Needle-free injection technology in swine: Progress toward vaccine efficacy and pork quality

Christopher C. L. Chase, DVM, MS, PhD; C. Scanlon Daniels, DVM, MBA; Roberto Garcia, DVM, MS; Frank Milward, DVM, MS; Tiffany Nation, DVM, MS

Summary

Needle-free injection devices (NFIDs) have been available for humans since the 1930s. Their implementation in the swine industry has been slow because of the low cost and ease of use of needle-syringe injection. Recently, there has been a renewed interest in needle-free devices in swine due to two main factors: immunology research, indicating that targeting dendritic cells in the skin and the subcutaneous tissues results in improved immune response with minimal antigen doses, and implementation of pork quality assurance standards to minimize needle-site lesions that are the result of broken needles, bacterial contamination, or both. In this article, we review the peer-reviewed and non-peer-reviewed literature on the use of NFIDs in swine.

Keywords: swine, needle-free, transdermal, vaccines, pork quality

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Resumen - Tecnología de inyección sin aguja en cerdos: Progreso hacia la eficacia de vacunación y calidad de la carne de cerdo

Los dispositivos de inyección libres de aguja (NFIDs por sus siglas en inglés) han estado disponibles para los humanos desde 1930. Su implementación en la industria porcina ha sido lenta debido al bajo costo y la facilidad de uso de la inyección con jeringa de aguja. Recientemente, ha habido un renovado interés en los dispositivos libres de aguja en cerdos debido a dos factores principales: investigación inmunológica, que indica que tocar las células dendríticas en la piel y los tejidos subcutáneos resulta en una respuesta inmunológica mejorada con dosis mínimas de antígeno, y la implementación de los estándares de calidad porcina para minimizar las lesiones en el sitio de aplicación que son el resultado de agujas rotas, contaminación bacteriana, o ambos. En este artículo, revisamos la literatura editada y no editada en el uso de NFIDs en cerdos.

Résumé - Injection sans aiguille chez le porc: Progrès vers l'efficacité des vaccins et qualité du porc

Les appareils à injection sans aiguille (NFIDs) sont disponibles pour utilisation chez les humains depuis les années 1930. Leur implantation dans l'industrie porcine a été lente compte tenu du faible coût et de la facilité d'utilisation de la seringue avec aiguille. Récemment, un intérêt renouvelé pour l'utilisation chez les porcs de NFIDs s'est manifesté du à deux facteurs principaux: la recherche en immunologie, qui a démontré qu'en ciblant les cellules dendritiques dans la peau et les tissus sous-cutanés il en résulte une meilleure réponse immunitaire avec des doses minimales d'antigènes, et l'implémentation de standards d'assurance qualité visant à minimiser les lésions aux sites d'injection qui résultent d'aiguilles brisées, la contamination bactérienne, ou les deux. Dans le présent article, nous faisons une revue de publications avec arbitres et sans arbitre sur l'utilisation de NFIDs chez les porcs.

Vaccination is a significant component of standard management practices in swine husbandry. Improvements in vaccines and their delivery systems to increase vaccine efficacy, safety, or compliance and to minimize animal stress are essential in the swine industry. This article reviews needle-free technology and its uses in disease control in swine.

Needle-syringe devices have been the predominant method for vaccine and drug delivery for swine. Although needle-syringe devices are inexpensive and easily adaptable to different settings, needle-free technology offers advantages over conventional vaccine delivery methods, including elimination of broken needles,[1] consistent vaccine delivery,

CCLC: Department of Veterinary Science, South Dakota State University, Brookings, South Dakota.

CSD: Circle H Animal Health, LLC, Dalhart, Texas.

RG, FM, TN: Merial Limited, Athens, Georgia.

Corresponding author: Dr Chris Chase, Department of Veterinary Science, ADR Room 125, N Campus Drive, PO Box 2175, South Dakota State University, Brookings, SD 57007; Tel: 605-688-5652; Fax: 605-688-6003; E-mail: christopher.chase@sdstate.edu.

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lower vaccine volume and greater antigen dispersion,[2,3] elimination of accidental worker needle sticks,[3,4] elimination of needle disposal,[5] and less pain and stress[6,7] (Table 1). The elimination of broken needles and associated carcass trim are important in pork quality assurance (PQA). These factors were targeted by the National Pork Producers Council in the "One Is Too Many" needle awareness campaign and are part of Good Production Practice 7 of the PQA Plus Program.[8] Administration of swine vaccines using a needle-free injection device (NFID) requires half to a tenth of the dose necessary for intramuscular vaccines.[9-12] However, optimal NFID doses have not been determined for most swine vaccines. Greater antigen dispersion and contact with the antigen-presenting cells have been described in human studies and will be described later in this review.[2,3,13]

Accidental needle-sticks in human healthcare workers occur five of 100 times worldwide.[3] The number of needle-stick injuries associated with swine workers is unknown, but accounted for the highest number of physical injuries in swine veterinarians, with 580 out of 794 surveyed veterinarians (73%) suffering needle-stick injuries.[14] Thirty-six percent of these injuries resulted in adverse effects (pain, local swelling, hematoma, infection, superficial abscess, or cellulitis).

In humans, the newer generation NFIDs cause less pain and stress at the time of vaccination than do needle-syringe devices,[6,7] although there have been some complaints of post-vaccination pain.[3]

Disadvantages of NFIDs include start-up cost of the equipment, exhaustible gas-storage infrastructure (for systems using compressed or CO_2 gas system), technical and operational expertise (training of the operators and maintenance of the units), and inability to completely replace needle-syringe devices in the swine production unit (Table 1).[1] The cost of the equipment ranges from $2500 to $3000 for needle-free swine units, and there are additional costs associated with maintenance. Compressors and CO_2 tanks are also an additional expense, along with proper storage areas and equipment. Needle-free administration requires a consistent application method. Needle-free devices are calibrated to deliver the vaccine when the NFID is perpendicular (90°) to the skin. Administering vaccine at more acute or oblique angles will affect distribution of the vaccine in the tissue. In addition, because of the moving parts and gas system, regular maintenance of the NFID is required. Finally, there is no "one-size-fits-all" NFID for all applications that require injections. Varying pig age, treatment dose, and viscosity of injection substance require different injection volumes, injection pressures, and even different NFIDs.

Table 1: Advantages and disadvantages of needle-free injection devices (NFIDs) over needle-syringe devices in swine production

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

Adoption of NFIDs has been slow in the US swine industry, with an estimated usage of < 2% of growing pigs and < 5% of sows (R. B. Baker, e-mail communication, 2007). One major swine integrator has adopted the use of NFIDs in a large farrow-to-finish operation (> 200,000 sows; C. S. Daniels, oral communication, 2007). Reasons for this low industry rate of implementation include cost of the unit and associated maintenance and gas infrastructure costs, greater complexity than needle-syringe device, uncertainty if the animal was vaccinated (ie, no physical sensation that the animal was vaccinated), and requirement for training (proper application methods) (Christa Irwin, Darin Madson, and Locke Karriker, Iowa State University Swine Group, e-mail communication, 2008).

Needle-free technology: Origin and methodology

Needle-free injection devices, first called "jet injectors," were developed in the 1930s and used extensively for over 50 years in mass human vaccination programs for smallpox, polio, and measles.[15,16] Using mechanical compression to force fluid through a small orifice, these devices produced a high-pressure stream 76 to 360 μm in diameter (compared to 810 μm for a 21-gauge needle) that could penetrate skin and subcutaneous tissue. Most older devices used the same nozzle faces and fluid pathways to dose all individuals, thereby causing potential safety hazards of transferring blood-borne pathogens between individuals. Although the carryover volume of the NFID was small (5.5 μL carryover in a 20-gauge, 1.9-cm needle is 0.5×10^6 times more than the approximately 10 pL carryover in an NFID), multi-use-nozzle jet injectors were no longer recommended for routine mass human vaccination programs.[3] New-generation needle-free technology for humans uses disposable single-dose cartridges, eliminating re-use of the nozzle face and fluid path. Most needle-free technology in production animals uses non-disposable nozzle faces. Newer veterinary devices use disposable nozzle faces that allow for fast and easy nozzle changes when necessary and when transferring to a different farm.

Although all NFIDs use compressed gas to deliver the vaccines, they can be divided into three types based on the source of power: spring-powered, battery-powered, or compressed-gas-powered (Table 2). Spring-powered devices, which are compact and lower cost, have limited range of force and versatility and have been used primarily for subcutaneous administration of drugs. The battery-powered device is compact, but also has a limited range of force and versatility and has been available only outside the United States. Gas-powered devices have sustained force generation,

Table 2: Needle-free injectors used with swine health products

Type of needle-free device	Brand name	References
Spring-loaded jet injector	Dermo-jet Vacci Jet*	11
	Medi-Jector†	17
Battery-powered jet injector	Intra Dermal Application of Liquids (IDAL)‡	18-21
Gas-powered jet injector	Agro-Jet and Med-Jet§	4, 9, 34
	Biojector¶ and Derma-Vac NF**	22-26
	Pulse Needle-Free††	10, 27-33

* Société AKRA Dermojet, Pau, France, distributor, Robbins Instruments, Chatham, New Jersey.
† Antares Pharma, Ewing, New Jersey.
‡ Intervet, Boxmeer, The Netherlands.
§ Medical International Technologies (MIT Canada) Inc, Montreal, Quebec, Canada.
¶ Bioject, Tualatin, Oregon.
** Manufactured exclusively for Merial Limited, Duluth, Georgia, by Bioject.
†† Felton, Lenexa, Kansas.

more flexibility, and ability to deliver larger volumes than the other two types of NFIDs.[2,5] The main disadvantages of gas-powered units are the cumbersomeness of units with multiple components and their reliance on an exhaustible energy source.

Needle-free injection devices have been used in animals 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 injector.[2,13] In swine, needle-free injection technology has been used to deliver antibiotics,[27,28] iron dextran,[34] and vaccines[9,10,12,18-21,26,29,30,32] comfortably, accurately, and quickly.

The vast majority of swine vaccine trials have used gas-powered jet injectors (Table 2). Needle-free injection technology uses force generated by a compressed gas (air, CO_2, or nitrogen) to propel the vaccine at high velocity through a tiny orifice. An ultra-fine stream of fluid penetrates the skin, delivering the vaccine transdermally in a fraction of a second (Figure 1). Use of the term "intradermal" to describe the site of injection is a misnomer. Because of the force generated, vaccine is deposited in adjacent tissues (subcutaneous tissue and underlying shallow muscle) in addition to the dermis or the skin, thus the correct term is "transdermal." One major objection to needle-free injection has been the "wetness" associated with residual vaccine on the skin surface,[2,11] derived from the first stream that hits the skin (Figure 1B). The wet appearance may cause the vaccine administrator to think that the vaccine was improperly administered, even though the animal was vaccinated correctly. This residual vaccine volume is quite small (400 nL or 0.0004 mL).

Needle-free injection is precise and reliable, with the dose being virtually identical every time.[15] The three stages of needle-free delivery (Figure 2), requiring a total time of < 0.3 second (Richard Stout, Bioject, e-mail communication, 2007), are the peak pressure phase, with optimal pressure used to penetrate the skin (Stage 1, < 0.025 second); the delivery or dispersion phase (Stage 2, approximately 0.2 second); and the drop-off phase (Stage 3, < 0.05 second). 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 depends on equipment (eg, needle length and gauge) and technique.[35]

For vaccines, an enhanced dispersion field is a significant consideration that affects the animal's immune response to an antigen.[2,3,36] Traditional needle-syringe administration results in a bolus forming in the tissue adjacent to the tip of the needle. Needle-free injection technology improves the dispersion of vaccines throughout the tissue (Figure 3).[37] 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 vaccine.[35,38] The lower force in the dispersion phase allows the fluid to disperse in the tissue. This wide dispersion of vaccine is thought to increase exposure of the antigen to antigen-presenting cells, thereby resulting in an enhanced immune response.[39]

Needle-free injection delivery has no effect on the antigenic component. Theoretically, vaccine delivery via the small needle-free orifice could damage the vaccine's antigenic component via nicking or degradation, thereby altering its antigenicity. An effective immune response to a variety of protein antigens, including *Mycoplasma hyopneumoniae*,[9-11,22-24,29,30] porcine reproductive and respiratory syndrome virus (PRRSV),[18,19,30] pseudorabies virus,[20,21,32] hepatitis B virus,[25] *Actinobacillus pleuropneumoniae*,[33] and swine influenza virus,[9,10,12,26] have been elicited, indicating no degradation of the vaccine antigens. DNA vaccines, which are likely to be the vaccines of the future, can be effectively administered with NFIDs to elicit protective immune responses in swine.[17,25]

Needle-free technology: Effective immune response

Needle-free vaccine delivery has been studied in other species besides humans, including dogs,[17] cats,[37] cattle,[40] and rabbits.[41] Several studies[17,40,41] demonstrated that needle-free vaccine delivery resulted

Figure 1: Visualizing the process of transdermal injection. 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 (> 100 m per second); 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 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. The final distribution of the liquid varies by the type of device, injection site, thickness of the skin, viscosity of the liquid, and pressure. Reprinted with permission from Macmillan Publishers Ltd.[2]

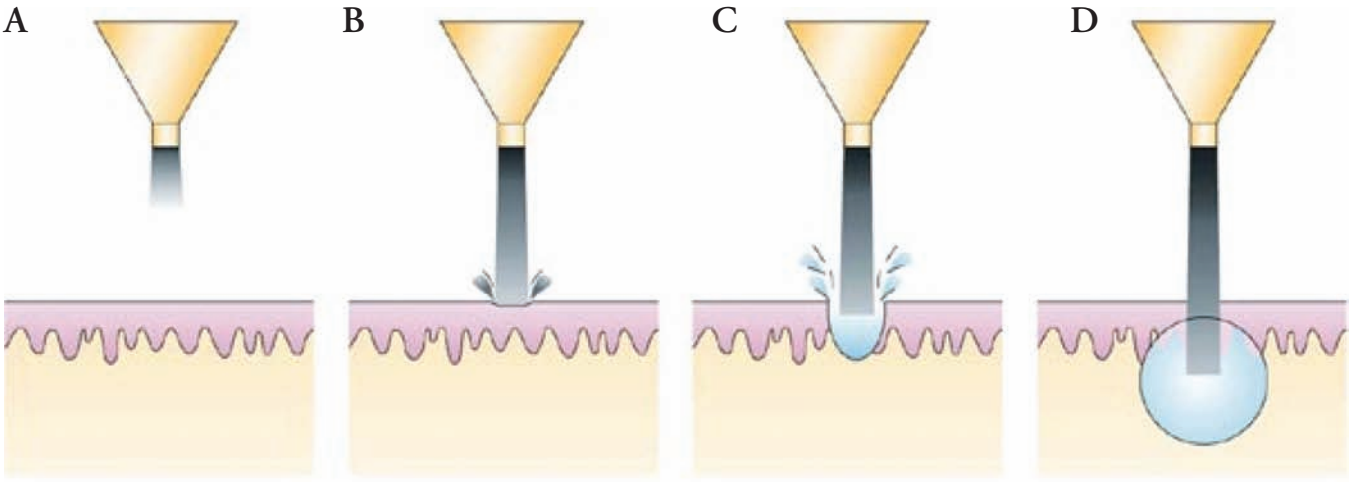


Figure 2: Pressure profile in simulated injection of 0.5 mL fluid by needle-free injector device demonstrating Stage 1, peak pressure phase, optimal pressure used to penetrate the skin (< 0.025 second); Stage 2, delivery phase (approximately 0.2 second); and Stage 3, drop-off phase (< 0.05 second). Reprinted with permission from Bioject Inc, Portland, Oregon.

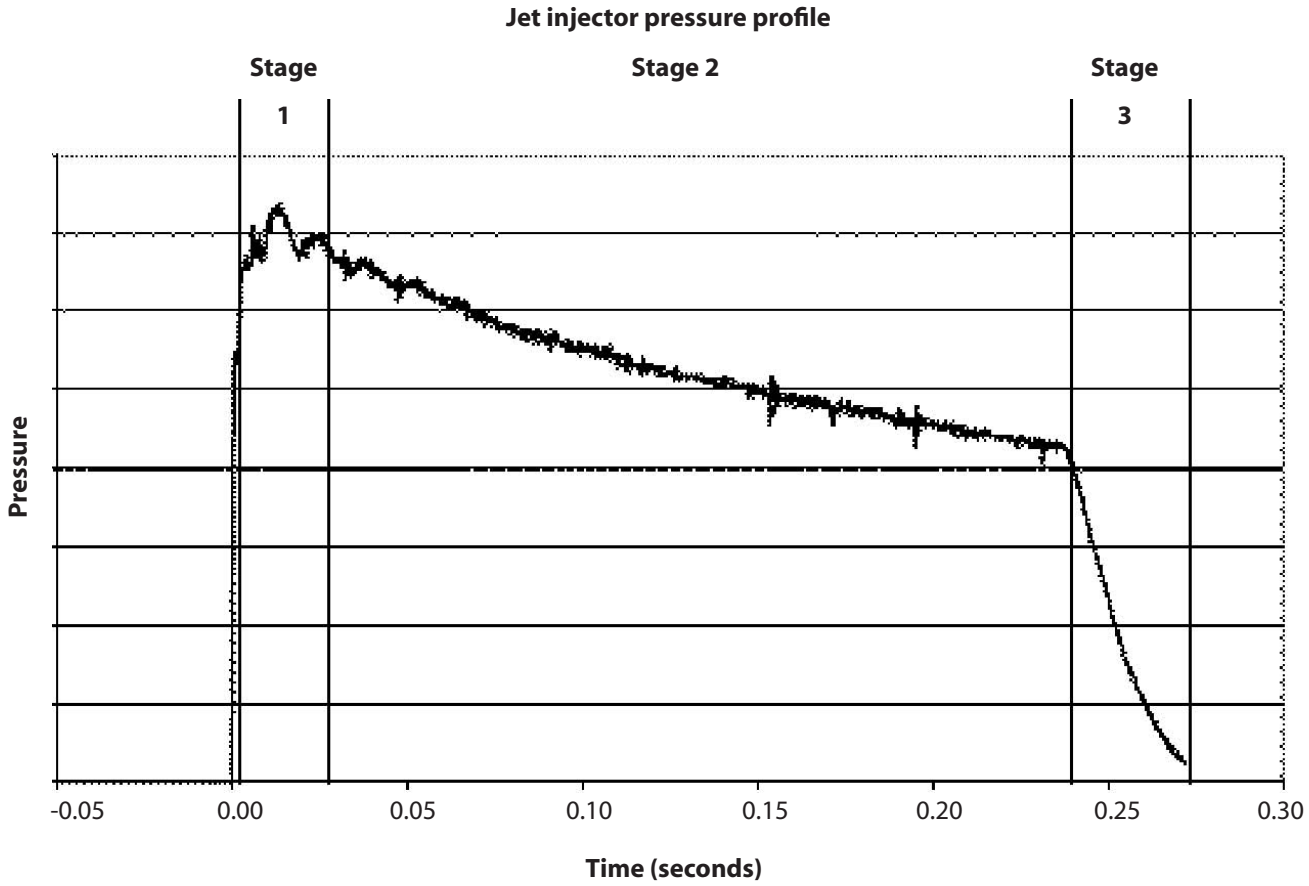
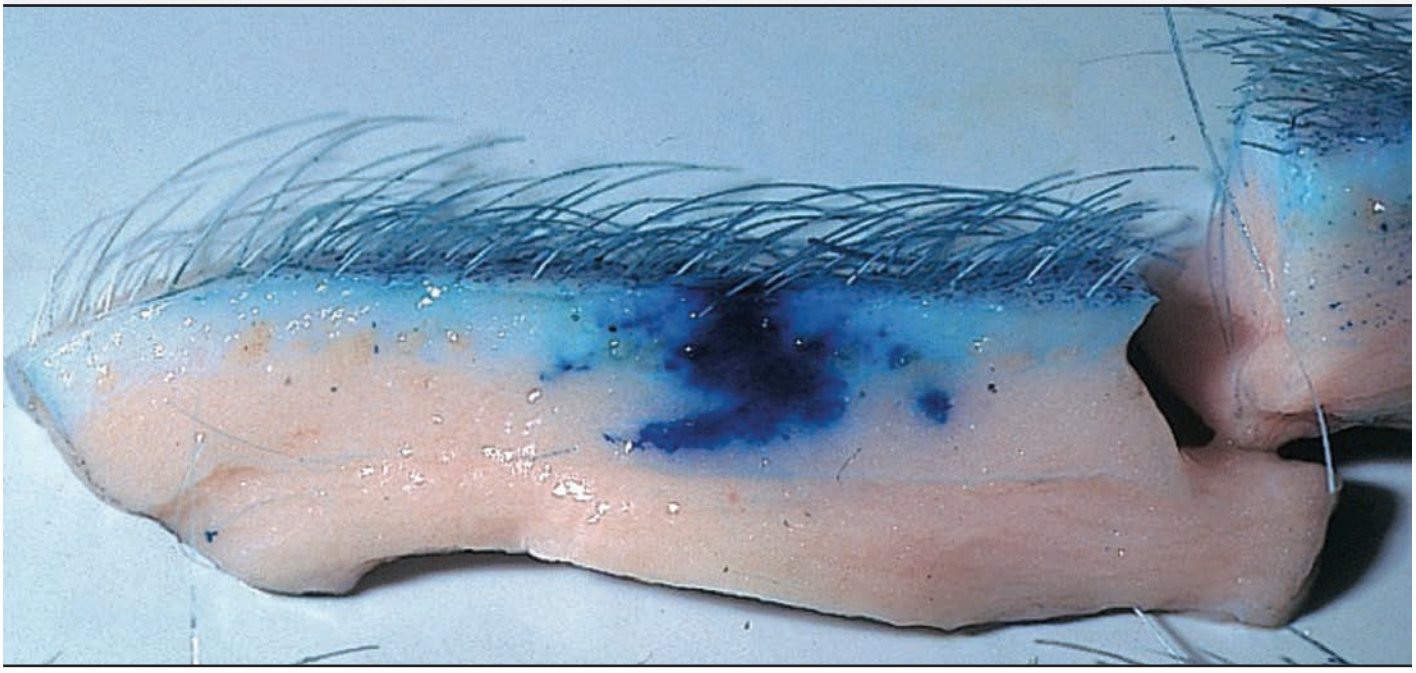


Figure 3: Distribution of methylene blue in the skin and underlying tissue following injection with a needle-free injection device. Distribution will vary by type of device, injection site, thickness of the skin, viscosity of the liquid, and pressure. Reprinted with permission from Reed Business.[37]



in an enhanced immune response, when compared to traditional needle-syringe vaccine delivery. Rabbits vaccinated with three doses of plasmid-encoding malarial antigen (*Plasmodium falciparum* circumsporozoite protein) by needle-free injection had eight- to 50-fold greater antibody titers than those injected intramuscularly with a traditional needle-syringe device.[41] In another study, dogs vaccinated subcutaneously or intramuscularly by NFID with a plasmid expressing human growth hormone had antigen-specific titers ranging from three-fold to 20-fold higher than titers in animals vaccinated by needle-syringe injection.[17] Cattle vaccinated with a bovine herpesvirus 1 subunit vaccine using an NFID had enhanced cellular immune responses, but, more importantly, protection against challenge was better and there was less virus shedding than with needle-mediated delivery.[40]

Many human trials have also demonstrated comparable or enhanced immune response when needle-free injectors are used.[2,3,6,38,42-46] When delivered by the needle-free injection technique, compared with needle-syringe injection, all vaccines induced either equivalent or superior immunogenicity, as measured by seroconversion rates (geometric mean titers).

There have been many vaccine studies with NFIDs in swine.[9-12,17-33] This is not an all-inclusive list, but represents most studies presented. Only four studies[11,17,25,26] were published in peer-reviewed journals, with the remainder presented in proceedings of various swine health conferences. Results indicate an equivalent or better immune response when transdermal vaccination with NFID was compared with intramuscular vaccination using needle-syringe devices. No studies indicated a poorer response when an NFID was used.

In several studies, commercial *Mycoplasma hyopneumoniae* vaccines were administered using an NFID. Four studies[9,10,29,30] compared needle-syringe administration to NFID administration of vaccines. Serological response was similar for the NFID and the needle-syringe delivery system in all four studies. In a challenge study, the use of an NFID with a commercial *M hyopneumoniae* vaccine resulted in 88% lower lung lesion scores following challenge.[31]

Four studies[11,22-24] compared needle-syringe administration to NFID administration of experimental *M hyopneumoniae* vaccines. In a report including three studies,[11] a single dose of *M hyopneumoniae* vaccine administered with an NFID produced significantly higher titers than a single dose of the same vaccine administered by intramuscular injection. Both groups were protected against *M hyopneumoniae* challenge. Three studies used an *M hyopneumoniae* bacterin developed specifically for administration by NFID.[22-24] The first study[22] established the optimal transdermal *M hyopneumoniae* formulation administered to 16- to 19-day-old pigs that provided protection against challenge at 35 days post vaccination. In the second study,[23] pigs were challenged with *M hyopneumoniae* 160 days post vaccination with the transdermal formulation. The average percentage of pneumonic tissue was 4.35% in the unvaccinated controls and 1.72% for the vaccinated group ($P < .05$).[23] A third study[24] using the same vaccine and device was performed using a dual *M hyopneumoniae* and PRRSV model in which 10- to 12-day-old pigs were vaccinated and infected with PRRSV and then challenged 6 days later with *M hyopneumoniae*. In the vaccinates, PRRSV lung lesions involved 25.7% of the lung, compared with 48.9% in the control animals. *Mycoplasma hyopneumoniae* lung lesions were also 27% lower in the vaccinates (13.0% lung involvement in the vaccinates compared with 18.4% in the controls).

Administration of *Actinobacillus pleuropneumoniae* (APP) bacterin by NFID has also been tested. In one experimental challenge,[4]

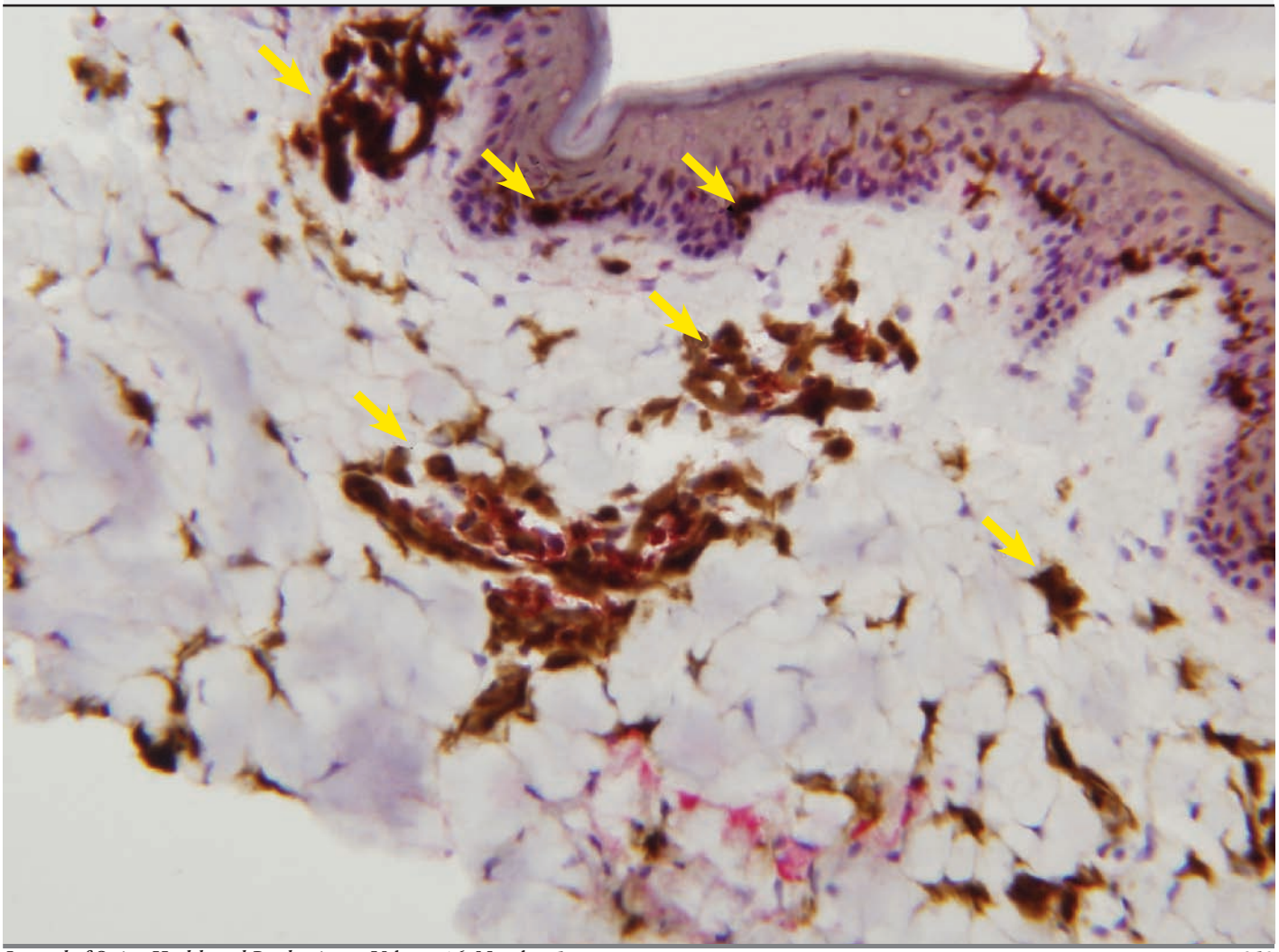
pigs receiving the vaccine by the NFID route had significantly fewer clinical signs than pigs vaccinated intramuscularly. In another trial,[33] the responses of pigs to antigens were similar regardless of the route of administration (needle-syringe versus needle-free), and there were no clinical differences in the two vaccinated groups on a farm with endemic APP.

There have also been several studies[9,10,12,18-21,26,29,30,32] that used NFID for viral vaccines. Four studies using commercial pseudorabies virus vaccines demonstrated a similar serological response[20,21,29,32] or cell-mediated response[21] when pigs were vaccinated by the NFID or the needle-syringe delivery system. Serological[18,30] or cell-mediated responses[19] to commercial PRRSV vaccines administered using needle-syringe or NFID were also similar. Serological responses to swine influenza vaccine were also similar when vaccines were administered by the NFID or the needle-syringe delivery system.[9,10] In a challenge study,[12] a group receiving a tenth of a dose of a commercial influenza vaccine using an NFID had 77.0% lower median scores for influenza lung lesions than did unvaccinated controls. In two other studies[12] using the same vaccine via the intramuscular route, median scores for lung lesions were 92.7% and 87.7% lower in vaccinates than in unvaccinated controls. In a second swine influenza challenge study,[26] nasal shedding of influenza virus was completely blocked in both needle-syringe and NFID groups. Protection against challenge in both groups was similar, with the NFID group having four normal and five mild lung-lesion scores compared with three normal and five mild lung-lesion scores and one moderate score in the needle-syringe group.

Mechanism for inducing an efficacious immune response using needle-free technology

The mechanism for evoking an equal or enhanced immune response using less antigen with the needle-free injector seems to hinge on the larger dispersion pattern generated by these devices.[2,3] More efficient exposure of antigen to cells of the immune system increases immunogenicity in humans and mice.[5,47,48] The skin (including the epidermis and dermis) and subcutaneous tissue comprise one of the largest immune organs of the body, rich with antigen-presenting cells (APCs) such as dendritic cells (Figure 4) (William Golde, oral and e-mail communication, 2007).[49-51] Characteristics of porcine dendritic cells from blood, gut, lymph nodes, Peyer's patches, and skin are similar to those of

Figure 4: The distribution of dendritic cells in the epidermis, dermis, and subcutaneous tissue in the pig (original magnification × 100). Dendritic cells (arrows) are stained brown. Photo courtesy of Drs William Golde and Charles Nfon, Plum Island Animal Diseases Center, Agricultural Research Service, USDA.



dendritic cells of humans and mice.[49,52] Studies in humans and mice have shown that delivery of antigen to dermal and subcutaneous tissues increases targeting of APCs and results in an enhanced immune response.[3,53] Dendritic cells in the skin and adjoining tissues, the primary APCs bridging the innate and adaptive immune systems, can initiate a primary T-cell response and efficiently stimulate memory response.[54]

Dendritic cells in the skin and adjacent tissue are immature.[48,53,54] Once they encounter a powerful immunological stimulus such as an antigen, the dendritic cells take up and process the antigen, reducing it to 11 to 18 amino-acid peptides, which causes maturation of the dendritic cells and their migration to the dermal lymphatics.[53,54] Once the dendritic cells reach the T-cell areas of regional draining lymph nodes, processed antigen is presented in the cleft of major histocompatibility complex (MHC) class II molecules on the dendritic cell surface. When processed antigen is presented to naive T cells, they are activated, eliciting the immune response.[53,55] Studies in primates and mice[56-58] have demonstrated that often a larger quantity and wider variety of antibodies are induced by antigen delivered dermally rather than via intramuscular injection, owing to the greater numbers of dendritic cells in dermal tissues that are APCs. The wider dispersion pattern of the antigen using transdermal delivery allows greater surface area contact with APCs, compared with conventional needle injections delivered to the muscle, which result in a bolus dispersion.[3,5]

Implications

- Advantages of needle-free vaccine delivery over conventional needle-syringe administration include elimination of broken needles, lower vaccine volume and greater antigen dispersion, elimination of accidental worker needle sticks, elimination of needle disposal, and less pain and stress.
- Adoption of NFIDs has been slow due to the cost of the unit and associated maintenance and gas infrastructure costs, greater complexity than needle-syringe devices, higher labor costs, and requirement for training.
- Immune responses to vaccines administered by NFID and needle-syringe technology are similar.
- Further studies under field conditions in commercial swine operations are needed to confirm the advantages of NFID vaccine delivery over conventional needle-and-syringe vaccine delivery.

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