17], and 12 months versus 4 weeks for a measles, mumps, rubella, and varicella (MMRV) combination vaccine in infants[22]. Determination of an optimal interval may be more likely if three or more intervals are examined. It was shown that a minimal interval of ≥ 12 weeks was needed to induce a better immune response after testing different intervals of 4, 8, 12, 16, or 24 weeks between the prime and boost immunizations of H5-HA DNA vaccine prime and monovalent inactivated influenza A vaccine boost in humans[23]. An interval of at least two weeks was needed between two immunizations of MF59-adjuvanted H5N1 influenza vaccine (7.5 μg dose) after testing 1, 2, 3, or 6 weeks intervals in healthy volunteers[24]. In addition, longer intervals might be associated with reduced side effects; for example, intervals < 2 years between vaccinations for tetanus-diphtheria (Td) or tetanus-diphtheria-acellular pertussis (Tdap) vaccines in adults might be associated with an increased incidence of local injection site reactions upon review of historic data[25]. These results suggest that the number of immunizations and intervals between vaccinations need to be taken into full consideration for optimal vaccine efficacy and reduction of potential side effects associated with any given vaccine.

1.2 Heterologous prime/boost immunization regimen—Recently, many studies using different disease models have demonstrated the advantage of heterologous prime/boost vaccination, which uses different types of vaccines for prime and boost, compared to homologous prime/boost immunization, which uses the same type of vaccine, for improving immunogenicity in both animals and humans. Below are only a few examples of the use of DNA prime – protein, inactivated vaccine, live attenuated, or viral vector-based vaccine boost, a combination of bacterial and viral vector prime-boost, and a combination of

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inactivated whole virus and subunit vaccine prime-boost vaccine modalities against infectious diseases and cancer. Inactivated whole influenza virus prime followed by split influenza vaccine boost elicited enhanced antibody and protective immune responses when compared with whole virus vaccine alone in mice[26]. DNA vaccine prime/protein vaccine boost induced better antibody and T cell responses then either type of vaccine alone against Schistosomiasis in mice[27], influenza HA DNA vaccine prime followed by trivalent split vaccine boost generated significantly improved protective antibody responses compared to either vaccine alone in rabbits[28], and HIV-1 gp120 DNA vaccine prime-protein boost elicited better neutralizing antibody responses compared to DNA or protein alone HIV in rabbits[29-31]. H5N1 influenza HA DNA vaccine prime-inactivated vaccine boost had significantly improved immunogenicity compared to inactivated vaccine alone in humans[23]. It is also demonstrated that the combination of recombinant Listeria monocytogenes expressing human p53 (LmddA-LLO-p53) and modified vaccinia Ankara (MVA) vaccine expressing human p53 (MVA-p53) prime-boost immunizations resulted in a significant increase in p53-specific CD8 and CD4 T cells and improved tumor regression compared with homologous single vector p53 immunization in mice[32]. The combination of DNA vaccine prime and adenoviral vector intranasal boost improved mucosal antibody responses against HIV-1 gp41 in mice[33]. It is also noted that in the combination of HIV Env/Gag-Pol-Nef plasmid DNA prime followed by MVA-C (HIV Env/Gag-Pol-Nef) with HIV CN54 gp140 protein (+/−GLA-AF adjuvant), the DNA were able to mount a statistically significant anamnestic response to the boost vaccines in mice[34].

2.3 Inclusion of immune modulators (adjuvants)—Immune modulators and adjuvants are important components of modern vaccines, subunit-based vaccines, in particular. Many studies have shown that the use of proper immune modulating agents could have a positive effect on improving vaccine efficacy. One of the problems for subunit-based vaccines, including protein, peptide, and DNA vaccines, is that when administered alone and without adjuvant, they are not very immunogenic and do not elicit protective immunity against infectious agents or cancer. In such cases, adjuvants or immune modulators are needed to improve the vaccine's immunogenicity. Although conventional Alum and oil-in-water emulsion adjuvants have been used for vaccination, novel adjuvants will be required to further improve immune responses and the efficacy of novel vaccines.

It has been known that activation of toll-like receptors (TLRs) of the innate immune system can have a significant impact on adaptive immune responses[35]. Activation of TLRs results in stimulation of antigen presenting cells (APCs) and enhanced B cell and T cell activation. Ligands for different TLRs have been identified and TLR agonists are considered promising vaccine adjuvant candidates. Topical imiquimod cream (Aldara), for example, is a TLR7 agonist used to enhance both the innate and acquired immune pathways (particularly T helper cell type 1-mediated immune responses) for vaccination[36].

In animal studies, imiquimod was shown to expedite the immune response against influenza virus infection when combined with influenza vaccine in mice[37]. Topical imiquimod enhanced anti-OVA antibody responses by 100-fold and markedly increased cellular responses compared to mice not given imiquimod[38]. Topical imiquimod enhanced the antitumor immunity induced by human papillomavirus (HPV) DNA vaccination in mice[39].

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Topical imiquimod cream (Aldara) has been approved for the treatment of cutaneous tumors[40] and other types of tumors, including intracranial tumors[41]. However, topical imiquimod cream has also been shown to diminish immune responses; specifically, imiquimod cream on the skin prior to intradermal vaccination did not enhance the humoral response to hepatitis B vaccine in humans[42] and administration of imiquimod resulted in a lower immune response after intradermal or subcutaneous administration of the hepatitis C virus (HCV) peptide vaccine, IC41, in healthy subjects[43].

Another commonly used immunomodulator is unmethylated CpG oligonucleotide. The immune modulation effect is through activation of TLR-9[44, 45]. It has been used as a stand-alone agent to combat cancer, including lymphocytic leukemia[46] and glioblastoma[47], or in combination with other agents or therapies[48]. It has also been used successfully to enhance the efficacy of many vaccines for infectious diseases[49]. It has a strong (mainly Th1) immune-enhancing effect as observed in a tuberculosis vaccine[50] and in a Her2 positive cancer vaccine[51].

Monophosphoryl lipid A (MPL), as an adjuvant, is an TLR4 agonist with greatly reduced toxicity while maintaining most of the immunostimulatory activity of lipopolysaccharide, has also been used extensively in clinical trials as a component in prophylactic and therapeutic vaccines targeting infectious disease, cancer, and allergies[52]. Two approved vaccine products, Cervarix and Fendrix, are approved for the prevention of HPV and HBV, respectively, that contain the immune potentiator adjuvant, MPL, with alum as the delivery system. The MPL immune potentiator is located on the surface of alum particles by adsorption, similar to the vaccine antigen[53].

In addition to TLR agonists, many other adjuvants or combinations of different forms of adjuvants have also been under rapid development and in different stages of the pre-clinical and clinical study pipeline, including MF59, AS04, ISCOMATRIX™ adjuvant, and QS-21 for novel vaccine development[53, 54]. Studies demonstrated that MF59-adjuvanted influenza vaccine (FLUAD) was more immunogenic and elicited higher antibody responses in both elderly and non-elderly adults compared with the non-adjuvanted influenza vaccine (Fluzone)[55, 56], and a MF59-adjuvanted inactivated influenza vaccine containing A/Panama/1999 (H3N2) induced broader serological protection against an heterovariant influenza virus strain when compared to conventional subunit or split influenza vaccines in elderly people[57]. In a phase III clinical trial, AS04-adjuvanted HPV-16/18 vaccine was well-tolerated in women 15–25 years of age, and highly immunogenic and conferred 100% protection against HPV-16/18 persistent infection and associated cervical lesions up to 27 months[58].

2. Route of vaccine delivery

Route of delivery can affect the vaccine localization that may influence the priming of immune cells as well as consequential local and systemic immune responses. Conventional vaccination approaches include mucosal and parental administration, and the choice of one strategy over the other depends on the type of vaccine and protective immunity needed to conquer the disease based on the route of infection and transmission.

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2.1 Mucosal vaccination—Most pathogens enter the human host via the mucosal membranes of the respiratory, digestive, and genital tracts. Mucosal vaccination using subunit-based vaccines may not be able to elicit adequate systemic immune response because many enzymes that are present in the mucosal tissues can easily degrade vaccine immunogens. However, it is more favorable to generate mucosal immunity where infection and transmission occur. In addition, there are clearly other advantages associated with mucosal vaccination, such as the avoidance of a needle injection, which not only causes pain but also requires the assistance of a professional; suitability for mass vaccination[59], and fewer systemic adverse events compared to parenteral administration[60].

Targeting of mucosal compartments to induce protective immunity at both the mucosal site and at the systemic level remains a great challenge. In the last decade, progress has been made in the development of new mucosal candidate vaccines by selecting appropriate antigens with high immunogenicity, designing of new mucosal routes of administration (oral, nasal, pulmonary, and vaginal) and selecting immune-stimulatory adjuvant molecules and carriers[61, 62]. Due to the relatively weak immune response of mucosal vaccines, inclusion of safe and effective mucosal adjuvants remains a priority for vaccine formulation in order to improve both mucosal and systemic immune responses, which can potentially prevent infection at the portal of pathogen entry[63]. Many different types of vaccine adjuvants have been tested in different mucosal vaccines[64]. One type of effective mucosal adjuvant is toxins, such as cholera toxins (CT)[63, 65] or lymphotoxins (LTs)[66]. These mucosal adjuvants seem to promote movement of dendritic cells from the skin to Peyer's patches[67]. Lipids[65] and bile salts[68] are also quite effective for oral vaccines because of their potential effect on membranes. Furthermore, mucosal immunization may produce more IgAs at the mucosal site, an effect generally not seen with parenteral administration[64].

Several preclinical studies have shown that mucosal vaccines could not only elicit mucosal immune responses, but could also achieve equal or comparable systemic immune responses to parenteral vaccination. These studies demonstrated that an inactivated influenza virus vaccine administered intranasally or sublingual immunization with an adjuvanted subunit influenza vaccine could achieve similar levels of influenza virus-specific B cell memory responses to those induced by intramuscular injection in mice[69, 70]. Another study also showed that intranasal and intramuscular administration of an anthrax vaccine could achieve similar protection in rabbits[71]. Studies have demonstrated that intranasal vaccination of highly pathogenic H5N1 or seasonal adjuvanted influenza vaccine produced better protection against influenza virus in mice than that produced by subcutaneous injection of the same vaccine[72].

Aerosol inoculation of a recombinant adenoviral vaccine encoding H1N1 hemagglutinin induced comparable protection compared to parental immunization by intramuscular injection in ferrets[73]. Aerosols are the most promising non-injectable method of measles vaccination studied so far and their efficacy is thought to be comparable to injected vaccine. In one clinical trial, aerosolized measles vaccine appears to be equally or more immunogenic than subcutaneous vaccine in children aged 10 months and older. In another clinical trial, aerosol measles vaccination was more immunogenic than subcutaneous administration as a

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booster in school aged children, and immunogenic in 12-month-old children as a primary dose.[74, 75]

Oral administration of bile salt-incorporated lipid vesicles (bilosomes) containing influenza A antigen actually generated significantly higher antibody titers than intramuscular injection in mice[68]. Sublingual administration of an adenovirus (Ad5)-based Ebola vaccine protected more mice with pre-existing immunity to Ad5 than intramuscular injection[76]. Pulmonary aerosol vaccination in rats with a viral-like particle(VLP)-based vaccine targeting the HIV co-receptor, CCR5, could elicit, not only vaccine-specific IgG and IgA antibodies in serum, but also IgA antibodies at local mucosal sites, while intramuscular vaccination could only induce serum IgG and IgA antibody responses[77]. Since the development of a plant-derived edible vaccine against hepatitis B virus in 1999[78], plant-based edible vaccines have been widely studied against infectious diseases, including HIV, plague, and piglet enterotoxigenic *Escherichia coli* (ETEC) diarrhea, and showed promises of being immunogenic in preclinical studies[79–81].

Another merit is that mucosal immunization can also be applied as a boost vaccination to enhance mucosal immune responses. Hunter et al. reported that an intramuscular prime followed by an aerosol boost using HIV-1 VLP-based vaccine resulted in strong serum and mucosal antibody responses[77]. Herpes simplex virus type 2 (HSV-2) glycoprotein D (gD) DNA vaccine prime followed by liposome intranasal boost induced significantly improved protective immunity against HSV-2 mucosal challenge in mice[82]. Although the currently licensed HPV vaccine is effective by intramuscular injection in human subjects, preclinical study demonstrated that sublingual administration of human papillomavirus 16 L1(HPV16L1) protein vaccine produced the most effective mucosal secretory IgA (sIgA) and serum IgG responses compared to several other modes of mucosal and parenteral administration, including intranasal, intravaginal, and transdermal in mice[83], which could be potentially useful to further improve the mucosal immunity of HPV vaccines.

Mucosal immunization can be delivered though different mucosal sites, and which site is chosen may be based on the pathogen that is being vaccinated against. For example, previous studies have shown that intranasal vaccination with killed whole cell pneumococcal antigens provided better protection than those administered via sublingual and buccal routes in mice[84].

1.2 Parenteral vaccination—Most vaccines are administered through parenteral routes, despite the disadvantage of rarely inducing detectable mucosal immunity. Parenteral vaccine administration generally includes three major routes: intramuscular (IM), subcutaneous (SC), and intradermal (ID) inoculation, either using conventional hypodermic needles or using alternative or needle-free injection devices. Intravenous injection is generally not used for vaccination, as it generally leads to a relatively low immune response compared to other injection routes[85, 86] and can also cause anaphylaxis, including allergic reaction and toxicity. It has been well documented that inadvertent intravenous vaccination can cause fatal adverse pulmonary reaction in calves[87].

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The relative immunogenicity of vaccines by these three routes (IM, SC, and ID) can vary, depending on individual vaccines (Table 1 and Table 2). Other external factors could potentially influence the outcome, such as gender of the vaccinee[88] and type of adjuvant used[89]. In general, ID immunization generates greater immune responses than IM injection (Table 1) while SC and IM immunizations induce very similar responses in clinical studies (Table 2). Presumably, the reason for this may be that the dermis contains more dendritic cells (DCs), which facilitate the capture of antigens, and local inflammation induces maturation of the DCs and their migration into draining lymph nodes[90], which leads to vaccine dose sparing[91]. Intradermal vaccination has been used for populations that do not respond well to an IM injection, such as the HBV vaccine in dialysis patents[20]. A major challenge of ID delivery is correct placement of the needle with commercially available syringes. Another option is to use ID delivery devices to enable more accurate ID delivery[91].

Despite the fact that ID injection of a vaccine is more effective in inducing immune responses, local adverse reactions seem to be more serious with ID administration followed by SC and then IM, with the least local reaction. For example, in human subjects, ID delivery of a DNA vaccine at a lower dose (10% of a full dose) or SC delivery of a full dose was similarly associated with mild local pruritus (itchiness), superficial skin lesions, and injection site nodules but no local site reactions were observed following IM injection[92]. For an alum-adjuvanted inactivated whole-virion influenza A vaccine in adult men[93] and a diphtheria and tetanus toxoids (DT) vaccine in children[94], local adverse events were less severe with IM injection compared with SC injection. Another study showed similar levels of local reactions upon IM or SC administration of two doses of MMRV combination vaccine in healthy children[95]. It has also demonstrated that more pain might be associated with SC/ID injection compared to IM injection during administration of 0.5 ml of *Haemophilus influenzae* type B polysaccharide vaccine (Hib) in children 15 months to 5 years of age[96]. Therefore, the CDC recommends that inactivated vaccines containing an adjuvant be injected into a muscle because SC and ID administration can cause local irritation, induration, skin discoloration, inflammation, and granuloma formation[2].

3. Site and depth of parental injection

The anatomical site of injection has been shown to affect vaccine efficacy. This is partly because antigen administered via different anatomical sites interacts with diverse subsets of APCs, which directs a drastically different immune response[97]. Several studies have shown that the immunogenicity of a vaccine is lower after IM injection into the buttocks than in other regions, such as the thigh for the pertussis vaccine[98], the thigh for the diphtheria, tetanus, and pertussis (DTap) vaccine[98], and the deltoid muscle for the HBV vaccine[99, 100]. For a cancer vaccine, vaccine efficacy is closely associated with the distance from the injection site to the cancer site[101]. Therefore, it is very important to select appropriate anatomical sites for vaccine administration. The CDC recommends the anterolateral aspect of the thigh for infants/toddlers (up to 2 years of age) and the deltoid for children aged 3-18 years for IM injection. The thigh is also recommended for infants, while the upper-outer quadriceps area is recommended for people >12 months of age for SC injection[2].

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Besides the site of injection, another related variable is the depth of injection related to needle length by IM injection. A longer needle may be associated with a greater vaccine efficacy compared to a shorter one in several HBV vaccine studies (Table 3). Side effects have also been found related to needle length, as deeper injections generally lead to less local reaction. Several studies have shown that IM immunization with 25 mm needles significantly reduce the rate and/or magnitude of local reactions relative to a 16 mm needle of the same diameter in infants[102] and in children[103, 104].

Partially related to needle length is the thickness of different tissue layers in multiple age groups. It was reported that the subcutaneous tissue layer thickness of the anterolateral thigh changes from an average 8.6 mm at 2 months to 9.4 mm at 4 months to 10.2 mm at 6 months and to 8.1 mm at 18 months of age, while the corresponding muscle layer thickness in these children is 10.5 mm, 12.2 mm, 14.8 mm, and 16.5 mm, respectively[105].Obviously, a minimum length may be needed for IM injection. Different needle lengths may be required depending on the angle of penetration (90 or 45 degrees to skin's surface)[105].

4. Alternative vaccine delivery tools and methods

In addition to traditional needle injection, novel vaccine delivery methods or devices have been designed and evaluated to enable safer, more comfortable, and/or more reliable administration than conventional injection methods[91]. Since the efficacy of a vaccine appears to be strongly dependent on route, site, and depth of administration, alternative delivery methods as described below may have a profound impact on vaccine efficacy.

4.1 Microneedle delivery—Microneedle delivery may be useful for delivery of large- and small-sized biological agents, including vaccines[106-112]. Different types of microneedles can be made for vaccine delivery, including solid and dissolvable microneedles[113], coated microneedles[114], and hollow microneedles[115].

Theoretically, the use of microneedles could be more effective than a single-needle injection, as the antigens might be more evenly distributed after injection and have a more targeted delivery to antigen-presenting cells in the dermis and epidermis layers under the skin. Several studies demonstrated that administration of microneedle-based vaccines could induce enhanced antibody responses relative to ID delivery for an adenovirus-based malaria vaccine[116], and comparable immune response could be elicited at one-fifth of the dose used in a SC immunization for a measles vaccination[117]. Studies also showed that microneedle delivery of influenza vaccines using a lower dose could generate similar immune response as the full vaccine dose by IM injection[114, 118, 119], aluminum-based recombinant protective antigen vaccine[120], and inactivated rotavirus vaccine[121]. A DNA vaccine was shown more effective when delivered by microneedle array than by IM administration in mice[122].

Another advantage for microneedle delivery is the accommodation for patients' preference for self-vaccination[123]. On the other hand, microneedle-based delivery may cause more frequent local reactions, due to the shallow penetration[119].

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4.2 Needle-free injection—Needle-free injections can be delivered by liquid jet injectors and ballistic injectors[124, 125], which are driven by a high-pressure gas or spring, can respectively deliver liquid-based vaccines and powder vaccine particles intradermally, subcutaneously, or intramuscularly[126-128]. The liquid jet injector was developed in the 1930s and had been used in human mass vaccination campaigns against measles, polio, smallpox and HBV from 1950s to 1980s[129, 130]. While the earlier jet injector devices were multi-use nozzle injectors, the recent advanced jet injectors are disposable-cartridge injectors. Due to potential splash-back contamination, single-dose injector devices are preferred[131]. Compared to traditional needle injection, vaccines delivered by jet injection may lead to superior vaccine efficacy by enabling a wider dispersion of the vaccine in the tissue for better uptake by APCs[132]. The immunogenicity results, however, have not always been superior for jet injection, partly due to variations in injection site and depth, although several studies have shown superior efficacy with jet injection relative to IM or SC, as was the case for a hepatitis A vaccine[132, 133] and a trivalent influenza virus vaccine[134]. Pre-clinical and clinical studies also demonstrated that jet injection could more effectively deliver DNA vaccines to achieve better immune responses against various pathogens including HIV and malaria [135, 136]. Other studies demonstrated either equal[137] or decreased efficacy with jet injection, as shown by a human adenovirus-5 vaccine[138]. Unlike jet injectors, which accelerate a liquid stream, ballistic injectors including gene gun and particle-mediated epidermal delivery (PMED) devices deliver dry, solid particles towards the skin. DNA immunization by gene gun or PMED administration allows the DNA plasmids, which are coated onto gold bead microparticles, to penetrate directly into the cytoplasm, presumably resulting in the DNA being processed by APCs and subsequently presented to B and T cells. Studies have demonstrated that DNA vaccination by gene gun could be much more efficient to elicit improved antibody responses compared to needle injections[139]. A phase I clinical trial showed that an influenza HA DNA vaccine achieved the criteria on all three parameters (seroprotection rate, mean fold increase, seroconversion rate) required for licensure in the European Union at 21 days after a single vaccination by PowderJet gene gun[140]. Another study demonstrated that gene gun delivery of DNA vaccine expressing hepatitis B surface antigen (HBsAg) in naive volunteers resulted in the generation of seroprotective antibody levels and T cell responses against HBV in all 12 vaccinees[141]

Although many advantages are associated with jet/ballistic injection, including more reproducible administration, reduction in vaccination manpower (due to self-administration), decreases in needlestick injuries and cross-contamination, increased patient compliance, and decreased side effects compared to traditional injection, jet/ballistic injection could cause more pain compared to traditional needle and syringe injections[131, 142], including higher rates of pain on injection and injection site reactions for a trivalent influenza virus vaccine[134], greater local reactions in all categories for a hepatitis A vaccine[132], and twice as many adverse events per immunization for a DNA vaccine[143].

4.3 Transcutaneous administration—Transcutaneous immunization (TCI), another needle-free vaccination method, has been widely reviewed[144-147]. Transcutaneous delivery can lead to comparable or better efficacy than traditional injection, as seen with a

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trivalent inactivated influenza vaccine with heat-labile enterotoxin from *Escherichia coli* (LT) as an adjuvant in a dry patch[148].A clear advantage of TCI is self-administration and patient compliance.

A major obstacle for TCI is the antigen permeation barrier of the lipid-rich stratum corneum (SC). A lipid-based vaccine formulation, such as lipid C-based vaccines[149] and emulsion-based vaccines[150] would be ideal due to their compatibility with different forms of vaccines. Several methods have been shown effective, including partial removal of the SC by mild abrasion[151], tape-stripping[152], or device-facilitated creation of aqueous micropores (laser microporation)[153]. A transcutaneous patch could also be designed to contain only a vaccine adjuvant for efficacy enhancement for an injectable vaccine[151].

4.4 Ultrasonication—Ultrasound has found its application in vaccine delivery and cancer immune therapy[154]. Using tetanus toxoid as a model vaccine, it was shown that low-frequency ultrasound (as a potent physical adjuvant) could enhance delivery of tetanus toxoid into the skin without any help of an actual adjuvant[155]. Ultrasonication can be used to trigger release of antigens from a nanoparticle product film for transdermal delivery[156], and to promote DNA vaccine transfection/expression from ultrasound-responsive bubble lipoplexes[157].

Conclusion

A variety of administration-related factors can affect the efficacy of a vaccine product, including vaccination strategy, vaccine delivery route, instruments used for vaccine delivery, and number of, site of, and interval between administrations. These parameters should be taken into account for vaccine design in both preclinical and clinical studies in order to achieve a more satisfactory outcome in inducing more effective immunity against a designated pathogen.

From the prospective of delivery route, more work needs to be done to identify optimal vaccine delivery routes and approaches for different types of vaccines in order to achieve the greatest efficacy with the fewest side effects. At the same time, adjuvant and immune modulator development should be considered part of vaccine formulation development to achieve desirable immune responses.

In most cases, two and more immunizations are required to achieve an adequate immune response, especially in humans. The interval between two vaccinations and the dosage of each injection should be optimized by multiple pilot experiments. A vaccine should be designed with minimal visits/injections, as both the healthcare providers and the vaccinees may miss or delay vaccination. Recently, novel vaccination strategies, including heterologeous prime/boost, have been established and studies to further improve vaccine effectiveness in both preclinical and clinical trials against various pathogens, including infectious diseases and cancer, are underway. These novel vaccination strategies and optimization of vaccine administration approaches may be useful for the design and development of vaccines that induce protective immunity against both emerging infectious diseases, such as highly pathogenic influenza virus or the deadly Ebola virus, in addition to

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those diseases, such as HIV and malaria, for which vaccination by conventional methods do not appear effective.

Other administration-related factors, including needle length and site of injection, have been well documented. Some advanced vaccination devices have been developed and applied in human vaccine studies, including microneedle, needle-free, and ultrasonic delivery methods. Through the incorporation of previous experience and knowledge and contemporary devices, vaccination becomes more effective, exact, reliable, and safe.

Due to our limited understanding and knowledge of the general immune system, the exact mechanism of administration-related differences in vaccine efficacy remains elusive. This short review provides a summary of historical experience and knowledge, and a summary of advanced technology and devices that may be used to optimize administration parameters for improved vaccine efficacy. This important information will be helpful to guide vaccination procedures in order to achieve a better immune response and protection against currently prevalent diseases and also to pave the way for a rapid response to emerging infectious diseases, such as the recently deadly Ebola virus crisis in West Africa.

Expert commentary

In the last several decades, the field of vaccine research and development has experienced significant progress in novel vaccine designs and optimization of vaccination strategy against a wide range of targeted infectious diseases. While the majority of reports have demonstrated that specific immunogen designs and variations among individual vaccine recipients can affect vaccine immunogenicity and efficacy, the impact of administration-related factors on the efficacy of vaccine products has not been well studied. Administration-related factors, including vaccination approach, route of vaccine delivery, instruments for vaccine delivery, the number and site of immunization, and interval between vaccine administrations, should also be taken into account when designing both preclinical and clinical studies in order to achieve the maximal immune responses to prevent a target pathogen.

Five-year view

We anticipate that more attention will be paid to vaccine administration-related factors to further improve vaccine immunogenicity and efficacy over the next 5-years. Comparative studies on the immunogenicity and efficacy of a given vaccine by different vaccination approaches will provide more insight on the impact of vaccine administration-related factors in both pre-clinical and clinical studies. In addition to the conventional parental and mucosal vaccine administration approaches, a number of novel vaccine delivery approaches and strategies will be developed. The combination of optimized vaccine design and vaccination strategies will be tested in both animal models and human clinical trials, including the use of heterologous prime-boost and novel adjuvants as part of the overall vaccination design. Whether a novel delivery approach will be accepted by the field will depend on the safety and immunogenicity results from clinical trials. The field of vaccine research and

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development will make further progress if more efforts can be made toward further optimization of current vaccination administration methodologies.

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Abbreviations

ACIP	Advisory Committee for Immunization Practices
APC	antigen presenting cell
CBER	The Center for Biologics Evaluation and Research
CDC	U.S. Centers for Disease Control and Prevention
CT	cholera toxin
DC	dendritic cell
DT	pediatric diphtheria-tetanus toxoid
FDA	U.S. Food and Drug Administration
Hib	influenzae type B polysaccharide vaccine
HPV	human papillomavirus
ID	intradermal injection
IM	intramuscular injection
LTs	lymphotoxins
MMRV	measles, mumps, rubella, and varicella
SC	subcutaneous injection
Td	adult tetanus-diphtheria toxoids
TDaP	pediatric tetanus-diphtheria toxoids and acellular pertussis
TLR	toll-like receptor
VLP	viral like particle
TCI	transcutaneous immunization

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* Of interest

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Key issues

- Overall, although vaccine administration-related factors may not be physically part of a vaccine, the immunogenicity and safety of a vaccine can be greatly impacted by vaccination administration factors, including vaccination schedules and methods.
- Most vaccines require multiple prime-boost immunizations in order to achieve adequate protective immunity. However, other vaccines may require fewer or more immunizations in order to achieve protective immunity and optimal intervals between immunizations appear to differ among these different vaccines.
- Although conventional intramuscular injection has been used and recommended for many licensed vaccines in the market, the vaccine efficacy and safety profile can be further improved by using an alternative route of vaccine delivery (including subcutaneous and intradermal injection, and needle-free injection) or by taking other administration factors into account, such as inoculation sites and needle length.
- Targeting mucosal compartments to induce protective immunity at both the mucosal site and at the systemic level remains a great challenge. Investigation and understanding of the best way to incorporate the mucosal immunizations into prime-boost vaccination regimens in combination with parenteral vaccination to enhance both mucosal and systemic immune responses is critical.
- With the development of novel vaccine delivery methods, including needle free injection, microneedle delivery, topical application and ultrasonication, safety profile and vaccine delivery efficiency will need to be evaluated individually and in combination with other vaccination approaches.

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Table 1

Comparison of intradermal (ID) and intramuscular (IM) immunization methods for generation of immune responses in clinical studies

Vaccine	Vaccine type	Subject	Immunogenicity: ID vs IM vaccination	Reference
Hepatitis B vaccine	Plasma-derived hepatitis B subunit vaccine	Healthy adults	ID group had higher serum conversion when using the same dose as IM groups; similar seroconversion rates and antibody titers as ID group with 10% of dose used in IM group.	[158, 159]
Hepatitis B vaccine	Recombinant HBsAg vaccine	Hemodialysis patients	Higher seroprotection rates in the ID groups compared to IM groups	[20, 160]
Hepatitis B vaccine	Recombinant HBsAg vaccine	Healthy adults	ID group had higher serum conversion when using the same dose as IM groups; similar seroconversion rates as ID group with 20% of dose used in IM group	[161, 162]
Influenza vaccine	Trivalent inactivated split influenza vaccine	Healthy adults	Similar seroconversion rates as ID group with 20-60% of dose used in IM group	[163, 164]
Influenza vaccine	Trivalent inactivated split influenza vaccine	Infants	Similar seroconversion rates as ID group with 40% of dose used in IM group	[165]
Influenza vaccine	Trivalent inactivated split influenza vaccine	HIV-1 infected adult patients	Similar seroprotection and HAI titers as ID group with 60% of dose used in IM group	[166]
Influenza vaccine	Virosomal adjuvanted trivalent influenza vaccine	Healthy adults	Similar seroconversion rates as ID group with≤40% of dose used in IM group	[167]
Human papillomavirus (HPV) vaccine	HPV16 and HPV18 Recombinant proteins	Healthy adults	Similar seroprotection as ID group with 20% of dose used in IM group	[168]
Hepatitis A vaccine	Virosomal HAV vaccine	Healthy adults	Similar seroprotection rate as ID group with 20% of dose used in IM group	[88]
Rabies vaccine	Inactivated Rabies vaccine	Healthy Adults	Similar immune response as ID group with 10% of dose used in IM group	[169]
Rabies vaccine	Live attenuated Rabies vaccine	Healthy adults	Similar immune response as ID group with 25% of dose used in IM group	[170]

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Table 2

Comparison of intramuscular (IM) and subcutaneous (SC) immunization methods for generation of immune responses in clinical studies

Vaccine	Vaccine type	Subject	Immunogenicity: SC vs IM vaccination	Reference
Hepatitis B vaccine	Recombinant HBsAg protein	Healthy adults	Lower level of antibody responses in SC group compared to IM group	[99]
Influenza vaccine	Inactivated split trivalent influenza vaccines	Female elderly	Lower level of antibody responses in SC group compared to IM group	[171]
Influenza vaccine	Inactivated whole-virion influenza A vaccine with alum adjuvant	Adult men	Lower level of antibody responses in SC group compared to IM group	[93]
Influenza vaccine	Inactivated split trivalent influenza vaccines	Children with neuromuscular disease	Similar antibody titers in both SC and IM groups	[172]
Hepatitis A vaccine	Virosomal HAV vaccine	Healthy adults	Similar seroprotection rates in both SC and IM groups	[88]
Hepatitis A Vaccine	Inactivated HAV Vaccine	Healthy Adults	Similar antibody titers in both SC and IM groups	[133]
Measles-mumps-rubella-varicella (MMRV) vaccine	Live attenuated MMRV vaccine	Healthy children	Similar seroconversion rates in both SC and IM groups	[95]
Measles, mumps and rubella (MMR) vaccine	Live attenuated MMR vaccine	Healthy children	Similar antibody and T cell responses in both SC and IM groups	[173]
Diphtheria, tetanus (DT) vaccine	Toxoid	Children	Similar antibody responses in both SC and IM groups	[94]
Meningococcal vaccine	Quadrivalent polysaccharide vaccine	Adults	Similar antibody responses in both SC and IM groups	[174]
HIV vaccine	DNA vaccine prime - Ad5 viral boost	Healthy adults	Similar antibody and T cell responses in both SC and IM groups	[92]

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Table 3

Antibody responses induced by Hepatitis B vaccines using different injection sites and needle length in clinical studies

Vaccine type	Subjects	Injection site and needle length	Immunogenicity	Reference
Plasma-derived hepatitis B subunit vaccine	Healthy adults	Arm (1-inch), buttock (1-inch or 2-inch)	Injection at arm with 1-inch needle, at buttock using 2-inch needle or 1-inch needle achieved highest, intermediate, or lowest rate of seroconversion and titers to HBsAg, respectively	[100]
Recombinant HBsAg vaccine	Healthy infants	Quadriceps (1-inch or 5/8-inch)	1-inch needle achieved significantly higher antibody titers to HBsAg compared to 5/8-inch needle	[175]
Recombinant HBsAg vaccine	Healthy individuals aged 14-24 years	Deltoid muscle (1 - inch or 1.5-inch)	1.5-inch needle achieved significantly higher antibody titers to HBsAg compared to 1-inch needle	[176]