# Needle-Free Injection: Pros and Cons

C. Scanlon Daniels, DVM, MBA
Circle H Headquarters, LLC, Dalhart, TX

## SUMMARY

Needle-free injection devices (**NFID**) have been available for humans since the 1930s. Their implementation in farm production systems has been slow because of the low expense and ease of use of needle-syringe injection. Recently, there has been a renewed interest in needle-free injection devices in farm animal production systems due to two main factors: 1) immunology research indicates that targeting dendritic cells in the skin and the subcutaneous tissues results in improved immune response with minimal antigen doses and 2) implementation of meat quality assurance standards to minimize needle site lesions that are the result of broken needles and/or bacterial contamination. In this paper we review the literature, both peer and non-peer reviewed, on the use of needle-free injection devices. These devices offer at least an equivalent and often improved immune response to needle-syringe injection without the carcass defects and needle stick worker safety issues associated with conventional injection techniques.

## INTRODUCTION

Vaccination is a significant component of standard management practices in dairy cattle husbandry. Improvements in vaccines and their delivery systems that increase vaccine efficacy, safety, or compliance and minimize animal stress would be valuable for the dairy industry.

Needle-syringe devices have been the predominant method for vaccine and drug delivery for dairy cattle. Although needle-syringe devices are inexpensive and easily adaptable to different settings, needle-free technology offers significant advantages compared to conventional vaccine delivery methods including enhanced safety, enhanced immunogenicity, and fewer injection site lesions (Willson, 2004).

Needle-free injection devices can be divided into 2 types based on the source of power: spring-powered or compressed gas-powered (Table 1). Spring-powered devices are compact and lower cost, but suffer from limited range of force and reduced versatility. Spring-powered devices have been primarily used for subcutaneous administration of drugs. Gas-powered devices (jet injectors) have sustained force generation, greater flexibility, and the ability to deliver larger volumes (Mitragotri, 2006; Baizer et al., 2002). The main disadvantage is its reliance on an exhaustible energy source. Jet injectors have been used for mass vaccinations and can deliver the target molecule at a variety of tissue depths ranging from the dermis to the muscle depending on the force generated by the jet injector (Mitragotri, 2006). The vast majority of vaccine trials in animals have used gas-powered jet injectors (Table 2). This article reviews needle-free technology and its uses in disease control.

**Table 1.** Advantages and disadvantages of needle-free injection devices (**NFID)**

| Advantages | Disadvantages |
|---|---|
| Elimination of broken needles | Higher start-up costs |
| Consistent vaccine delivery | Infrastructure for exhaustible gas systems |
| Reduced vaccine volume | Higher requirement for training and |
| Higher antigen dispersion | maintenance |
| Elimination of worker needle sticks | No one size fits all NFID |
| Elimination of needle disposal | Worker confidence in NFID |
| Lower pain and stress | |

## NEEDLE-FREE TECHNOLOGY: ORIGIN AND METHODOLOGY

Needle-free technology, first called *jet injectors*, were developed in the 1930s and used extensively over 50 yr in mass vaccination programs in people for smallpox, polio, and measles (Reis et al., 1998; Hingson et al., 1963). Using mechanical compression to force fluid through a small orifice, these devices produced a high-pressure stream that could penetrate skin and subcutaneous tissue to deliver the vaccine. Most of the older devices used the same nozzle faces and fluid pathways to dose all the individuals; thereby causing potential safety hazards of transferring blood-borne pathogens between individuals.

In people, new generation needle-free technology uses disposable single-dose cartridges eliminating re-use of the nozzle face and fluid path. Most needle-free technology in production animals use non-disposable nozzle faces. Newer devices use a disposable nozzle face that allows for fast and easy nozzle changes, when necessary, and when transferring to a different farm.

Needle-free injection technology uses force generated by a compressed gas (typically air, $CO_2$ or nitrogen) to propel the vaccine at high velocity through a tiny orifice. When administered through the skin, an ultra-fine stream of fluid penetrates the skin, delivering the vaccine in a fraction of a second to the skin, subcutaneous tissue, and underlying shallow muscle. One major objection to needle-free injections has been the *wetness* associated with residual vaccine on the skin surface (Jones et al., 2005). This *wet* appearance may cause the vaccine administrator to think that the vaccine was improperly administered. Needle-free injection technology has been designed to deliver antibiotics (Apley et al., 2003; Senn et al., 2004), iron dextran (Almond and Roberts, 2004) or vaccine comfortably, accurately, and quickly - without the use of a needle. In contrast, needle-based injections may result in animal stress, vaccine residues, injection site lesions, and broken needles (Willson, 2004; McDowell et al., 2010).

Needle-free injection is precise, reliable, and virtually the same every time (Senn et al., 2004; Schloesser et al., 2008). There are 3 stages in needle-free delivery, and the total amount of time required to deliver the vaccine is less than 1/3 of a second (Figure 1). The three stages are: Stage 1, the peak pressure phase, optimal pressure used to penetrate the skin (< 0.025 sec); Stage 2, the delivery or dispersion phase (~ 0.2 sec); and Stage 3, the drop-off phase (< 0.05 sec). This pressure profile is consistent with each administration of vaccine ensuring each animal is vaccinated at the proper tissue depth. This is not the case with needle-syringe administration of vaccine, which is equipment (e.g. needle length and gauge)

**Table 2.** Needle-Free injectors used with animal health products

| Type of needle-free device | Brand Name/Manufacturer | References |
|---|---|---|
| Spring-loaded | DERMOJET®/VACCI-Jet Société AKRA, France | Diggle et al., 2006 |
| | MEDI-JECTOR®-Antares Pharma, Ewing, NJ | Davies and Simon, 1969 |
| Battery-powered jet injector | Intra Dermal Application of Liquids (IDAL) ®- Intervet, Boxmeer, The Netherlands | Wesley and Lager, 2005<br>Anwer et al., 1999-<br>Aguiar et al., 2001<br>Wang et al., 2001 |
| Gas-powered jet injectors | BIOJECTOR®-Bioject, Tualatin, OR | Thacker et al., 2007<br>Babiuk et al., 2003<br>Rosales et al., 2006<br>Williams et al., 2000<br>Clark et al., 1965 |
| | PULSE® Needle-Free - Felton, Lenexa, KS | Baizeret al., 2002<br>Grosenbaugh et al., 2004<br>Charreyre et al., 2005<br>Jolie and Hoover, 2004<br>Royer et al., 2006<br>Thacker et al., 2003<br>Van Drunen Little-van denHurk, 2006<br>Parent du Chatelet et al., 1997 |
| | AGRO-JET®/MED-JET®-MIT, Montreal, Quebec, CANADA | Reis et al., 1998<br>Jackson et al., 2001<br>Jolie and Hoover, 2004 |

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and technique dependent (Diggle et al., 2006).

In the case of vaccine dispersion, an enhanced dispersion field is a significant consideration that affects the animal's immune response to a given antigen (Baizer, 2002). Traditional needle-and-syringe administration results in a bolus forming in the tissue adjacent to the tip of the needle. The needle-free injection technology improves the dispersion of medication throughout the tissue. As the fluid stream forces its way through the tissue, it follows the path of least resistance, resulting in a widely dispersed, spider-web-like distribution of the medication (Grosenbaugh et al., 2004). Slightly reduced force in the dispersion phase allows the fluid to disperse in the tissue. This wide dispersion of vaccine

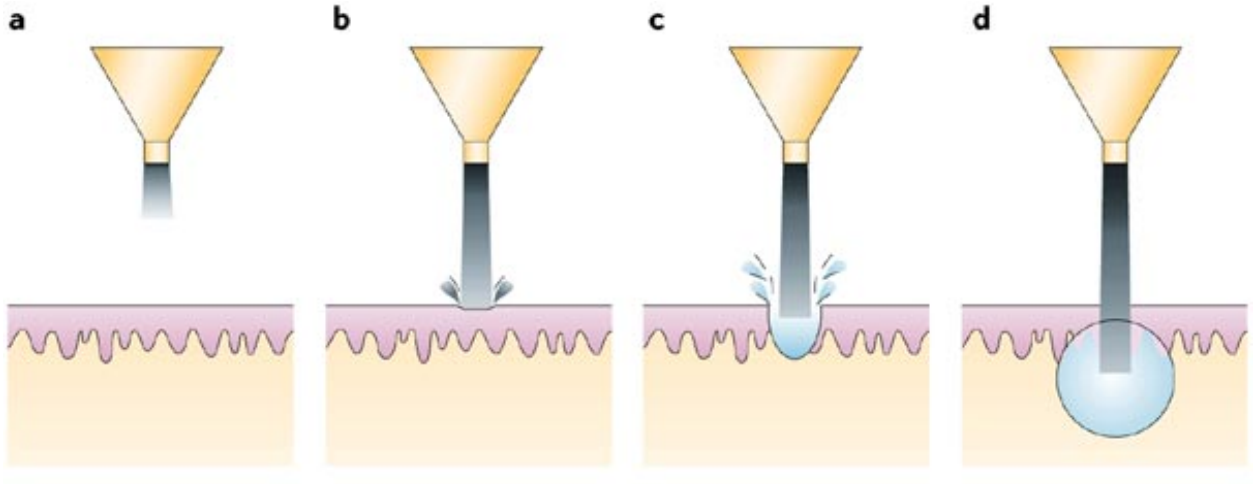




**Figure 1.** Transdermal injections: Visualizing the process. A) Impact of a piston on a liquid reservoir in the nozzle increases the pressure, which shoots the jet out of the nozzle at high velocity (velocity > 100 m/s). B) Impact of the jet on the skin surface initiates formation of a hole in the skin through erosion, fracture, or other skin failure modes. C) Continued impingement of the jet increases the depth of the hole in the skin. If the volumetric rate of hole formation is less than the volumetric rate of jet impinging the skin, then some of the liquid splashes back towards the injector. D) As the hole in the skin becomes deeper, the liquid that has accumulated in the hole slows down the incoming jet, and the progression of the hole in to the skin is stopped. The dimensions of the hole are established very early in the process (a few tens of microseconds) from the time of impact. Stagnation of the jet at the end of the hole disperses the liquid into the skin in a near-spherical shape. Reprinted by permission from MacMillian Publishers Ltd: Nature Reviews: Drug Discovery (Mitragotri , 2006).

is thought to increase exposure of the antigen to antigen-presenting cells; thereby resulting in an enhanced immune response (Jackson et al., 2001).

Theoretically, vaccine delivery via the small needle-free orifice could damage the vaccine's antigenic component via nicking or degradation, thereby altering its antigenicity. A few cattle studies that will be discussed in the next section, have demonstrated enhanced immune system response to antigens delivered via needle-free injection versus conventional needle and syringe (Hollis et al., 2008 a,b). There are a number of studies in swine that have demonstrated an effective immune response to a variety of protein antigens including *M. hyopneumonia* (Jones et al., 2005; Houser et al., 2002; Paquin et al., 2005; Charreyre et al., 2005; Jolie and Hoover, 2004; Royer et al., 2006; Thacker et al., 2007), porcine respiratory and reproductive syndrome virus (**PRRSV**; Paquin et al., 2005), pseudorabies virus (Houser et al., 2002; Thacker et al., 2003), hepatitis B virus (Babiuk et al., 2003), *A. pleuropneumoniae* (Rosales et al., 2006), and swine influenza (Wesley and Lager, 2005). Needle-free DNA vaccines have also been shown to elicit immune responses in swine (Babiuk et al., 2003; Anwer et al., 1999)

## NEEDLE-FREE TECHNOLOGY: EFFECTIVE IMMUNE RESPONSE

Needle-free vaccine delivery has been studied in numerous species besides humans, including cats (Grosenbaugh et al., 2004), dogs (Anwer et al., 1999), cattle (Van Drunen Little-van Hurk, 2006), and pigs (Jones et al., 2005; Houser et al., 2002; Paquin et al., 2005; Charreyre et al., 2005; Jolie and Hoover, 2004; Royer et al., 2006; Thacker et al., 2007; Thacker et al., 2003; Babiuk et al., 2003; Rosales et al., 2006; Wesley and Lager, 2005; Anwer et al., 1999). The vast majority of the needle-free studies demonstrated that needle-free vaccine delivery resulted in an enhanced immune response when compared to traditional needle-and-syringe vaccine delivery. Rabbits vaccinated with 3 doses of plasmid encoding malarial antigen (*Plasmodium falciparum* circumsporozoite protein, pfCSP) by needle-free injection had 8- to 50-fold greater antibody titers than those injected intramuscularly with traditional needle-syringe device (Aguiar et al., 2001). In another study, pigs or dogs vaccinated with a needle-free device subcutaneously or intramuscularly with a plasmid expressing human growth hormone (**hGH**) had antigen-specific titers ranging from 3- to 20-fold higher than titers in animals vaccinated by needle-syringe injection (Anwer et al., 1999).

Like animal studies, many human trials also have demonstrated comparable or enhanced immune response when using needle-free injectors (Jackson et al., 2001; Wang et al., 2001; Williams et al., 2000; Parent du Châtelet et al., 1997; Clark et al., 1965; Davies and Simon, 1969). Overall, when delivered by the needle-free injection technique, all of the vaccines induced either equivalent or superior immunogenicity as measured by seroconversion rates (geometric mean titers, **GMT**).

There have been a few studies evaluating needle free injection in cattle (Houser et al., 2002; Paquin et al., 2005; Reinbold et al., 2007). Two studies performed in dairy and beef cattle demonstrated a greater immune response to some antigens when administered with a needle-free injection device versus conventional needle and syringe (Houser et al., 2002; Paquin et al., 2005). In a third cattle study, the blood born parasite *Anaplasma marginale* was not transmitted by a needle-free injection device, while conventional needle and syringe use did result in transmission in some animals (Reinbold et al., 2007).

There have been several studies with needle-free injection devices in swine (Houser et al., 2002; Paquin et al., 2005; Charreyre et al., 2005; Royer et al., 2006; Thacker et al., 2007; Thacker et al., 2003; Babiuk et al., 2003; Rosales et al., 2006; Wesley and Lager, 2005; Anwer et al., 1999). The use of a NFID with a commercial *M. hyopneumoniae* vaccine demonstrated a serological response to *M. hyopneumoniae* and a reduction in lung lesions following challenge (Jolie and Hoover, 2004).

Another study comparing NFID, intradermal needle-syringe, and intramuscular needle-syringe administration of experimental *M. hyopneumoniae* vaccine formulations was done (Jones et al., 2005). Following the administration of 2 doses of vaccine, the pigs receiving the vaccine using the NFID had higher *M. hyopneumoniae* serological response. In pigs given a single dose of experimental *M. hyopneumoniae* vaccine with a NFID, there was no *M. hyopneumoniae* serological response; but the

**Table 3.** Summary of NFID *Mycoplasma hyopneumoniae* vaccine challenge studies

| Pathogen | Time of Challenge Post Vaccination | Clinical Outcome | Reference |
|---|---|---|---|
| *M. hyopneumoniae* | 28 d | 88% reduction in lung lesions; No difference in ADG | Thacker et al., 2003 |
| *`M. hyopneumoniae* | 20 d | 92% reduction in lung lesions; No difference in ADG | Hollis et al., 2008a |
| *M. hyopneumoniae* | 21 d | 90% reduction in lung lesions; No difference in ADG | Hollis et al., 2008a |
| *M. hyopneumoniae* | 35 d | 78% reduction in lung lesions; No difference in ADG | Thacker et al., 2007 |
| *M. hyopneumoniae* | 160 d | 60% reduction in lung lesions; | Babiuk et al., 2003 |
| *M. hyopneumoniae* | 16 d | 66% reduction in lung lesions | Rosales et al., 2006 |
| PRRSV/*M. hyopneumoniae* | PRRSV 0 d *M. hyopneumoniae* 16 d | 48% reduction in PRRSV lung lesions; 30% reduction in *M. hyopneumoniae* lung lesions | Rosales et al., 2006 |

*M. hyopneumoniae –Mycoplasma hyopneumoniae*
ADG- Average daily gain
PRRSV- Porcine respiratory and reproductive syndrome virus

vaccine was protective against *M. hyopneumoniae* challenge.

A third study was done comparing dosages and needle-and-syringe administration to NFID administration using commercial pseudorabies virus (**PRV**) and *M. hyopneumoniae* vaccines (Houser et al., 2002). In this study, 2 trials evaluated the serological response, injection site reactions (localized site reactions evaluated a few hours to 2 days after vaccination),and injection site lesions (evaluated at slaughter), comparing the needle-free delivery system and the conventional needle-syringe delivery system. Serological response was similar between the NFID and the needle-syringe delivery system in both studies. Evaluation of the injection site reactions demonstrated transient transdermal thickening in 15 % of the NFID group compared to < 1 % thickening in the needle-injected pigs. Injection site lesions at slaughter were low in both groups (3 pigs in each group), and the lesions were mild (small, no granulomas or abscesses) and had no consequence to meat quality. This study was under controlled conditions (needle change, small groups, careful administration), so no difference in carcass defects was expected. The study also used a larger dose of vaccine (2 ml) than would be normally used in a NFID procedure (0.2 - 0.5 ml).

Two additional studies that measured the serologic response to commercial PRV had similar antibody responses between needle-syringe and needle-free administration (Thacker et al., 2003; Rosales et al., 2006). In another research study, the serological response of commercial *M. hyopneumoniae* and PRRSV vaccines administered were

compared following needle-syringe or NFID administration (Paquin et al., 2005). The serological response to both vaccines was similar regardless of the route of administration. Injection site reactions were low (< 2 %) in either vaccinate group and there were no injection site lesions. In a report by Rosales et al. (2006), the ELISA post-vaccination titer responses of pigs to App proteins were similar regardless of the route of administration, and there were no clinical differences in the 2 groups.

In a swine influenza trial, the serological response and protection against challenge were assessed using an experimental recombinant swine influenza vaccine in pigs vaccinated with needle-syringe or NFID (Wesley and Lager, 2005). The study used 3 different doses of recombinant vaccine and found that the highest dose in both vaccinated groups was the most effective. There was no statistical difference in the serological responses of the 2 groups regardless of the route of administration. Shedding of influenza virus post challenge was completely blocked in both groups that received the highest dose. Protection against challenge in both groups was similar with the NFID group having 4 normal and 5 mild lung lesion scores compared to 3 normal, 5 mild, and 1 moderate lung lesion scores in the needle-and-syringe group.

Three additional studies have been done with a *M. hyopneumoniae* bacterin developed specifically for transdermal needle-free injection device (**TNFID**; Charreyre et al., 2005; Royer et al., 2006; Thacker et al., 2007). The first study compared 3 different *M. hyopneumoniae* formulations and found that the formulation stimulating the fastest and highest serological response provided the best protection against challenge (Charreyre et al., 2005).

In a second study, 24 pigs were vaccinated with a *M. hyopneumoniae* vaccine developed specifically for TNFID and 24 pigs served as unvaccinated controls. All pigs were challenged intranasally with *M. hyopneumoniae* lung homogenates between d 160 and 162 and with *M. hyopneumoniae* culture on the following day. At necropsy, the lungs were scored for percentage of pneumonic lesions. The average percentage of pneumonic tissue in the control group was 4.35 versus 1.72 % for the vaccinated group ($P < 0.05$).

The third study was a co-infection study where pigs vaccinated with a TNFID using a TNFID-formulated *M. hyopneumoniae* vaccine were challenged with *M. hyopneumoniae* and/or PRRSV. There were 5 groups of pigs: group 1 was vaccinated with TNFID-formulated *M. hyopneumoniae* and challenged with *M. hyopneumoniae*; group 2 was vaccinated with TNFID-formulated *M. hyopneumoniae* and challenged with *M. hyopneumoniae* and PRRSV; group 3 was not vaccinated and was challenged with *M. hyopneumoniae*; group 4 was not vaccinated and challenged with *M. hyopneumoniae* and PRRSV; and group 5 was not vaccinated and not challenged. With the *M. hyopneumoniae* challenge, the vaccinated animals had 5.8 % lung lesions compared to 17.2 % in the controls. With the dual *M. hyopneumoniae* and PRRSV model, the PRRSV lung lesions were 25.7 % in the vaccinates compared to 48.9 % in the control animals. The *M. hyopneumoniae* lung lesions were also reduced in the vaccinates in the dual challenge model, 13.0 % lung lesions in the vaccinates compared to 18.4 % in the controls. The presence of *M. hyopneumoniae* specific T memory cells was also assessed in this study, and both of the vaccinated groups developed *M. hyopneumoniae* specific T memory cells

following vaccination. This study showed that transdermal vaccination with a TNFID-formulated *M. hyopneumoniae* vaccine significantly reduced the percentage of mycoplasmal pneumonia and reduced the severity of PRRSV pneumonia in the group challenged with both pathogens.

Taken together, these 3 studies indicate that the specifically designed *M. hyopneumoniae* bacterin administered using the TNFID led to a cell-mediated immune response resulting in protection of pigs from a challenge with *M. hyopneumoniae*.

## NEEDLE-FREE TECHNOLOGY: MECHANISM OF INDUCING AN EFFICACIOUS IMMUNE RESPONSE

The mechanism for an enhanced immune response to antigen delivered via a needle-free injector seems to hinge on the larger dispersion pattern invoked by these devices. More efficient exposure of antigen to cells of the immune system has been demonstrated to facilitate increased immunogenicity (Baizer et al., 2002; Hsu et al., 1995; Cui et al., 2003). Skin (including the epidermis and dermis) and the subcutaneous tissue, as opposed to muscle, is one of the largest immune organs of the body rich with antigen-presenting cells (**APC**) such as dendritic cells (**DC**; Figure 2; William Golde, personal communication; Bautista et al., 2002, 2005). Delivery of antigen to this area increases the targeting of APC and results in an enhanced immune response (Bautista et al., 2002; Banchereau and Steinman, 1998). Dendritic cells in the skin and adjoining tissues are the primary APC to bridge the innate and adaptive immune systems. They can initiate primary T-cell response and efficiently stimulate memory response (Jamin et al., 2006). Porcine DC from blood, gut, lymph nodes, Peyer's Patches, and skin have been

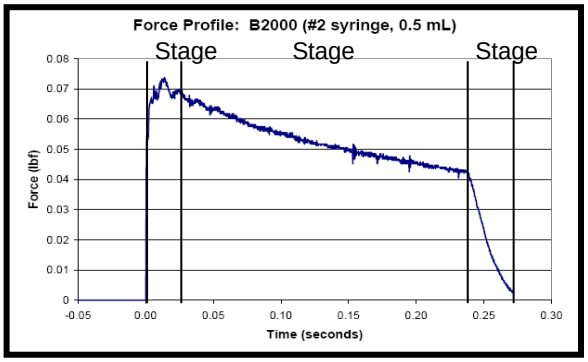


**Figure 2.** Pressure profile of 0.5 mL fluid in needle-free injector device simulated injection demonstrating peak pressure (Stage 1), the delivery phase (Stage 2), and the drop off phase (Stage 3). (Courtesy of Bioject Inc., Portland, OR)

characterized (Bautista et al., 2002; Jamin et al., 2006).

In the skin and adjacent tissue, DC are present in an immature state. Once they encounter a powerful immunological stimulus such as an antigen, the DC take-up and process the antigen, which causes their maturation and migration to the dermal lymphatics (Banchereau and Steinman, 1998; Itano et al., 2003). Once in the T-cell areas of regional draining lymph nodes, the DC presents the processed antigen which has been reduced to 11-18 amino acid peptides on their surface in the cleft of major histocompatibility complex (**MHC**) class II molecules (the peptide is like a hot dog and the MHC class II molecule is the bun) to naïve T cells causing activation to elicit the immune response (Itano et al., 2003; Ludewig et al., 1998). Studies demonstrate that often a larger quantity and wider variety of antibodies are induced by antigen delivered dermally rather than via intramuscular injections (Gramzinski et al., 1997, 1998; Lodmell et al., 2000). This is due to the increased numbers of DC in dermal tissues that are APC. The wide dispersion pattern of the antigen using

transdermal delivery allows increased surface area contact with APC compared to conventional needle injections delivered to the muscle resulting in a bolus dispersion (Baizer et al., 2002).

## ADVANTAGES OVER CURRENT NEEDLE-SYRINGE ADMINISTRATION

In addition to delivering vaccines that result in a protective immune response, needle-free vaccine delivery offers significant advantages for dairy producers over conventional needle-and-syringe vaccine administration including:

- Targeted immune response,
- Improved carcass quality by eliminating broken needles and reducing carcass bruising and abscesses,
- Smaller volume of vaccine,
- Reduced mechanical spread of infectious disease, and
- Improved safety for workers by eliminating accidental needle sticks when using traditional needle-and-syringe administration.

## SUMMARY

Needle-free vaccine delivery offers advantages over conventional needle-syringe administration. Controlled studies have shown an equivalent or enhanced immune response. Further studies under field conditions in commercial dairy operations are needed to confirm the advantages that needle-free transdermal vaccine delivery with a needle-free device offer over conventional needle-and-syringe vaccine delivery for dairy producers.

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