FMD Vaccination of Pig Breeders Designed to Give Newborn Piglets Adequate Immunity After Birth

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ABSTRACT

Recurrent incursions of Foot and Mouth Disease (FMD) strains cause several outbreaks in Israel on yearly basis, almost all of them occurring in ruminants; however, in 2015 and 2022 pig farms were also involved and Type O strain was confirmed in the outbreaks. Vaccination against FMD is compulsory for pigs in Israel, but only in breeders as routine vaccination. Furthermore, only a single vaccination per year is performed. The 2022 outbreak presented the occasion to verify if a single vaccination/year/breeder may be considered protective against FMD. Vaccinated sows and their suckling piglets were serologically tested on the eve of the outbreak and 5 months later. Results indicated that breeders vaccinated once a year only, presented with low/non-protective immunity against FMD virus on the eve of the outbreak. Furthermore, a single booster vaccination in course of outbreak, but much overdue from the last routine vaccination, also did not induce a protective immunity in sows. Likewise, Maternally Derived Antibody (MDA) levels in their piglets, which depended on the antibody titer of the sow, were very low and not protective. Repeated breeders' vaccinations during pregnancy are recommended in the literature and by the World Animal Health Organization (OIE), in order to achieve a population coverage >80% with a viral neutralization titer (VNT) of at least ≥1:32, ≥1.5 Log_{10}.

Keywords: FMD; Vaccination; Sows; Piglets; Antibodies; Protection.

INTRODUCTION

Recurrent incursions of Foot and Mouth Diseases (FMD) strains cause several outbreaks on yearly basis in Israel. (1) Most of outbreaks occur in ruminants but in 2015 and 2022 pig farms were also involved (2). Vaccination against FMD is mandatory in Israel. While the vaccination protocol is well defined in ruminants, it is less precise in pigs where a single mass/blanket vaccination of breeders only, once a year, in autumn/winter is recommended (2, 3). Last vaccination course, before 2022 outbreak, was implemented between December 2021 and January 2022; a double-oil emulsion, inactivated FMD vaccine was used, which contains the strains O-Manisa, O-3039, O-Israel 85, O-Pan-Asia 2, A-Iran 05, A-GVII 2015 (Aftopor, Boehringer Ingelheim AH, UK Ltd, Pirbright GU24 0NQ, UK), 2 ml/head, single dose in breeders.

In April 21st 2022, a FMD outbreak occurred in farrow to finish pig units located in the Northern Region of Israel, caused by a FMD virus O, Topotype ME-SA Strain PanAsia-2ANT-10 (4), named O/Tubas 21, after the name of the town, Tubas, in the Palestinian Authority (PA) territories, where the strain was firstly isolated on December 2021. The last time this FMD lineage appeared in Israel, was in the years 2011-2012 (5). As in 2015, the outbreak clinically developed mainly in the farrowing unit, with high mortality in suckling piglets. The event was unexpected,

affecting offspring from breeders which had received their yearly booster just a few months before (January 2022). A booster between April 4th and 22nd 2022, was carried on account of the above mentioned FMD outbreak, which spread to Israel in ruminants in February 2022, and later on affected also pig farms due to uncontrolled movements of ruminants (beef cattle) in the Ibblin area, Northern District of Israel, where 23 pig farms are located. It was decided to investigate immediately, following the appearance of the very first clinical signs, whether there was any vaccination efficacy problem or failure in the application of the vaccination protocol.

While a description of clinical signs induced by FMD virus in pigs has been already presented (6), the purpose of this communication is to present and discuss the results obtained from the serological investigations performed and to possibly correlate with the vaccination protocol in place in pig farms in Israel.

MATERIALS AND METHODS

On April 29nd 2022, in a farm of about 3,000 sows, 12 lactating sows and one suckling piglet from each sow were blood-sampled. Unfortunately, only 5 samples from sows and 7 samples from their piglets were suitable for serological investigation. On September 3rd 2022, in the same farm, a further 12 lactating sows and one suckling piglet from each sow were sampled again, where all the 24 samples were suitable for serological investigation. In both samplings, piglets were not vaccinated, therefore their positivity should be considered, either MDA or infection.

Sows were blood-sampled between their 2nd and 3rd lactation week; they were immobilized with a hog-snare and sampled with a new 40 mm length needle for each sow, from the right external jugular vein, with a blind puncture in the jugular dimple. Piglets were blood-sampled on the same day; they were manually immobilized up-side down, and blood was collected with a new 20 mm length needle, from the right anterior vena cava. Red-cap vacutainers (without anti-coagulant) were used for the collection for both sows and piglets.

Blood-samples were examined at FMD Laboratory, "Kimron" Veterinary Institute, Beit Dagan, Israel. Samples were submitted for Virus Neutralization Test (VNT) against the FMDV strain O/Tubas 21 outbreak isolate and VNT against the FMDV O/Manisa reference strain. The VNT results were presented as the Log_{10} of the last dilution with neutralizing activity on 100 TCID 50/50µl of the outbreak virus isolate, or of the reference FMDV vaccine strain.

Both samplings were also submitted to ELISA antibody test against Non-Structural Proteins (NSP) of FMD Virus. The test detected antibodies against the highly conserved NSP of the FMDV; the test can be used for all species. The detection of antibody to one or more of the NSP of FMDV allowed for the differentiation of infected animals from vaccinated animals (7). The results returned as positive (infected animal) or negative (non-infected animal). Laboratory methods have been already described (5).

Due to the outbreak, on April 2022 a mass/blanket vaccination was initiated in all pig farms in the Ibblin area, including all the breeders, with exceptions of sows less than 2 weeks before farrowing, however including piglets and growing pigs of all ages. A monovalent inactivated FMD vaccine was used, which contained the strain O1-Campos (Biogenesis Bago, R. Panamericana km 38.2, Garin, Buenos Aires, Argentina). The O1- Campos strain has been proved to induce satisfactory cross-protection against Asian isolates since 2017 (8).

RESULTS

Table 1. Summarizes the results of serological investigation at first sampling, that was carried out shortly after a FMD outbreak originated in ruminants on February 1st 2022. The last vaccination in sows was between April 4th – 22nd, 2022.

The average VNT titers in sows, at the eve of the outbreak, were:

- O/Tubas 21 VNT: 1:3.09 (Std. Dev±1.26). No sow presented with a VNT titer ≥1:24, ≥1.4 Log_{10}.
- O/Manisa VNT: 1:5.27 (Std. Dev±5.46). No sow presented with a VNT titer ≥1:32, ≥1.5 Log_{10}.

Average VNT titers in piglets, at the eve of the outbreak: in this calculation, the piglet 17 was excluded; most probably the high VNT titer was the result of exposure to FMDV due to the course of the outbreak.

- O/Tubas 21 VNT: 1:3.17 (Std. Dev ±2.54). Not one of other piglets presented a VNT titer ≥1:24, ≥1.4 Log_{10}.
- O/Manisa VNT: 1:4.5 (Std. Dev ±3.55). Not one of other piglets presented a VNT titer ≥1:32, ≥1.5 Log_{10}.

All the samples resulted in ELISA SNP negative, including

Table 1: Serological results in sows and piglets on the eve of the outbreak.

Sampling of April 29th 2022						
NSP-Ab	O/Manisa		O/Tubas 21		animal	sample
	VNT	Log_{10}	VNT	Log_{10}		
NEG	0.30	2	0.30	2	sow	10
NEG	0.90	8	0.60	4	"	11
NEG	0.00	1	0.00	1	"	12
NEG	1.20	16	0.60	4	"	15
NEG	0.60	4	0.60	4	"	16
NEG	0.60	4	0.60	4	piglet	1
NEG	0.00	1	0.00	1	"	3
NEG	0.30	2	0.00	1	"	4
NEG	1.08	12	0.90	8	"	9
NEG	2.58	96	2.58	384	"	17
NEG	0.60	4	0.00	1	"	18
NEG	0.60	4	0.60	4	"	22

piglet 17. Overall, the VNT values between vaccine strain (O/Manisa) and field strain (O/Tubas 21) did not differ significantly (t-test>0.5).

The table 2 below summarizes the results of serological investigation at second sampling, that is five months after the beginning of the outbreak and five months after the booster vaccination, performed on April 26th 2022.

The average VNT titer in sows were:

- O/Tubas 21 homologous VNT: 1:63.83 (Std. Dev ±63.83). Ten sows presented a VNT ≥1:24, ≥1.4 Log_{10}
- O/Manisa heterologous VNT 1:50 (Std. Dev±52.50). Five sows presented a VNT ≥1:32, ≥1.5 Log_{10}; two sows (No. 4, 11) resulted negative at a VNT threshold of 1:4;

The average VNT titer in piglets were:

- O/Tubas 21 homologous VNT: 1:18.33 (Std. Dev±9.99). Four piglets presented a VNT ≥1:24, ≥1.4 Log_{10}
- O/Manisa heterologous VNT 1:9.33 (Std. Dev±7.85); one piglet presented a VNT titer ≥1:32, ≥1.5 Log_{10};

On the other hand, O/Tubas 21 homologous VNT, between SNP positive and NSP negative, differ significantly: in NSP positive, average VNT=64.4 (Std. Dev±59.83); in NSP negative, average VNT=24.42 (Std. Dev±18.58), (t-test<0.05).

Six sows and four piglets resulted ELISA SNP positive. In four cases a sow and her piglet resulted both SNP positive: SNP positive piglets 18, 19, 20, 22 resulted offspring from SNP positive sows 6, 7, 8, 10; there was no correlation between SNP positive sow 12 and her SNP negative piglet 24.

Table 2: Serological results at second sampling (September 2022), five months after the beginning of the outbreak and five months after the booster vaccination of April 2022.

sampling of September 3rd 2022						
NSP-Ab	O/Manisa		O/Tubas 21		animal	sample
	VNT	Log_{10}	VNT	Log_{10}		
POS	2.0	96	1.5	32	sow	1
NEG	1.4	24	1.4	24	"	2
NEG	2.3	192	1.4	24	"	3
NEG	0.3	<4	1.8	64	"	4
NEG	1.2	16	0.9	8	"	5
POS	1.5	32	1.8	64	"	6
POS	1.7	48	2.1	128	"	7
POS	1.4	24	2.1	128	"	8
NEG	1.4	24	1.8	64	"	9
POS	1.5	32	2.3	192	"	10
NEG	0.3	<4	0.8	6	"	11
POS	1.1	12	1.5	32	"	12
NEG	0.6	4	0.9	8	piglet	13
NEG	1.1	12	1.5	32	"	14
NEG	1.5	32	1.5	32	"	15
NEG	0.3	2	1.1	12	"	16
NEG	0.6	4	0.9	8	"	17
POS	1.2	16	1.1	12	"	18
POS	0.9	8	1.2	16	"	19
POS	0.9	8	0.9	8	"	20
NEG	0.3	2	1.1	12	"	21
POS	0.9	8	1.5	32	"	22
NEG	0.9	8	1.5	32	"	23
NEG	0.9	8	1.2	16	"	24

Albeit in NSP positive pigs, VNT titer may result from both vaccination and infection, O/Manisa heterologous VNT, between SNP positive and SNP negative, did not differ significantly: in SNP positive, average VNT=28.40 (Std. Dev±25.83); in SNP negative, average VNT=23,57 (Std. Dev±47.68), (t-test >0.5).

DISCUSSION

As indicated in the OIE – WAHIS Follow-up report 2 (6), last vaccinations in pig farms were executed on April 2022

(emergency vaccination in course of/risk of outbreak), and previously on January 2022. As to the onset of the outbreak (April samples), the antibodies represent mainly if not solely a response to the vaccine, which included the O/Manisa antigen. The results, in Table 1, against reference strain O/Manisa revealed low, unprotective VNT titers, all below 1:32, 1.5 Log_{10}. The results, in Table 2, were ≥1:32, ≥1.5 Log_{10}, that is considered protective, in five sows (vaccinated on April 2022) and one piglet only (MDA).

The results, in Table 1, indicate that on the eve of the outbreak, also relative to homologous VNT against the outbreak isolate O/Tubas 21, neither sows (sampled on April 29th 2022) nor piglets presented a VNT considered protective against the field isolate, e.g. ≥1:24, ≥1.4 Log_{10}. Piglet No 17 presented a high VNT titer, but still resulted NSP negative. NSP antibodies, which develop following infection, may take up to 9-14 days to develop. The results, in Table 2, indicate that VNT ≥1:24, ≥1.4 Log_{10}, which is considered protective for homologous challenges, was present in ten sows and four piglets; it should be underlined that VNT in NSP positive pigs was significantly higher (T-test <0.05) than in NSP negative pigs, indicating to consider a booster effect induced by infection.

Heterologous VNT can be used in post vaccination monitoring, rather than matching to outbreak strain; extrapolating protective threshold/VNT against heterologous challenges/infection is difficult; although VNT corresponds to antibodies level for protection, it is considered difficult to establish a threshold at which animals are protected, for the different test conditions, including laboratories variables.

Nevertheless, the literature (9, 10) and OIE (11) strictly recommend that vaccination strategies should be designed to achieve "mass coverage" and that "coverage should be at least 80%" in the vaccinated population. In homologous challenge experiments with FMDV, VNT ≥1:24, ≥1.4 Log_{10} corresponds with high protection against disease; this could not be easily applied to heterologous protection (e.g. emerging outbreak strains), where the VNT titer may be considered protective at ≥1:32, ≥1.5 Log_{10} at the least (11).

FMD vaccine distribution and use is strictly regulated by the Veterinary Services, which directly provide the farmers and indicate the vaccination protocol (3).

A retrospective investigation relative to distribution of FMD vaccine and vaccination cycles revealed that, in the last 8 years, on average, only one single dose per breeder per year was provided to pig farms in the Northern District, with exception in 2015 and 2022 due to the above mentioned outbreaks (2, 5) when the whole pig population was vaccinated. The provided FMD vaccine doses are summarized in Table 3.

Table 3: FMD vaccine doses distributed by The Veterinary Services to pig farms in Northern District of Israel in the last 8 years

Vaccination round	Doses Distributed	Target Animals	
2022	11350	breeders	
2022	*75000*	*all*	*outbreak*
2021	13200	breeders	
2020	13180	breeders	
2019	13570	breeders	
2018 + 2017	22557	breeders	
2016	21900	breeders	
2015	8100	breeders	
2015	*101600*	all	*outbreak*
average/year	12982	breeders	
average/outbreaks	*88300*		

In a previous study (12), it was demonstrated that mass/blanket vaccination, with a single dose, in breeders, even every 6 months, induced a limited protection both in breeders and suckling piglets (limited percentage of animals with VNT ≥1:32, ≥1.5 Log_{10} titer against heterologous FMDV strains). In this communication we show that a much lower protection is induced if a mass/blanket single-dose vaccination is practiced only once a year. At the eve of outbreak, neither sows nor piglets tested presented with VNTs considered protective neither against homologous nor heterologous challenge.

Table 1 showed VNT/Log_{10}, low, non-protective titers, as a result of the uncomplete vaccination protocol practiced on January 2022. The emergency vaccination on April 2022 did not boost the previous vaccination of January 2022; the extended time between the two vaccinations was too long. In facts in basic vaccination, the distance between two doses (priming and booster) should 2 to 4 weeks at the latest. Furthermore, the last previous vaccination was also too distant: between December 2020 and January 2021.

Serological testing of September 2022 revealed, that emergency vaccination of April 2022, again, did not boost enough: only few sows (5 out of 12; 41.6%) reached a protective titer VNT ≥1:32, ≥1.5 Log_{10} in a heterologous challenge. 83% of tested sows (10 out of 12) and 33% of piglets (4 out

of 12) presented with VNT ≥1:24, ≥1.4 Log_{10} considered protective against homologous challenge. The latter results may be considered responding to OIE recommendation for sows, but not for piglets.

Six sows out 12 resulted NSP positive, which indicated that they had been infected by FMDV during the outbreak. If pigs are adequately immunized by vaccination, transmission of FMDV will be discontinued: within animals in same pen, within pens and even within herds (13). When immunity is still developing or incomplete, e.g. incomplete vaccination plan, FMDV continues spreading (13). It is therefore imperative to ensure a fully efficacious vaccination protocol against FMDV. Anti-NSP responses are influenced by the immune status of pigs on the day of infection: In well vaccinated pigs a lower percentage and shorter duration of responses against NSP is expected (14).

AFTOPOR® – אפטופור

Inactivated vaccine against foot and mouth disease (FMD) In cattle and pigs. Emulsion for Injection.

Composition in a dose:
Active ingredient (antigen): Inactivated foot and mouth disease (FMD) viruses, at least 6PDso, of the strains:
O Manisa
O3039
O Israel 85
O PanAsia 2
A GVII-2015
A Iran 05
Adjuvant: Double oil emulsion (DOE): water-in-oil-in-water.

Indication:
Active immunization of cattle and pigs against foot and mouth disease.

Side effects and contraindications:
Vaccination may be followed by a small local swelling and/or slight pyrexia, both of short duration. The purity of this vaccine ensures that hypersensitivity reactions are very unlikely. To report side effects please email to:

Target species: Cattle and pigs.
Dosage. route and method of administration, and directions for use:
Before use, mix thoroughly the content by rotating the bottle end over end about 20 times. Avoid bubble formation which can be very irritating at the site of injection.
Intramuscular route (IM).
Preferred injection site in pigs: the neck, behind the ear. In cattle: the neck, in front of the shoulder.
Dose for cattle and pigs: 2 ml.
Primary course in animals from non-vaccinated dams:
Calves from 14 days old: 2 vaccinations at least 4 weeks apart
Revaccinate every 6 months.
Revaccinate annually all 1+ year old.
Piglets above 14 days must be vaccinated once.
If grown more than 6 months. It must be vaccinated twice, at least 4 weeks apart Revaccinate every 6 months.
Gilts should be vaccinated before first insemination. Revaccinate every 6 months. Pregnant sows must be vaccinated up to 4-5 weeks before farrowing.
Primary course in animals from vaccinated dams (with maternally derived antibodies)
Calves from 3 months old: 2 vaccinations at least 4 weeks apart.
Revaccinate annually all 1+ year old.
Piglets for fattening-from vaccinated sows: no need to vaccinate.
If grown after 6 months. needed to be vaccinated by the protocol mentioned above.
In case of an outbreak, veterinary services will give instruction for vaccination protocol.

Withdrawal period:
None.

Storage Instructions:
Store in the refrigerator (between 2-8°C). protected from light Do not freeze.
Once opened, bottles of vaccine should be used within 36 hours, provided they have been stored between 2-8°C and not multi-punctured.
Keep out of the reach of children.
Do not use the vaccine after the expiry date listed on the package.

Precautions and special warnings:
Vaccinate healthy animals only.
Observe usual aseptic conditions.
In case of self-injection or e sure of people to the vaccine, seek medical help straight away and present the vaccine package leaflet or label.
For use In animals only.

Use during pregnancy:
Vaccination during pregnancy or lactation is not contra-indicated.
Handle pregnant animals with great care.

Incompatibilities and drug Interactions:
No information is available about incompatibilities or interactions wi1h other medicinal products. Do not mix with any other vaccines.

Pack type and size:
Polyethylene or Polypropylene bottle containing 200 ml of liquid for Injection. 100 doses.

Directions for the disposal of waste, packaging, and unused veterinary product materials
Any unused veterinary vaccine, or waste materials derived from such veterinary vaccine, should be disposed of as biohazardous waste.
Do not discard via wastewater.

Manufacturer: Boehringer lngelheim Animal Health UK Lid., Pirbright. GU24 ONO, UK.

Registration holder:
This leaflet was revised and approved by the Veterinary Services In: 05.2021 Vaccine registration number in the Registry of Veterinary Vaccines Is:
2-002-10-04 for cattle and 4-004-10-04 for pigs.

From December 2021, to December 2020, to December 2019 and so on, all of these vaccination protocols were performed with a single dose per breeder per year only, even without the second dose required in basic vaccination, and appear therefore widely incomplete and non-protective. This is in contrast to the recommendations of the manufacturer of the vaccine as indicated in the leaflet above.

CONCLUSIONS

When adopting FMD prophylactic vaccination protocols based only on periodic vaccination of breeders, it should be taken into account to what extent passive immunity/maternally derived antibodies (MDA) in piglets may contribute to the overall population immunity (11). Therefore, vaccination plans should also aim to achieve high MDA piglet's protection. Young pigs develop poor immunity to FMD vaccines; their protection in endemic areas depends by efficient sow vaccination (15).

The outbreaks of 2015 and 2022 confirmed how direct losses induced by FMD in unvaccinated/unprotected pig farms are mainly concentrated in piglets. In 2022, in the examined farm, losses attributed to FMDV outbreak (that means, excluding stillbirth, crushed piglets, enteric diseases, other causes*) totalized 1,008 dead out of 4,609 live/suckling piglets (21.9%) from 527 farrowings, in a few weeks.

Vaccination must to be carried out on breeders: at first, with a priming and a booster vaccination before first insemination (7^{th}-8^{th} months of age; same age in young boars). Vaccination against FMD in pigs only provides a short-lived protection (4-6 months) (16), therefore it should be boostered twice a year at least. Considering that MDA in piglets are protective (10), a routine FMD booster vaccination should be performed at every reproductive cycle, in pregnant animal at their 80^{th} day of pregnancy, in order to ensure transfer of adequate MDA protective titers to piglets. In industrial pig farming, sows deliver an average of 2.1 to 2.4 farrowing/year, therefore a vaccination on the 80^{th} day of every pregnancy will ensure a routine vaccination in all the inseminated breeders every 152 to 180 days at the latest. Because farrowing in sows occur all the year round, vaccination is more likely to be delegated to the supervision of the Veterinary Practitioner of the pig unit.

According to this survey, and to previous communications about vaccination plans, sow vaccination should be implemented at every pregnancy; at least until significant changes in the epidemiological data relative to FMDV spread in Israel would justify a less intensive vaccination protocol.

VNT-MDA in piglets are assumed to remain at protective level until 60 to 90 days of age according to the vaccine used (11).

Therefore, in a situation of emergency/mass vaccination, because of outbreak containment, while sows, lactating sows and suckling piglets, may be considered as protected, FMD vaccines in piglets can be given starting at 8 (13) to 10-12 weeks (13) of age; then repeated in 2 weeks (14) according to vaccine used. It should also be considered that depending on the formulation used, adjuvanted vaccines in pigs may require a single injection to promote a protective immunity, starting approximately 8 days and lasting for about 6 months.

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* September 3rd samples were also submitted to RT-PCR for PRRS, PCV2. All the sows and 11 piglets out of 12 tested RT-PRRS negative; all the sows and piglets tested negative for RT-PCR for PCV2. Data not shown; conferment 2022/299582; Animal Health Institute IZSLER, Brescia, Italy.

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