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Use of an automatic needle-free injection device for foot-and-mouth disease vaccination in dairy heifers

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Abstract: The foot-and-mouth disease (FMD) vaccination of Thai dairy cows is routinely conducted to control and prevent the disease. In Thailand, FMD control strategies include a subcutaneous route (s.c.) vaccination with 2 ml of inactivated FMD vaccine 2–3 times a year produced by the Department of Livestock Development (DLD). A new way of vaccination was introduced in the form of an automatic needle-free injection device. This technology has several important advantages, such as requiring less animal restraint, reduced time and labour with high precision, and a consistent delivery system. Here, the effectiveness of an automatic needle-free injection (ANFI) device was evaluated in 30 dairy heifers (randomly divided into three groups, 10 in each group) in the FMD vaccine delivery. The first group was subcutaneously (s.c.) vaccinated using a conventional hypodermic needle with 2 ml of the vaccine, the second group received the same, but using a CO_2-powered ANFI device, and the third group received the vaccine using the same ANFI device, but administered intradermally (i.d.) with only 1 ml of the vaccine. The blood samples collected up to 120 days post-vaccination revealed that both injection methods resulted in a similar serological response. The results suggest that the i.d. and s.c. ANFI systems are effective and safe. Moreover, the i.d. use of the ANFI enabled the possibility to half the vaccination dose with the same efficacy. Therefore, the ANFI can be used as an alternative approach for FMD vaccination by s.c. or i.d. routes in dairy cows in Thailand. Ultimately, reducing the use of restraint devices and labour will improve the vaccination for the prevention and control of FMD and may improve the cows' welfare.

Keywords: antibody; dairy; foot-and-mouth disease; needle-free; vaccine

It is reported that Thailand is an endemic area for foot-and-mouth disease (FMD) (OIE 2017a). Due to the high frequency of FMD reports, the control and prevention of FMD are carried out regularly, including intensive vaccination programmes, biosecurity, the restriction of animal movement, and the reduction of the viral load by disinfectants. In terms of the prevention and control of FMD in Thailand, the predominant method used is a routine vaccination with an inactivated FMD virus two or three times a year following the guidelines of the Department of Livestock Development (DLD).

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The FMD vaccine used in cattle in Thailand is typically trivalent (against FMD virus serotype A, O, and Asia-1) and is formulated with an alum gel as an adjuvant manufactured by DLD. The usual route of administration of the FMD vaccine is the subcutaneous (s.c.) injection of 2 ml. However, FMD outbreaks are still continually reported. Previous studies on FMD immunity indicated that the level of protective immunity against FMD in susceptible animals was less than 60% (Jithlang and Sirimongkolrat 2008; Prakotcheo and Premashthira 2010), which is low in comparison with the recommended level of 85% (Doel 1996).

The fact that outbreaks are still occurring may be related to the low immunity of the animals, which may have two reasons. Firstly, the difficulty of restricting livestock during the vaccination prevents some farmers from vaccinating their animals. During a routine vaccination process, the animals need to be handled with sheer force. This may harm both the livestock and farmers. Secondly, the immune response after vaccination with the FMD vaccine by conventional methods will not cause a reactive long-term protection (Rodriguez and Grubman 2009). Therefore, it is important to improve the efficiency of the vaccine administration. Presently, introducing automatic needle-free injection (ANFI) devices has opened up new ways to improve vaccination strategies against FMD.

Due to the high performance with the accuracy, convenience, and usability of ANFI, it can be an alternative method of vaccination against FMD in dairy cattle. Also, it has many advantages, including significant time savings, no cross-contamination from repeated needle use, less pain and stress for animals, reduced trauma to injury sites, and no biological waste (Skilton and Thompson 2005; Weese and Jack 2008; Rey 2013).

The ANFI method is affordable for farmers because it is practically designed for free movement, reducing the need to restrain the animals. Also, the cost of labour will be reduced and occupational needlestick injuries will also decrease. The horizontal transmission of blood-borne diseases through needle sharing, such as an *Anaplasma marginale* infection, could also be prevented by the ANFI method (Rao et al. 2006; Weese and Jack 2008; Chen et al. 2017).

The ANFI devices provide an adjustable route of administration by intradermal (i.d.), subcutaneous (s.c.), or intramuscular (i.m.) injections, and the dosage units can vary. The ANFI is safer, faster, and more accurate than the needle injection method. Also, for jobs that require dispersion or mist in the dermal tissues, s.c. or i.m., this mode of injection increases the surface area that is exposed to the drug, resulting in a more enhanced immune response than conventional practice, while bypassing needle inoculation (Kale and Momin 2014).

Recently, several studies have demonstrated the success of the ANFI method in vaccinating cattle. For example, Rey et al. (2013) showed that both the needle-free and needle-syringe systems induced a significant antibody response, with the former causing a reduced skin reaction and adverse effects on carcass quality. Chen et al. (2017) suggested that the ANFI system resulted in a lower rate of adverse reactions in the animals, and the high injection speed resulted in a higher vaccination efficiency. Furthermore, van Drunen Littel-van den Hurk (2006) found that the administration of the i.d. vaccine using the ANFI system was effective for a vaccination with the bovine herpesvirus type 1 DNA vaccine. Hollis et al. (2005) also used an ANFI system in calves against the infectious bovine rhinotracheitis (IBR) virus, *Mannheimia haemolytica* bacterin-toxoid, and *Leptospira pomona* bacterin, while Pires et al. (2007) reported that an i.d. ANFI vaccination with a *Brucella abortus* RB 51 vaccine resulted in an enhanced immune response with minimal doses of the antigen. Furthermore, the total number of animals that could be vaccinated from a batch could be increased (Pandya et al. 2012).

For an i.d. vaccination, the ANFI system could be substituted for the conventional method, where effective protection against FMD was achieved with 1/16 of the recommended vaccine dose for the conventional syringe-needle system (Pandya et al. 2012). Cattle vaccinated with doses of 1/16 and 1/4 using the ANFI device were protected when challenged at 7 and 28 days, respectively, post-vaccination (dpv) (Pandya et al. 2012).

We suggest that ANFI become a routine practice for the i.d. vaccination of dairy cattle. The device provides at least an equivalent tool, and an enhanced level of the immune response, compared to a conventional injection. However, detailed studies on the ANFI device compared to the conventional method in dairy cattle are lacking. Therefore, this study on the i.d. and s.c. administration of an FMD vaccine in dairy cows using the ANFI system represents a promising direction.

The purpose of this study was to evaluate the immune response of the ANFI vaccination via i.d. and s.c. in heifers in comparison with the conventional method when using the inactivated FMD vaccine.

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MATERIAL AND METHODS

Animals

This study was conducted on a large Holstein-Friesian dairy farm with 1 200 dairy cows. The FMD vaccination programme is routinely carried out three times a year on this farm. In accordance with the World Organisation for Animal Health (OIE) recommendations for field studies, at least ten heifers were used per group (Ferrari et al. 2016), so this study population included 30 heifers for the evaluation of the immune response after the FMD vaccination.

The study design was approved by the Chulalongkorn University Animal Care and Use Committee in accordance with university regulations and policies governing the care and use of laboratory animals (Protocol No. 1731078).

The heifers received a two-dose trivalent FMD primary vaccination cycle. The heifers were randomly assigned to one of three groups: (1) conventional s.c. vaccination of 2 ml of the vaccine using a hypodermic needle, (2) s.c. vaccination (2 ml) using the ANFI device, and (3) i.d. vaccine (1 ml) using the ANFI device.

The clinical signs of FMD were continuously monitored throughout the study period. The heifers were examined for any clinical signs of FMD and adverse effects after vaccination by a veterinarian from this farm.

ANFI device

The Pulse 250 Needle-Free Systems (Pulse®, Lenexa, KS, USA) model was used in this study. Maintenance work was carried out before using the system. The device works with compressed carbon dioxide (CO_2). We delivered the vaccine through a high-pressure hose into a 0.35 mm diameter handpiece in 1 or 2 ml doses. According to the company's guidelines and the heifer carcass skin testing before conducting the experiment, the pressure was set to 50 or 60 psi (ca. 344.74 or 413.69 kPa, respectively) for the i.d. and s.c. route, respectively. Any apparent change in the injection's surface site was recorded as a vaccination reaction.

Vaccine and vaccination

The vaccine used in this study was the trivalent FMD vaccine (serotype O, A, and Asia-1) that contains at least three times the dose that protects 50% of the exposed animals (PD_{50}) per dose. The vaccine batch was T60D, which contained the FMDV strains O189 (O/TAI/189/87), A-sakol (A/TAI/118/97), and Asia-1 (Asia-1/TAI/85).

The heifers were vaccinated at the beginning of the experimental study. Cattle serum was collected before the initial vaccination and at 7, 14, 21, 60, 86, and 120 dpv and stored at –80 °C until subsequent analysis.

Virus neutralisation test (VNT)

The neutralising antibody titre (NAT) in the serum was measured by a VNT in the Quality Control Unit of the Bureau of Veterinary Biologics, DLD, Pak-Chong, Nakorn-Ratchasima province, using the homologous vaccine strain to compare the immunogenicity and protective effects between the various experimental groups. The procedure was carried out following the OIE standard procedure of the VNT for FMDV serotype O (O/TAI/189/87), A (A/TAI/118/97), and Asia-1 (Asia-1/TAI/85) (OIE 2017b).

Briefly, the serum sample was inactivated at 56 °C for 30 min in a water bath before testing the VNT. The test was performed with lamb kidney cells in a flat-bottom tissue culture grade micro-titre plate. The stock virus was grown in cell culture monolayers and stored at 20 °C after the addition of 50% (v/v) glycerol (the virus is stable under these conditions for at least 1 year). The standard control serum was a post-vaccination serum that included positive and negative controls. A suitable choice of medium was the Eagle's complete medium or LYH (Hanks balanced salt solution with yeast extract, and lactalbumin) with a HEPES [4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid] buffer and antibiotics. The sera were diluted in a series of two-fold dilutions across the plate using two rows of wells, with a volume per well of 50 µl. The dilution started with a 1/4 dilution and the sera were diluted two-fold in the medium, followed by a series of dilutions across the plate using two rows of wells per serum. The previously titrated virus was added so that each 50 µl unit volume of the virus suspension contained approximately 100 $TCID_{50}$ (50% tissue culture infectious dose) and incubated at 37 °C for 1 h with the plates covered. Then 50 µl of cell suspension (10^6 cells/ml) were added to each well, the plates were sealed with pressure-sensitive tape and incubated at 37 °C for 2 days before the evaluation of the NAT, expressed as $\log_{10}$ serum 100 $TCID_{50}$.

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Data processing and analysis

The data were analysed with SPSS v22 (IBM, Armonk, NY, USA). The NAT was estimated using a generalised linear mixed model (GLMM) and was presented as the average NAT ± one standard error (SE). A Bonferroni pairwise comparison was used to compare the estimated NAT between the groups and to compare the sampling times within each group.

The different averages of the NAT were analysed by linear regression in GLMM, with NAT as the response variable, the animal as a random variable, and the sampling time and group as the explanatory variables.

To compare within an experimental group, the estimated NAT after vaccination was compared between the sampling time points. For the comparison between the experimental groups, the estimated NAT was compared at each sampling time.

For all analyses, a P-value < 0.05 was considered statistically significant. The variance of the error of all models was verified by plotting the residual against the predicted value of the final model.

RESULTS

Clinical assessment

All the animals received the FMD vaccine on day 0 and subsequently, a veterinarian evaluated the clinical signs of FMD and the adverse effects of the vaccination. No clinical signs of FMD were observed during the study period.

NAT response

All the heifers were vaccinated with the dead FMD virus produced by DLD on day 0. In the three groups of heifers, the NAT values against serotypes O, A, and Asia-1 increased significantly by 7 dpv (Tables 1, 2, and 3). The NAT against the FMD virus serotype O and A did not show any significant difference compared to groups I, II, and III in 7 dpv (P > 0.05), while the NAT against the Asia-1 serotype FMD virus was significantly different in group II compared to group III at 7 dpv (P < 0.05). Regarding the duration

Table 1. Neutralising antibody titres NAT (log_{10}) against FMDV serotype O (O/TAI/189/87) in the heifers

Group	NAT against serotype O expressed as log_{10} (average ± SE) at the indicated days post-vaccination						
	0	7	14	21	60	86	120
I	1.13 ± 0.17^{*,A}	1.92 ± 0.17^{**,***,A}	1.78 ± 0.17^{**,***,A}	1.62 ± 0.17^{***,A}	1.36 ± 0.17^{*,A}	1.47 ± 0.17^{*,A}	1.20 ± 0.18^{*,A}
II	0.89 ± 0.17^{*,A}	1.75 ± 0.17^{**,A}	1.59 ± 0.17^{***,A}	1.40 ± 0.17^{***,A}	1.15 ± 0.18^{*,***,A}	1.20 ± 0.18^{*,***,A}	1.02 ± 0.18^{*,***,A}
III	0.90 ± 0.17^{*,A}	1.83 ± 0.17^{**,A}	1.74 ± 0.17^{**,***,A}	1.60 ± 0.17^{***,A}	1.34 ± 0.17^{*,A}	1.32 ± 0.18^{*,A}	1.22 ± 0.18^{*,A}

Group I = conventional s.c. vaccination with 2 ml of the FMD vaccine; group II = s.c. ANFI vaccination with 2 ml of the FMD vaccine; group III = i.d. ANFI vaccination with 1 ml of the FMD vaccine

*,**,***Indicate significant differences in the NAT means between the sampling times within the same group (P < 0.05); $^{A–C}$Indicate significant differences in the NAT means between the groups at the same sampling time (P < 0.05)

Table 2. Neutralising antibody titres (NATs) (log_{10}) against FMDV serotype A (A/TAI/118/97) in the heifers

Group	NAT against serotype A expressed as log_{10} (average ± SE) at the indicated days post-vaccination						
	0	7	14	21	60	86	120
I	0.75 ± 0.09^{*,A}	1.26 ± 0.09^{**,A}	1.16 ± 0.09^{***,A}	1.01 ± 0.09^{***,A}	0.75 ± 0.09^{*,A}	0.77 ± 0.09^{*,A}	0.75 ± 0.10^{*,A}
II	0.75 ± 0.09^{*,A}	1.25 ± 0.09^{**,A}	1.10 ± 0.09^{***,A}	1.02 ± 0.09^{***,A}	0.79 ± 0.10^{*,A}	0.76 ± 0.10^{*,A}	0.80 ± 0.10^{*,A}
III	0.75 ± 0.09^{*,A}	1.28 ± 0.09^{**,A}	1.14 ± 0.09^{**,***,A}	1.01 ± 0.09^{***,A}	0.90 ± 0.09^{*,A}	0.84 ± 0.10^{*,A}	0.78 ± 0.10^{*,A}

Group I = conventional s.c. vaccination with 2 ml of the FMD vaccine; group II = s.c. ANFI vaccination with 2 ml of the FMD vaccine; group III = i.d. ANFI vaccination with 1 ml of the FMD vaccine

*,**,***Indicate significant differences in the NAT means between the sampling times within the same group (P < 0.05); $^{A–C}$Indicate significant differences in the NAT means between the groups at the same sampling time (P < 0.05)

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Table 3. Neutralising antibody titres (NATs) (log_{10}) against FMDV serotype Asia-1 (Asia-1/TAI/85) in the heifers

Group	NAT against serotype A expressed as log_{10} (average ± SE) at the indicated days post-vaccination						
	0	7	14	21	60	86	120
I	0.81 ± 0.16^{*,A}	1.74 ± 0.16^{*,**,AB}	1.67 ± 0.16^{**,AB}	1.43 ± 0.16^{**,AB}	1.10 ± 0.17^{*,A}	1.44 ± 0.17^{**,A}	1.05 ± 0.16^{*,A}
II	0.75 ± 0.16^{*,A}	1.53 ± 0.16^{**,A}	1.44 ± 0.16^{***,A}	1.19 ± 0.16^{***,A}	1.12 ± 0.17^{*,**,***,A}	1.17 ± 0.17^{**,A}	1.06 ± 0.16^{*,***,A}
III	0.78 ± 0.16^{*,A}	1.86 ± 0.16^{**,B}	1.79 ± 0.16^{**,B}	1.65 ± 0.16^{**,B}	1.25 ± 0.16^{***,A}	1.36 ± 0.17^{**,***,A}	1.13 ± 0.17^{***,A}

Group I = conventional s.c. vaccination with 2 ml of the FMD vaccine; group II = s.c. ANFI vaccination with 2 ml of the FMD vaccine; group III = i.d. ANFI vaccination with 1 ml of the FMD vaccine

*,**,***Indicate significant differences in the NAT means between the sampling times within the same group (P < 0.05); $^{A–C}$Indicate significant differences in the NAT means between the groups at the same sampling time (P < 0.05)

of the immunity, the NAT against serotype O in all the groups did not differ significantly at 60 dpv compared to day 0 (Table 1). There were also no significant differences between the different groups on each sampling date. The NAT against serotype A showed a similar pattern with serotype O (Table 2), while the NAT against Asia-1 serotype in group I was not significantly different at 60 dpv compared to day 0. On the other hand, the NAT against the Asia-1 serotype in group III was significantly different at 60 dpv compared to day 0. For the comparison of the NAT against the Asia-1 serotype between the groups, the NAT of group III was significantly higher than group I at 21 dpv, but this was not the case at 7 and 14 dpv. Finally, the NAT of group II did not vary significantly from that of group I for all the sampling dates (Table 3).

The validity of this study, on the effectiveness of the ANFI device compared to the conventional methods, was affected by the power of the analysis. This is because the statistical power is positively correlated to the sample size, thus requiring verification of the probability of significantly detecting a predefined clinical outcome between the groups (Suresh and Chandrashekara 2012). In this study, the power result (1-β) was 0.875, calculated by G*Power v3.1 (Kiel University, Kiel, Germany), where α is 0.05.

DISCUSSION

Our interest was in the improvement of an alternative administration of vaccines to animals to reduce any required animal restraints and to vaccinate many animals to increase the immunity of the population. In this study, the FMD antibody concentrations (such as NAT) in the ANFI and conventional vaccinated heifers increased significantly after the booster vaccination. This response is similar to that seen in other studies that have evaluated an FMD vaccination using an ANFI device (Pandya et al. 2012). These animals reached an effective level of immunity because they had previously been vaccinated at least twice, thus the memory B-cells in their immune system exhibited a rapid response (anamnestic) (Doel 1996). To maintain the NAT at a level of protective immunity to prevent FMD, animals must be revaccinated regularly, at least three times a year (Elnekave et al. 2016). The ANFI device can be used for regular vaccinations. The results revealed that the immune response after the s.c. vaccination with the ANFI device was not significantly different from the conventional needle-syringe s.c. vaccination. Furthermore, the i.d. vaccine with half the vaccine dose (1 ml) by the ANFI device was more effective than the conventional method (s.c. with a 2 ml vaccine) due to the reduced use of vaccine per dose for the same effect.

Also, the FMD antibody concentration (such as the NAT) in the ANFI vaccinated group is sometimes higher than that of the conventional group. Previous research in cattle has shown that ANFI vaccinations resulted in an equivalent, and sometimes improved, immune response compared to conventional vaccinations (Hollis et al. 2005; van Drunen Littel-van den Hurk 2006; Pires et al. 2007). The enhanced immune response that follows a needle-free vaccination could be due to the greater spread of the vaccine into the tissues and greater penetration through the skin (Bennett et al. 1971). This increases the inflammatory response, which normally induces the recruitment of immunocompetent inflammatory cells and allows a greater volume of contact between the vaccine antigen and the immune cells (Giudice and Campbell 2006). The greater area of the i.d. exposed to the vac-

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cine antigen in the i.d. vaccine by the ANFI method would likely find (and thus activate) more Langerhans cells, as they have a high migratory mobility that act as effective antigen-presenting cells and, therefore, they enhance the primary immune response (Liard et al. 2012). Therefore, the ANFI device can be an alternative method of an FMD vaccination in heifers. This study is in agreement with other studies in cattle. For example, Rey et al. (2015) demonstrated that an ANFI resulted in an immune response comparable to that performed by a needle-syringe injection. Furthermore, the FMD vaccine dose could be reduced to 0.5 ml when the i.d. vaccine is used with the ANFI device (Pandya et al. 2012). However, the specification of the device used in this study allowed only doses of 1, 2 or 5 ml and not, for example, 0.5 ml. Therefore, more studies are needed to assess the appropriate dose of the FMD vaccine from the device, and the efficacy of the antibody response with exposure to the virus should be performed after the vaccination.

The main advantages of a vaccination with the ANFI device are the ease of use, convenience, lower labour cost, less restraints needed on the animals, and less stress on the animals. This procedure can also eliminate the hidden danger of injecting needles and reap the benefits of reduced social costs, which are difficult to quantify financially. These include, for example, the safety of workers who may suffer needlestick injuries and wasted of disposable syringes for vaccinating.

Additionally, another benefit of the device is a reduction in the horizontal disease transmission and the spread of pathogens (Reinbold et al. 2010), such as the bovine leukaemia virus, which causes leukaemia/lymphoma mortality (Hopkins and DiGiacomo 1997; Weese and Jack 2008; Erskine et al. 2012), bloodborne infections (Otake et al. 2002), and infections due to the repeated use of dirty needles (Skilton and Thompson 2005).

Thus, the i.d. vaccination using an ANFI device can stimulate the immune response with a reduced amount of vaccine per dose, reducing the overall costs of vaccine production, delivery, and coverage.

In conclusion, the present study has indicated that an ANFI device can be an alternative method for an FMD vaccination, especially when using the i.d. vaccine, in dairy heifers with an immune response comparable to conventional methods. However, further studies and field experiments aimed at improving the results and reducing the volume dose should be examined.

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Conflict of interest

The authors declare no conflict of interest.

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