An alternate delivery system improves vaccine performance against foot-and-mouth disease virus (FMDV)

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A B S T R A C T
Foot-and-mouth disease virus (FMDV) causes vesicular disease of cloven-hoofed animals with severe agricultural and economic implications. One of the most highly infectious and contagious livestock pathogens known, the disease spreads rapidly in naïve populations making it critical to have rapidly acting vaccines. Needle inoculation of killed virus vaccine is an inefficient method of swiftly vaccinating large numbers of animals, either in eradication efforts or in outbreak situations in disease free countries. Although, to be efficient, this requires utilizing the same needle with multiple animals. Here we present studies using a needle-free system for vaccination with killed virus vaccine, FMDV strain O1 Manisa, as a rapid and consistent delivery platform. Cattle were vaccinated using a commercially available vaccine formulation at the manufacturer’s recommended dose as well as four and sixteen fold less antigen load per dose. Animals were challenged intradermally (ID), with live, virulent virus, homologous strain O1 Manisa, at various times following vaccination. All non-vaccinated control cattle exhibited clinical disease, including fever, viremia and lesions, specifically vesicle formation. Cattle vaccinated with the 1/16× and 1/4× doses using the needle free device were protected when challenged at both 7 and 28 days after vaccination. These data suggest that effective protection against disease can be achieved with 1/16 of the recommended vaccine dose when delivered using the needle free, intradermal delivery system, indicating the current vaccine stockpile can be extended by many fold using this system.

1. Introduction

Foot-and-mouth disease virus (FMDV) causes a high impact disease of cattle and other cloven-hoofed animals, with severe agricultural and economic implications [1,2]. Fortunately, foot and mouth disease vaccines confer rapid protection of susceptible animals in a single dose, thus allowing a quick response to control the spread of disease in outbreak situations [3,4]. Although the standard needle inoculation method is an efficient system of swiftly vaccinating large numbers of animals at once, this requires utilizing the same needle for all the animals. A needle free vaccine delivery system allows for rapid vaccination of large numbers of animals more efficiently and with increased safety than needle delivery [3,5]. Besides eliminating the cumbersome needle inoculation process, intradermal (ID) vaccination has advantages compared to intramuscular (IM) vaccination, the traditional method for FMD vaccines [3,5].

Prior studies by Eble and coworkers show ID vaccination of pigs against FMD with 1/10 dose confers comparable vaccine efficacy as IM vaccination with a full dose [3]. These results suggest that current vaccine stocks can be extended many fold, using ID inoculation. This is supported by other studies with hepatitis B, rabies and influenza virus vaccines suggesting that ID vaccination results in enhanced immunogenicity [5,6]. Reports indicate that such enhancement can be attributed to the skin being heavily populated with dendritic cells [6,7]. These cells are efficient and potent antigen-presenting cells that are required for the initiation of an adaptive immune response eventually leading to protective immunity [3,5,6].

We have developed a new vaccination system termed the Dermavac®, which uses compressed gas to deliver 0.5 ml doses of vaccine formulation either intradermally or subcutaneously by adjusting pressure for differential delivery. The Dermavac® takes up to a 25 ml syringe, allowing delivery of 50 doses of vaccine without changing syringes and with no requirement for needles. A clear
advantage of ID delivery of the vaccine is that it is less painful for the animal compared to the IM route. Importantly, there is minimal site reaction after vaccination when using appropriately formulated vaccines.

The Office International des Epizooties (OIE) standards for all registered FMD vaccines are based on inactivated viral particles in an adjuvant [8]. Different adjuvants confer different performance characteristics of the vaccine and further, some adjuvants are limited in the route of inoculation, such as ID, IM or subcutaneous [9]. In the present study, we evaluated the response to ID inoculation of killed virus vaccine in aluminum hydroxide and saponin adjuvant using this needle free system. We tested for protection against live virus challenge at the standard time of 4 weeks following vaccination as well as induction of rapid protection by challenging 7 days after vaccination. Results presented here provide data to support the use of this needle free device in vaccination for rapid protection, such as during outbreaks of FMD in disease free countries as well as for standard vaccination utility in eradication programs.

2. Materials and methods

2.1. Animals

All cattle experiments were performed in a secure biosafety level three laboratory at Plum Island Animal Disease Center following the protocol approved Institutional Animal Use and Care Committee. One week prior to the start of testing, castrated male Holstein cattle, ranging from 200 to 250 kg, were acquired from Thomas Morris Inc., Reisterstown, MD. Cattle were held for one week to allow for acclimation and recovery from shipping. Baseline temperatures, serum, and nasal swabs were taken before any inoculations.

2.2. Vaccine

The vaccine was provided following standard manufacturing protocols by Merial Animal Health Limited, Pirbright, UK, using inactivated, purified O1 Manisa strain of FMDV. The killed virus antigen was formulated with aluminum hydroxide and saponin as adjuvant and formulated according to OIE standards as described [10]. A placebo vaccine, containing no antigen in the aluminum hydroxide and saponin mixture, was also prepared by Merial Animal Health. The vaccines were administered at various doses in 0.5 ml volume per animal, using the needle free device intradermally in the neck.

2.3. Vaccine trials

To confirm that ID delivery of vaccine protects cattle as well as subcutaneous, needle delivery already established for this vaccine, the standard dose of killed virus vaccine was adjusted to a 0.5 ml volume for delivery with the Dermavac®. Further we tested 1/4 dose of both antigen and adjuvant as well as full dose of antigen with quarter dose of adjuvant. We tested at both doses of adjuvant as we were concerned that a full dose of saponin adjuvant in a 1/4 of the normal, prescribed volume would induce an injection site reaction. Groups of three animals each were vaccinated with each different formulation and animals were challenged 28 days later (Trial 1, Table 1).

In the second trial, we tested delivery 1 ×, 1/4× and 1/16× doses of killed virus antigen in the 1/4 dose of adjuvant by ID delivery with the Dermavac®. Groups of 7 animals were tested at each dose, and challenged 7 days later (Table 2).

In the final trial, three groups of three cattle were vaccinated at 31 days and three more groups of three cattle were vaccinated at 7 days prior to challenge. The cattle in the three different groups were vaccinated with either 1/4×, 1/16×, or a placebo (adjuvant but no antigen) vaccine (Table 3). Each experiment included at least two or three naive animals used as controls. The naïve animals co-mingled with the vaccinated animals until the end of each experiment. In the third experiment, six cattle vaccinated with the placebo vaccine were removed to a separate room prior to challenge to avoid overwhelming vaccinated animals with shedding virus from infected animals if, as expected, the placebo failed to protect cattle against disease.

2.4. Challenge

As previously described, the challenge virus was isolated from tongue epithelium macerate harvested from two cattle infected with FMDV strain O1 Manisa [4,11]. Virus aliquots were maintained and stored at −70 °C until use. The challenge virus was titrated in the tongue of a cow to determine 50% bovine tongue infectious doses (BTID₅₀). Animals were IDL challenged with 10⁴ BTID₅₀ [4].

2.5. Clinical assessment of cattle

Cattle were monitored for clinical signs of FMD during the vaccination and challenge periods. Temperatures were recorded daily for each experiment. Animals were examined with sedation for clinical lesions on days 0, 4, 7, and 10 post-challenge. A clinical score was determined based on the number of affected feet [4]. The

Table 1

<table>
<thead>
<tr>
<th>Vaccination formulation</th>
<th>Dose (volume)</th>
<th>Animal #</th>
<th>Clinical assessment</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen</td>
<td>Adjuvant</td>
<td></td>
<td>Day 0</td>
<td>Day 4</td>
</tr>
<tr>
<td>1×</td>
<td>1×</td>
<td>0.5 ml</td>
<td>689</td>
<td>0</td>
</tr>
<tr>
<td>1×</td>
<td>1/4×</td>
<td>0.5 ml</td>
<td>686</td>
<td>0</td>
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<tr>
<td>1/4×</td>
<td>1/4×</td>
<td>0.5 ml</td>
<td>683</td>
<td>0</td>
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<tr>
<td>PBS</td>
<td>PBS</td>
<td>0.5 ml</td>
<td>692</td>
<td>0</td>
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<td></td>
<td></td>
<td></td>
<td>693</td>
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</table>
Table 2
Challenge at 7 days postvaccination.

<table>
<thead>
<tr>
<th>Vaccination formulation</th>
<th>Dose (volume)</th>
<th>Animal #</th>
<th>Clinical assessment</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>979</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>980</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
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<tr>
<td></td>
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<td>0.5 ml</td>
<td>982</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>983</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>984</td>
<td>0</td>
</tr>
</tbody>
</table>

maximum clinical score is 4. Vesicles in the tongue and mouth were not part of the clinical scoring system due to IDL challenge.

2.6. FMDV neutralizing antibodies from serum

Serum samples were tested for the presence of neutralizing antibodies against FMDV by a standard protocol [4]. Serum samples were heat inactivated at 56 °C for 30 min. Serial dilutions were incubated with 100 TCID<sub>50</sub> of FMDV-O1 Manisa for 1 h at 37 °C. These samples were then transferred to preformed monolayers of BHK-21 cells and incubated at 37 °C for 72 h. Cytopathic effect (CPE) was determined microscopically where end-point titers were the reciprocal of the last serum dilution to neutralize virus in 50% of the wells (4 wells for each titration).

2.7. Virus titration

Virus titers in serum were established by determining the tissue culture infectious dose 50 (TCID<sub>50</sub>). Briefly, 10-fold serial dilutions of serum were added to pre-formed monolayers of LFBK cells transfected with αV86 (obtained from M. LaRocco and L. Rodriguez, USDA, ARS) in a 96-well microtiter plate, four replicates per

Table 3
Challenge at 7 or 31 days postvaccination.

<table>
<thead>
<tr>
<th>Vaccination formulation</th>
<th>Dose (volume)</th>
<th>Animal #</th>
<th>Day of challenge (after vaccination)</th>
<th>Clinical assessment</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
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<tr>
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<td>0</td>
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<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>9121</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1/16&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>9116</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1/16&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>9117</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>1/16&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>9118</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>0.5 ml</td>
<td>9122</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>9123</td>
<td>0</td>
<td>4</td>
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<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>9124</td>
<td>0</td>
<td>4</td>
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<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>9128</td>
<td>7</td>
<td>0</td>
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<tr>
<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
<td>0.5 ml</td>
<td>9129</td>
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<td></td>
<td>1/4&lt;sup&gt;x&lt;/sup&gt;</td>
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<td></td>
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<td>9125</td>
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<td></td>
<td>1/16&lt;sup&gt;x&lt;/sup&gt;</td>
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<td>0.5 ml</td>
<td>9132</td>
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<td>PBS</td>
<td>0.5 ml</td>
<td>9136</td>
<td>0</td>
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dilution. Tissue culture plates were incubated at 37 °C for 48–52 h and monitored for CPE in order to calculate TCID\(_{50}\) [12].

3. Results

3.1. Clinical assessments

In the first trial, all animals were housed in the same room and challenged on the same day, including two naïve cattle. All vaccinated animals were protected from infection after challenge at 28 days following vaccination with the exception of one cow. This animal received a 1/4 dose of viral antigen with a 1/4 dose of adjuvant and showed vesicles on 1 foot (#685, Table 1). There was no fever (Table 1) and no viremia (Fig. 1) exhibited by any of the vaccinated animals. Naïve cows showed fever 2–3 days following challenge and viremia that peaked on day 2, as expected (Fig. 1). Viremia and fever resolved by 5 days after challenge and vesicular lesions started to heal by day 10. It is noteworthy that Dermvac® delivery of FMDV vaccine with saponin adjuvant showed very mild adverse site reactions, and this site reaction was similar regardless of the dose tested. Any observed site inflammation resolved in 24–48 h.

A second trial was performed to determine if protection from disease can be induced as rapidly as the same vaccine in double oil emulsion as we previously reported [4]. In this trial, 3 groups of 7 cattle each were vaccinated 7 days prior to challenge with the needle free device. All animals were housed in the same room, and challenged the same day, including three naïve cattle. All of the cattle vaccinated with the quarter dose of antigen (of the recommended PD\(_{50}\)) were completely protected from clinical disease when assessed for clinical signs on day 4, 7 and 10 after challenge (Table 2). Two of the seven cattle in the 1X antigen group had vesicles after challenge, one with vesicles on a single hoof and one with vesicles on two feet, at day 4 post challenge. The rest of this cohort showed no clinical signs. These two protection failures could be a result of animal-to-animal variation in quality of antibody response, variations in the rate of decline of antibody for individual animals [13] or other variables in the humoral response of outbred cattle. Like many vaccines, this vaccine does not induce sterilizing immunity and commonly viral replication occurs, including at epithelial surfaces, causing lesions on the feet.

In the group of cattle vaccinated with 1/16× antigen load, one animal had vesicles on three feet by day 4 post challenge, and all four feet by day 10 post challenge. Again, the balance of this cohort, 6 cattle, showed no clinical signs. No vaccinated animals had fever or detectable viremia over the course of the trial, regardless of whether an animal had vesicles. As in the previous trial, naïve animals had vesicle formation on all 4 feet by day 4 post challenge. Fever was detected 1–2 days post challenge in all naïve animals (Table 2). As in the first trial, these naïve animals had detectable viremia, again peaking on day 2 and resolving by day 5 (Fig. 2).

The results in the second trial raised the possibility that protection at the early challenge time (day 7) may be mediated by a nonspecific innate response to the saponin adjuvant. Further, pathogen associated molecular patterns (PAMPs) [14] inherent in the virus could result in nonspecific stimulation via toll-like receptors (TLRs) or Nod-like receptors (NLRs). If so, such a response would have waned by weeks post-vaccination leaving the animals susceptible to infection. To test these possibilities, we conducted a third trial using 6 groups of 3 cattle each vaccinated with either 1/4× or 1/16× dose of viral antigen or with the saponin, aluminum hydroxide adjuvant alone (placebo vaccine). In addition, we challenged at both the early (day 7) or later (day 31) times following vaccination.

Cattle vaccinated 31 days prior to challenge with 1/16×, and 1/4× dose showed no signs of clinical disease. Cattle vaccinated at 7 days prior to challenge with 1/4× dose also showed no signs of clinical disease. However, 2 out of 3 cattle vaccinated with 1/16× dose 7 days prior to challenge, developed lesions on at least one foot by day 10 post challenge, i.e. reduced and delayed disease (Table 3). All antigen-vaccinated animals were free of fever regardless of antigen lode or day of challenge. As in the first two trials, no virus was detected in the serum on any day following challenge with analysis daily through day 10. Placebo groups challenged at either time point, as well as naïve cattle, had vesicle formation on all 4 feet by day 4 post challenge with elevated temperatures 1–2 days post challenge. All control and placebo animals also showed viremia that peaked on day 2 and resolved by day 5 following challenge (Fig. 3).

3.2. Neutralizing antibody responses

Virus neutralizing antibody titers are an indicator of protection from challenge [2,15]. All animals vaccinated with killed virus antigen showed measurable levels of anti-FMDV antibody detected by 7 days following vaccination. Titers of neutralizing antibody in serum were predictive of protection against FMDV (Fig. 4). Only a few animals developed signs of reduced and delayed disease and these all had equivalent titers to those animals protected from disease. As has been previously reported, there was increase in neutralizing antibody titer following challenge in all groups, including all vaccinated animals [3,4]. These data suggest that vaccinated animals were protected from disease but were not protected from infection. The boost in titer indicates the virus is likely to be systemic even
in vaccinated animals that had no detectable virus in blood samples taken daily after challenge. The lack of detection of viremia in these samples may be a result of vaccination reducing the duration of viremia from more than 24–48 h in naïve animals to less than 12–14 h. We do not anticipate it is a matter of sensitivity of the assay as real-time reverse transcriptase polymerase chain reaction (RT-PCR) for FMDV can detect 10 genome copies in a sample. When this assay was compared to the TCID$_{50}$ determination used here, Callahan, et al., found nearly 100% concordance between positive results of both assays [16].

### 4. Discussion

Outbreaks of FMDV in disease free countries continue to cause significant problems for livestock farmers and the economies of the effected regions. Developing tools to rapidly control such outbreaks, where the herds are completely susceptible to infection, is critical to minimizing slaughter of livestock and hardship to farmers. In addition, valuable breeding stock caught in an effected zone could be lost, as occurred in Japan in 2010. The spread of FMDV in naïve herds is remarkably rapid and a challenge to control [17].

In these studies we have tested the performance of the killed virus vaccine for FMDV using a rapid, needle free delivery system, the Dermavac®. The vaccine, in an aqueous preparation of aluminum hydroxide with the adjuvant saponin, was shown to be compatible with this delivery system, as cattle show minimal injection site reaction. This device can be loaded with a 25 ml syringe providing 50, 0.5 ml doses per refill of vaccine allowing animals to be vaccinated with much greater efficiency than using needle delivery. One important factor in the decision of whether or not to vaccinate in response to an outbreak of FMDV is the daunting logistics of deploying vaccine. Besides matching the vaccine strain to the strain of virus causing the present outbreak, recruiting professionals to administer vaccine and developing appropriate monitoring systems for tracking vaccinated animals is critical. The efficacy of a
rapidly applied, needle free delivery system such as the one tested here will enhance vaccination for FMDV.

Remarkably, the data we report here show that the vaccine, delivered intradermally by the device, has enhanced performance over the standard needle delivery of vaccine [4]. In all of the trials we report here, the vaccine protected against disease. The concentration of viral antigen can be reduced to 1/16 of the standard dose and still provide protection. Concentrations of anti-FMDV antibody that can neutralize virus in vitro were significant (more than 1 log) as early as 7 days following vaccination. This result was observed regardless of the concentration of viral antigen used in the vaccine. Further, efficacy was not dependent on concentration of the saponin adjuvant. The adjuvant alone (placebo with no viral antigen) conferred no protective effects, as placebo vaccinated animals were identical in disease assessment to naïve control animals. Fever and viremia were only detected in the placebo and naïve control animals following live virus challenge.

In the past two decades, formally FMD free countries have seen outbreaks that have raised awareness of the susceptibility of livestock and how rapidly the disease can spread [17,18]. In 1997, Taiwan suffered an outbreak that led to the island depopulating all pigs in order to re-obtain FMDV free status [19]. The virus spread too quickly for vaccination to even be considered. In addition, the strain of FMDV causing the outbreak had a unique tropism for swine, with little infectivity in cattle [20]. In 2000 there were outbreaks in both South Korea and Japan for the first time in many years [21,22]. Again, slaughter was the method chosen to eliminate the disease and regain disease free status [21,23]. Then, in 2001, the United Kingdom suffered a large outbreak encompassing England, Scotland, Wales and even Northern Ireland [24]. Animals shipped from England before detecting the outbreak, were a source of disease in Greece, Italy, Ireland, France and the Netherlands. With the exception of the Netherlands, all countries slaughtered infected animals and all susceptible animals that were in contact with the virus. This process was very difficult as millions of animals were slaughtered and quarantine zones had a severe effect on economic activity far beyond the livestock industry. The Netherlands vaccinated and removed all vaccinated animals over time.

The decision to slaughter infected and exposed livestock was the policy of most of the governments involved for economic reasons. The OIE rules in place called for a period of 3 months of no new disease detected before export of animal products was allowed after quarantine and slaughter. If animals were vaccinated, that period was longer, 6 months. The UK outbreak led to a modification of OIE recommendations making the export waiting period 3 months after the last known case of FMDV even if animals were vaccinated to control disease [8]. This change still requires the eventual slaughter of all vaccinated animals. New parameters are being discussed following new outbreaks of FMDV in Japan in 2010 and South Korea in 2010 and 2011. In both cases, vaccine was deployed to help control disease spread. If data from experimental studies and these new outbreaks can confirm newly available tests accurately distinguish infected from vaccinated animals (DIVA), there is support for vaccination strategies to allow vaccinated animals that do not become infected or come in contact with infected animals, to live and be processed normally [25,26].

Data from this study gives the responsible officials more support for using vaccination to control disease outbreaks. The device described here will allow for rapid and safe vaccination of many animals compared to needle inoculation. In addition, vaccine resources can be expanded as the effective dose for vaccination intradermally can be lowered compared doses required for IM application. More studies with much larger numbers are required to confirm these results, but the data presented here provide a clear indication of the potential advantage of the ID vaccination device.

References