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Estimation of the proper route and dose for trivalent oily FMD vaccine in sheep

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Abstract

This study aims to determine the proper dose and route for vaccination of sheep against foot and mouth disease (FMD), by using trivalent oil FMD vaccine in addition to gaining the highest protective antibody titers.

Six groups of sheep (6 sheep / each) were vaccinated with different doses of the trivalent oily FMD vaccine [full (1.5 ml), ½ (0.75ml) and ¼ (0.37ml) doses], S/C or I/M. The experiment included challenged non-vaccinated control group (2 sheep for each used viral strain).

Pre- vaccination blood samples of all groups then weekly blood samples were collected to follow up the level of induced antibody titers by using SNT and ELISA. Four weeks post vaccination all animal groups were challenged by inoculation intradermolingual (IDL) with 10.000 ID50 (infective dose fifty) sheep adapted FMD (O & A & SAT2 types) virus and subjected to clinical observation for 8 days. The results showed that the vaccinated animals with a full and ½ dose injected either S/C or I/M were able to withstand the virus infection while animals vaccinated with ¼ dose didn't. The vaccinated group given full dose through S/C route showed the highest protective antibody titers against all viral strains of the vaccine.

Key Words: trivalent FMD vaccine, sheep, dose and route.

Introduction

Foot and mouth disease (FMD) is a contagious viral disease of cloven-hoofed animals which has a great potential to cause severe economic losses It also affects wild animals such as buffalo and deer (Paton et al., 2009). Foot and Mouth disease virus (FMDV) is the etiologic agent of such devastating disease that spreads very rapidly and is characterized by fever, lameness and vesicular lesions on the feet, tongue, snout and teats, with high morbidity but low mortality (Juleff et al., 2012). *FMD* caused by a member of family *Picornaviridae*, genus *Aphthovirus* that occurs as seven distinct

serotypes of FMDV, have been identified such as O, A, C, SAT1, SAT2, SAT3 and Asia1 (Franki et al., 1991; OIE, 2010) which are widely distributed throughout South America, Africa, the Middle East, and Asia (Aggarwal et al., 2002).

Regarding Egypt, the disease is enzootic and many outbreaks have been reported since 1950. FMD serotypes SAT2, A and O were reported in years 1950, 1972 and 2000 respectively (Aidaros, 2002).Type O was the most prevalent since 1960 and onwards (Farag et al., 2005 ; Parida, 2009). Serotype A was recorded in Egypt recently when it was introduced to Egypt during 2006 through live animal's importation where sever clinical

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signs were recorded among cattle and buffaloes (Abd El-Rahman et al., 2006). In addition, serotype SAT-2 of FMD virus was later introduced to Egypt during 2012 through live animal's importation, isolated and typed by Veterinary Serum and Vaccine Research Institute, Cairo, Egypt (VSVRI) and confirmed by world reference Laboratories, Pirbright, United Kingdom (Shawky et al., 2013). Due to the presence of complicated epizootiological field aspect, FMD is a serious problem and it is difficult to be eradicated from Egypt. In a country, where control of FMD relies predominately on vaccination, the stability of the currently used vaccine with high potency is the only way to protect susceptible animals against FMD (Farag et al., 2005 [(2)] and Abdel El-Rahman et al., 2006). It was stated that serotypes O, A and SAT2 of FMD virus have been isolated from sheep (Kitching and Hughes, 2002 and Mohamed 2006).

It has been proved that inactivation of FMD virus type O with binary ethyleniemine instead of formalin improved the vaccine quality. Such vaccine adjuvanted with aluminum hydroxide gel was successfully used for immunization of cattle and buffaloes in Egypt (OIE. 20006 and Sonia et al., 2008). The efficacy of several adjuvants to induce such protection showed that the aqueous IMS1313 plus inactivated FMDV induces a higher protective immune response than the vaccine with inactivated virus alone (Quattrocchi et al., 2004).

Both cellular and humeral immune responses of animals usually share crucial role in the protection against FMD where the first one appears mainly more rapid than the second one but last shorter (Soos and Tuboly 1983, and Halima et al., 1999).

It was noticed that some vaccinated animals having sub-protective levels of FMD neutralizing antibody titers few days post vaccination could withstand the virulent virus (Abeer and Hegazi 2008, and OIE. 2004).

For routine vaccination programs in countries and zones recognized as free from, FMD with vaccination or in FMD endemic areas a 3 PD50 potency level is required (Council Directive 2003). However, for an FMD vaccine batch to be eligible for use in emergency situations within the European Member States, the PD50 content must be greater or equal to 6 (Barnett and Cox 1999).

The present work was designed to determine the proper dose and route for vaccination of sheep against foot-and mouth disease (FMD), by using trivalent oil FMD vaccine in addition to gaining the highest protective antibody titers against the used viral strains.

Material and methods

1-Animals:

Forty two local breed sheep of 3-4 months of age with 25-30 Kg body weight were used. They were clinically healthy and free from antibodies against foot and mouth disease virus types O Pan Asia-2, A Iran O5 and SAT2/Egypt /2012 as proved by serum neutralization test.

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2-Foot and mouth disease vaccine:

FMD virus was propagated in BHK21 cell line in roller bottles (Huang et al., 2011) and inactivated with Binary Ethyleneimine (BEI) as described by Soliman et al. (2013). The vaccine formulation was carried out according to the method described by Gamil (2010) as follows as equal parts of an aqueous and oil phase weight/ weight, and mixed thoroughly. The aqueous part contains FMDV concentration in the final vaccine formula was adjusted to be not less than 10^8TCID50 equal to 2.3 to 3.3 µg of 146s for each type of the virus per vaccine dose (Doel, and Chong1982), with saponin 1.5µg/dose as immunostimulant, sodium thio-mersal was added as preservative at a final concentration of 0.0001 (1ml of 10% Sod Thio-mersal /10 liter vaccine). (Daoud et al., 2013).

3-FMD virus:

Egyptian isolated FMDV type O Pan Asia-2, A Iran O5 and SAT2/Egypt /2012 with a titre 10^9TCID50/ml for each type were supplied by Foot and Mouth Vaccine Research Department (FMDRD), Veterinary Serum and Vaccine Research Institute, Abbasia, Cairo. The virus type O, A and SAT-2 were confirmed by the World Reference Laboratory for FMD (WRL) Pirbright London, UK. These viruses were used for production of the trivalent FMD vaccine and serological tests according to (Ferreira, 1976) and Hamblin et al. (1986).

4. Experimental Design

Forty two sheep were divided into seven groups vaccinated with **trivalent oily FMD vaccine** as follows:-

Group (1): 6 sheep vaccinated S/C with 1.5 ml	**Group (4): 6 sheep vaccinated I/M with 1.5 ml**	**(Full recommended dose)**
Group (2): 6 sheep vaccinated S/C with 0.75 ml	**Group (5): 6 sheep vaccinated I/M with 0.75 ml**	**(½ dose)**
Group (3): 6 sheep vaccinated S/C with 0.37 ml	**Group (6): 6 sheep vaccinated I/M with 0.37 ml**	**(¼ dose)**
Group (7): 6 sheep not-vaccinated (control). (For challenge as 2 sheep / each virus)		

Four weeks post vaccination the seven groups were challenged intradermolingual (IDL) with 10^4 $TCID_{50}$ (10.000 infective dose fifty) of virulent FMD virus types O Pan Asia-2, A Iran O5 and SAT2/Egypt /2012 according to Vianna et al., (1994) and Farag et al., (2005) and clinically observed for 8 days.

5. Samples:

Serum samples were collected from vaccinated sheep. The sera were collected and stored at -20°C and inactivated at 56°C for 30 minutes before being used in the serological tests (SNT and ELISA).

6-Estimation of Humeral immunity:

Was estimated by SNT which carried out using the micro titer technique according to (Ferreira, 1976) and ELISA according to Hamblin et al. (1986).

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Results and Discussion

The obtained results revealed that all the vaccinated animals exhibited detectable specific antibodies against the used serotypes of FMD virus by the first week post vaccination (1st WPV) using SNT and ELISA and the mean of serum neutralizing FMD antibody titers (log_{10}/ml) evaluated by SNT in (Tables 1, 2 and 3 & Fig: 1) for

Type (A) showing that antibody titers at the 4th week post I/M vaccination were 1.8, 1.65 and 1.2 log_{10}/ml and by S/C vaccination were 1.95, 1.8 and 1.35 log10/ml for animals vaccinated with full, ½ and ¼ doses respectively.

Type (O) antibody titers at the 4th week post I/M vaccination were 1.95, 1.8 and 1.2 log_{10}/ml and by S/C vaccination were 2.1, 1.95 and 1.35 log10/ml for animals vaccinated with full, ½ and ¼ doses respectively.

Type (SAT2) antibody titers at the 4th week post I/M vaccination were 1.8, 1.65 and 1.2 and by S/C vaccination were 1.95, 1.8 and 1.35 log10/ml for animals vaccinated with full, ½ and ¼ dose respectively.

Also the results revealed the mean of ELISA titer (log_{10} /ml) in (Tables 4, 5and 6 & Fig: 2) for **Type (A)** showing that antibody titers at the 4th week post S/C vaccination were 2.25, 2.1 and 1.65 log10/ml and by I/M vaccination were 2.1, 1.95 and 1.5 log_{10}/ml for animals vaccinated with full, ½ and ¼ doses respectively .

Type (O) antibody titers at the 4th week post S/C vaccination were 2.4, 2.25 and 1.65 log_{10}/ml and by I/M vaccination were 2.25, 2.1 and 1.5 log_{10}/ml for animals vaccinated with full, ½ and ¼ doses respectively..

Type (SAT2): antibody titers at the 4th week post S/C vaccination were 2.25, 2.1 and 1.65 log_{10}/ml and by I/M vaccination were 2.1, 1.95 and 1.5 log_{10}/ml for animals vaccinated with full, ½ and ¼ dose respectively.

Table (1): Mean FMD (type A) serum neutralizing antibody titers in vaccinated sheep

Mean serum FMDV (A) neutralizing antibody titer (log_{10} /ml)							
Route of Vaccination	S/C			I/M			
Dose / WPV	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	Unvaccinated Control
1st	0.9	0.75	0.6	0.75	0.6	0.45	0.3
2rd	1.35	1.2	0.9	1.2	1.05	0.75	0.3
3rd	1.65	1.5	1.05	1.5	1.35	0.9	0.3
4th	1.95	1.8	1.35	1.8	1.65	1.2	0.3

Table (2): Mean FMDV (type O) serum neutralizing antibody titer in vaccinated sheep

Mean serum FMDV (O) neutralizing antibody titer (log_{10}/ml)							
Route of Vaccination	S/C			I/M			
Dose / PV	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	Unvaccinated Control
1st	1.05	0.9	0.6	0.9	0.75	0.6	0.3
2rd	1.35	1.2	0.75	1.2	1.05	0.6	0.3
3rd	1.8	1.5	0.9	1.5	1.35	0.75	0.3

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4th	2.1	1.95	1.35	1.95	1.8	1.2	0.3

Table (3): Mean FMD (type SAT2) serum neutralizing antibody titers in vaccinated sheep.

Mean serum FMDV (SAT2) neutralizing antibody titer (log_{10}/ml)							
Route of Vaccination	S/C			I/M			
Dose / PV	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	Unvaccinated Control
1st	1.05	0.9	0.6	0.9	0.75	0.6	0.3
2rd	1.5	1.35	0.75	1.35	1.2	0.6	0.3
3rd	1.65	1.5	0.9	1.5	1.35	0.75	0.3
4th	1.95	1.8	1.35	1.8	1.65	1.2	0.3

NB. The recommended protective level for SNT: - 1.5 log_{10}

Table (4): Mean FMD (type A) ELISA antibody titers in vaccinated sheep

Mean serum FMDV (A) ELISA titer (log_{10}/ml)							
ıute of Vaccination	S/C			I/M			
Dose / PV	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	vaccinated Control
1st	1.2	1.05	0.9	1.05	0.9	0.75	0.6
2rd	1.65	1.5	1.2	1.5	1.35	1.05	0.6
3rd	1.95	1.8	1.35	1.8	1.65	1.2	0.6
4th	2.25	2.1	1.65	2.1	1.95	1.5	0.5

Table (5): Mean FMD (type O) ELISA antibody titers in vaccinated sheep

Mean serum FMDV (O) ELISA titer (log_{10}/ml)							
Route of Vaccination	S/C			I/M			
Dose / PV	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	Unvaccinated Control
1st	1.35	1.2	0.9	1.2	1.05	0.9	0.6
2rd	1.65	1.5	1.05	1.5	1.35	0.9	0.6
3rd	2.1	1.8	1.2	1.8	1.65	1.05	0.6
4th	2.4	2.25	1.65	2.25	2.1	1.5	0.6

Table (6): Mean FMD (typeSAT2) ELISA antibody titers in vaccinated sheep.

Mean serum FMDV (SAT2) ELISA titer (log_{10}/ml)							
Route of Vaccination	S/C			I/M			
Dose / PV	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	1.5 ml (Full)	0.75 ml (½)	0.37 ml (¼)	vaccinated Control
1st	1.35	1.2	0.9	1.2	1.05	0.9	0.75
2rd	1.8	1.65	1.05	1.65	1.5	0.9	0.75
3rd	1.95	1.8	1.2	1.8	1.65	1.05	0.75
4th	2.25	2.1	1.65	2.1	1.95	1.5	0.75

NB. The recommended protective level for ELISA: - 1.8 log10

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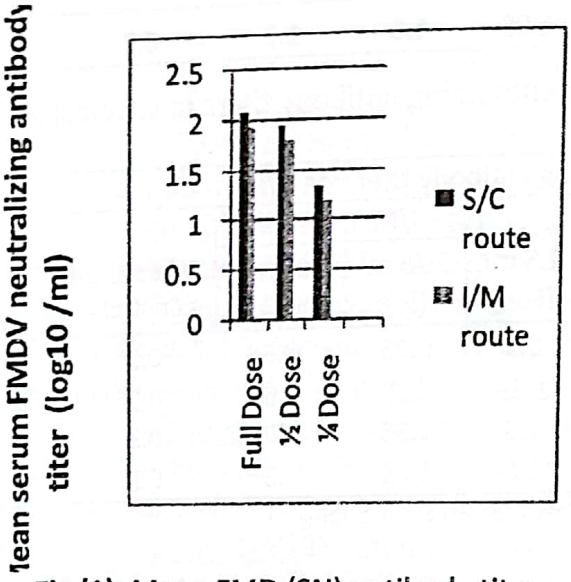

Fig (1): Mean FMD (SN) antibody titers in vaccinated sheep

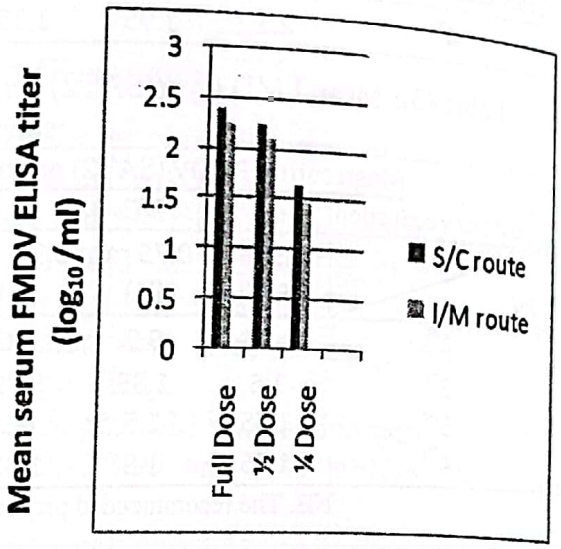

Fig (2): Mean FMD (ELISA) antibody titers in vaccinated sheep

Also the animals, vaccinated with a full, ½ dose, injected either S/C or I/M showed protection through challenge test. However the animals vaccinated with ¼ dose all went down.

The control of FMD in animals was considered to be corner stone to eliminate the disease outbreaks in endemic areas, through effective vaccination for limiting the spread of FMD (Depa et al., 2012). Also vaccine adjuvant prolongs the immune response and stimulate specific component either humeral or cell mediated immunity (Lombard et al.,2007) and the efficacy of the adjuvant plus inactivated FMDV induce a higher protective immune response than the vaccine with inactivated virus alone at seven DPV. (Quattrocchi et al., 2004).So the results are matching with those of Basarab and Pay (1982) who demonstrated that double w/o/w oil emulsion FMD vaccines will protect weaned pigs for the duration of their normal life span. This protection is achieved by inoculation by any of the usual routes, mainly S/C or I/M. The advantage of trivalent w/o/w Montanide ISA206 oil vaccine was attributed to depot formation at the site of injection, a vehicle for transport of the antigen throughout the lymphatic system and slow antigen release with the stimulation of antibody producing cells. Moreover, being oil emulsion, Montanide ISA206 had various advantages, like low viscosity, easy administration, greater stability and production of smaller nodules at the site of injection (Barnett et al., (1996) and Barnett and Cox (1999) who suggested that Montanide ISA206 could prevent the loss of potency was due to the proteolysis of VP1 or possibly the physical breakdown of the virus followed adsorption to the aluminum hydroxide gel. Also as stated by (Doel and Pullen (1990) agree with (Barnett and Carabin (2002) and (Quattrocchi et al., 2004). who mentioned that Montanide ISA206 ready to formulate oil adjuvant can be used in all target species is ideal for emergency vaccination. (Quattrocchi et al., 2004).

Also the present results agreed with those obtained by Selim et al. (2010) who reported that the mean antibody titers against FMD vaccine strain O1/3/93 were detected in sheep sera vaccinated with Alumhydroxide gel vaccine following one WPV by SNT and with those of Mohamed et al. (2013) who used FMD ISA206 oil bivalent vaccine alone and noticed that the specific FMD neutralizing antibody titer reached a protective level by the 4th WPV and also El-Sayed et al. (2012) who reported that vaccination of calves with the locally produced bivalent FMD adjuvant vaccine induced higher antibody titer than the

recommended protective level (1.5 log_{10} for SNT and 1.8 log_{10} for ELISA) for type A and O estimated by SNT and ELISA. This antibody titer remained within the protective level up to 34 WPV.

These results indicated that the detected protective vaccine induced antibodies were agreed with those of Fontaine et al.,(1966) and Bashkadov, (1967) who found that the vaccinated animals had protective antibodies revealed no viraemia or rise in body temperature and lameness when challenged with virulent vaccine strains of FMD virus.

The results of neutralizing antibody titers also agree with (Kardassis et al.,(1964), Moussa et al..(1976) , Bengelsdorff ,(1989) , Farag, (1989) , Samira El-Kilany (1989) , Kitching and Salts (1995) and Ebale et al (2006) who reported that more than 95% of vaccinated cattle with SN titers to 1.7 log_{10} SN_{50} at 21 days post vaccination were protected from generalizing FMD.

Also these obtained results revealed that there are good correlation between the potency values obtained by challenge and those obtained by SNT and ELISA, the same findings obtained by (Lorenz and withmann (1983), Hamblin et al. (1986), Barteling and Vreeswij (1991) and Bomford, (1989).

So we could conclude that S/C route can be used in vaccination against FMD in sheep and with lower doses (0.75ml) using Montanide ISA206 oil adjuvant which has a remarkable economic point of view.

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تحديد أفضل جرعه و طريقة حقن للقاح الحمى القلاعيه الثلاثى الزيتى فى الأغنام

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*المعمل المركزى للرقابه على المستحضرات الحيويه البيطريه قسم بحوث الحمى القلاعية – معهد بحوث الأمصال واللقاحات البيطرية**

أجريت هذه الدراسة لتحديد الجرعة والطريقه الأفضل لتحصين الأغنام ضد مرض الحمى القلاعية للحصول على أعلى معيار من الأجسام المناعيه الواقية باستخدام اللقاح الثلاثي العتره الزيتى المحضر من العترات الثلاثه (A,O and SAT2) لفيروس الحمى القلاعيه و المعزول ومصنف فى مصر وقد تم أستخدام عدد ست مجموعات من الأغنام حقنت بجرعات مختلفه { الجرعه الكامله (١,٥ مللى) أو نصف الجرعه (٧٥، مللى) أو ربعها (٣٧، مللى) }سواء تحت الجلد اوعن طريق الحقن فى العضل مع ترك المجموعه السابعه كمجموعه ضابطه لأجراء أختبار التحدى . تم تجميع عينات الدم لفصل المصل قبل أجراء الحقن و كذلك بالتتابع أسبوعيا بعد الحقن لمدة أربع أسابيع حيث تم تقييم الحالة المناعية باستخدام اختبارى السيرم المتعادل والأليزا لقياس المستويات المناعيه للأغنام سواء عن طريق الحقن تحت الجلد او بالحقن فى العضل بالجرعات المختلفه كما تم أجراء أختبار التحدى بإستخدام العترات الثلاثه (A, O and SAT2) بالحقن في اللسان و متابعة الأعراض لمدة ثمانية أيام بعد أجراء الأختبار. حيث استطاعت جميع الاغنام المحقونة بالجرعه الكامله و بنصف الجرعة سواء عن طريق الحقن تحت الجلد او بالحقن فى العضل من اجتياز اختبار التحدى للفيروس الضارى عند الاسبوع الرابع بعد التحصين فى الوقت اللذين أظهرت فيه المجموعات المحقونه بربع الجرعه سواء بالحقن تحت الجلد أوفى العضل بالأضافه للمجموعه الضابطه أعراض الأصابه بالفيروسات وقد توافق ذلك مع نتائج أختبارى السيرم المتعادل والأليزا الذين أظهرا أعلى المستويات المناعيه الوقائية للأغنام المحقونه سواء تحت الجلد أو فى العضل فى حالتى الحقن بالجرعه الكامله أو نصفها .

و قد أظهرت النتائج تفوقا واضحا في حالة الحقن تحت الجلد سواء بالجرعه الكامله أو نصفها و ذلك محدثا المستوى المناعى المطلوب للحمايه ضد الأصابه باى من العترات الثلاثه الموجوده فى مصر.