Use of Vaccines in Swine Diseases Control in Israel

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ABSTRACT

Vaccination is an important measure for controlling infectious diseases in pig production systems, and useful to prevent not only diseases spreading among animals but also the potential zoonotic risks associated with some of the swine diseases such as in the case of Leptospirosis. Although pig vaccination has never been a standard practice in Israel, during the last 20 years the situation has changed with an increased availability of vaccines. Vaccination protocols need to consider the different production phases (breeding-reproduction with gilts, sows, boars and fattening phase) and to follow the specific guidelines addressing each different circumstance. In addition, the animals' environment, the geographical location and the epidemiology of diseases should be considered during the planning of a vaccination protocol in pigs. The purposes of this review was to evaluate and describe (i) the vaccines available in Israel for controlling pig infectious diseases, (ii) route of administration [intramuscular (IM), subcutaneous (SC), intradermal (ID), oral (OR)] commonly used, and (iii) to compare vaccines availability in Israel in relation to the local pig diseases epidemiology.

Keywords: Swine; Pig Vaccination; Breeders; Fatteners; Recommendations; Israel.

INTRODUCTION

In Israel the pig production is limited to overall 25 farms that produce approximately 170-200,000 pigs per year (1, 2) which are located in three well defined areas in the Country. Specifically, one farm is located in the Negev District (Kibbutz Lahav), with around 1,000 sows and 19,000-20,000 pigs produced per year, while the other 24 farms are situated in the Northern District (1 farm in Fassuta, 23 farms in Ibblin), with a production of 150-180,000 pigs per year. In addition, there is another farm of 30 Sinclair (minipig) sows in Lower Galilee District (Yokneam) that produces purpose-bred laboratory pigs, not for human consumption.

Apart from the Sinclair pig farm mentioned above, all the other farms are close-cycle, or "breeding to slaughtering" farms, and therefore breeders of all the different stages of production (pregnant, lactating, at insemination), every phase of fattening (suckling piglets, weaners, growers, fatteners), and boars for both natural and artificial insemination, are simultaneously present in these farms.

Registered and approved pig vaccines in Israel

Only vaccines that have been approved by registration or by special import authorization can be used in Israel and the list of them is updated and published annually by the Israeli Veterinary Services at Ministry of Agriculture. (https://www.gov.il/en/Departments/DynamicCollectors/registered_veterinary_vaccines?skip=0). In some instances, other than registered vaccines may be allowed, without registration, for example, vaccines from autogenous origin and isolates for provisional use and only in very few circumstances, taking

Table 1: List of registered and approved pig vaccines at 05/2022, by the Israeli Veterinary Services (modified, harmonized); vaccines with special import authorizations and autogenous vaccines.

Name	Pathogens	Manufacturer	Registration date
Porcilis APP®	*Actinobacillus pleuropneumoniae* (OMP, Apx I, II, III toxoids)	MSD-Intervet (NL)	2016
Coglapix®	*Actinobacillus pleuropneumoniae* (somatic antigens, Apx I, II, III toxoids; expressed by serotypes 1, 9)	Ceva (F)	2018
Suivac APP®	*Actinobacillus pleuropneumoniae* (OMP, LPS, Apx I, II, III toxoids; expressed by serotypes 2, 9)	Dyntec (CZ)	2015
Suvaxin E®	*Erysipelothrix rhusiopathiae*	Zoetis (USA)	before 2012
Porcilis coliclos®	*Escherichia coli* (fimbrial adhesines F4ab; F4ac; F5; F6; LT toxoid); *Clostridium perfringens* type C (β toxoid)	MSD-Intervet (NL)	2015
Porcoli Porcilis DF®	*Escherichia coli* (fimbrial adhesines F4/K88 ab, F4/K88 ac, F5/K99, F6/987P)	MSD-Intervet (NL)	before 2012
Neocolipor®	*Escherichia coli* (fimbrial adhesines F4ab, F4ac, F4ad; F5; F6; F41)	Boehringer Ingelheim AH (F)	before 2012
Ecoporc Shiga®	*Escherichia coli* (Shiga-like toxin 2e antigen)	Ceva (F)	2022*
Aftopor®	Foot and Mouth Disease viruses (types: O-Manisa, O-3039, O-4625, A-Iran2005, A-4165, generally used)	Boehringer Ingelheim AH (F)	before 2012
Hyoresp®	*Mycoplasma hyopneumoniae*	Boehringer Ingelheim AH (F)	before 2012
Respisure®	*Mycoplasma hyopneumoniae*	Zoetis (USA)	before 2012
Respisure one®	*Mycoplasma hyopneumoniae*	Zoetis (USA)	before 2012
Ingelvac MycoFlex®	*Mycoplasma hyopneumoniae*	Boehringer Ingelheim AH (F)	2018
Hyogen 1®	*Mycoplasma hyopneumoniae*	Ceva (F)	2018
Suvaxin PL®	Porcine Parvovirus; *Leptospira interrogans* (serogroups: *Canicola, Grippotyphosa, Hardjo, Icterhaemorrhagiae, Pomona*)	Zoetis (USA)	before 2012
Farrowsure Gold B®	Porcine Parvovirus; *Erysipelothrix rhusiopathiae; Leptospira interrogans* (serogroups: *Bratislava, Canicola, Grippotyphosa, Hardjo, Icterohaemorrhagiae, Pomona)*	Zoetis (USA)	2016
Circovac®	Porcine Circovirus (type 2)	Boehringer Ingelheim AH (F)	before 2012
Ingelvac CircoFlex®	Porcine Circovirus type 2 (ORF2 antigen)	Boehringer Ingelheim AH (F)	2018
Porcilis PCV®	Porcine Circovirus type 2 (ORF2 antigen)	MSD-Intervet (NL)	before 2012
Porcilis PCV M Hyo®	Porcine Circovirus type 2 (ORF2 antigen); *Mycoplasma hyopneumoniae*	MSD-Intervet (NL)	2016
Fostera PCV MH®	Porcine Circovirus type 2 (type 1,2 chimera); *Mycoplasma hyopneumoniae*	Zoetis (USA)	2015
Parvoruvax®	Porcine Parvovirus; *Erysipelothrix rhusiopathiae*	Boehringer Ingelheim (F)	before 2012
Porcilis EPL®	Porcine Parvovirus; *Erysipelothrix rhusiopathiae; Leptospira interrogans* (serogroups: *Canicola, Australis/Bratislava, Icterohaemorrhagiae/Copenhageni, Grippotyphosa, Pomona, Tarassovi*)	MSD-Intervet (NL)	2017
Ingelvac PRRS MLV®	PRRS virus (USA Type 2 strain, ATCC VR 2332)	Boehringer Ingelheim AH (F)	2018
Porcilis PRRS	PRRS virus (EU Type 1 strain, DV)	MSD-Intervet (NL)	2022 special import
TGE-Vac	TGE Coronavirus (inactivated)	Pasteur Romania (RO)	2005 special import
Pestiffa ®	Classical Swine Fever MLV (Lapinized C strain)	Boehringer Ingelheim AH (F)	2009 special import
autogenous	*Pasteurella multocida*	Phibro (IL)	2020; 2021 special auth.
autogenous	*Haemophilus (Glasserella) parasuis*	Phibro (IL)	2022* special auth.

* In course of approval/registration at time of publication.

into account the epidemiological situation at the time and their use. All vaccines are indicated separately in Table 1, which describes the available registered Israeli vaccines and their registration dates.

Vaccination protocols, used in both breeder and fattening pigs, aim to control reproductive diseases in breeders, and enteric, respiratory and systemic diseases in fatteners. Disease control is based on both attempting to prevent the exposure of animals to pathogens and/or, when possible, to induce an immune response in susceptible populations through vaccination. All susceptible categories (breeders, fatteners) are usually vaccinated, but vaccination schedules may change according to age, passive maternal immunity interference or productive phase of the pigs (i.e. stage of pregnancy). In food production animals, the immunity of the population has priority, rather than immunity of the single animal. Specifically, the "herd immunity" represents the overall result to a vaccination in a susceptible population. For example, Rinderpest (now eradicated) required a 70%-90% population/herd immunity; while Foot and Mouth Disease (FMD) requires an 80% population/herd immunity. (3) This means that following the vaccination of 100% of susceptible subjects, an immune response will be expected to develop in a significant portion of the population (70%-90%). This results in the protection of the entire population, generally from the clinical signs of the disease rather than the infection (3); furthermore, the significant reduction in "susceptible/available guests", in which the pathogen can replicate and spread, will cause it to vanish.

Specific pig pathogens can induce mainly reproductive disease signs in breeder pigs and respiratory or multi-systemic diseases in other categories like growers. Some pathogen may develop even different clinical signs according to the different ages or growing phase (suckling, weaned, growing, fattening) of pigs.

Pig diseases in Israel and their control through vaccination

Different methods may be used to summarize the clinical manifestations of pig diseases (4): by etiology (viral, bacterial and parasitic), by age (suckling, weaned, growing, fattening, breeding) and by major clinical signs (enteric, respiratory, multisystemic and reproductive). However, in this article the attention will focus on the latter two systems because of a certain overlap between age or phase and the major clinical signs. In this review, only diseases diagnosed in Israel, and for which vaccines are/were allowed for use, will be considered. Thus, Aujeszky's Disease (Alfa-Herpesvirus), Swine Influenza (sub-types of Influenza A virus), Atrophic Rhinitis *(Pasteurella multocida Dermo-Necrotic Toxin producing)*, Ileitis (*Lawsonia Intracellularis)*, Swine Dysentery (*Brachispira hyodisenteriae*) and diarrhea from *Salmonella spp.* will not be considered. Vaccines used in reproduction, enteric, respiratory, multisystemic diseases, Classical Swine Fever (CSF), and Foot and Mouth Disease (FMD) vaccines, autogenous vaccines, are described below. Vaccination plans are detailed in Table 2.

REPRODUCTION DISEASES

Background and distribution

Pig reproduction may be affected by different pathogens and diseases at every stage, from a very early phase close to insemination/fecundation to farrowing. Pathogens responsible for reproductive diseases and for which vaccines are usually used in Israel are the following: Porcine Parvovirus (PPV), Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), *Erysipelothrix rhusiopathiae* (Ery) and *Leptospira sp.* (Lepto). In addition, Porcine Circovirus type 2 (PCV2) may also be involved in reproductive disorders (5) and its vaccination is practiced in some farms.

Different stages of gestation may involve different pathogens. Abortion at all pregnancy stages is typical of PRRSV, CSF, (6, 7, 8) while leptospirosis abortions mainly occur at the late stage of pregnancy (9, 10). Moreover, other than primary reproductive pathogens can also cause abortion, as a result of generalized symptoms such as high fever and anorexia which may be incompatible with the gestation. Therefore, during outbreaks of respiratory diseases, such as *Actinobacillus pleuropneumoniae* (App) or Haemophilus (*Glasserella) parasuis* (Hp) (Glasser disease), the abortion is the consequence of generalized symptoms induced by these infections (6, 10). Other consequences of both bacterial and viral diseases are the increased weaning-to-estrus intervals, decreased farrowing rates, reductions of total piglets born, reduction of (liveborn) litter size, with a very relevant economic impact. Infertility, return in estrus (RIE), early or late abortions, mummification, maceration, still-birth, early mortality, often altogether, represent the main clinical findings of reproductive diseases in pigs. A tentative diagnosis based on clinical findings only, is almost impossible, and therefore the use of laboratory testing and findings is obligatory (6, 10).

Vaccinations plans in pigs according to age and/or reproductive phase for breeders; alternative plans for some antigens; outbreak plans for FMD, CSF.

Table 2A: Fattening pigs and young breeders before their first service

Fattening pigs; very young breeders								
Weeks of age	**Antigen**	**Modified Live**	**Inactivated**	**Notes**	**Notes**	**Alternative Plans**	**FMD**	**CSF**
1	PRRSV	V		possible combinations				priming + booster; only outbreaks
	PCV2		V					
	Mhyo		V					
	E.coli-Shiga-like		V	mono dose	toxoid			
2						Mhyo±PCV2		
3		V				PRRSV		
4								
5								
6	App		V		toxoid			
7								
8							only outbreaks	
9								
10	App		V		toxoid			
11								
12								
14								
24								
25								

Ery is considered ubiquitous in worldwide swine farms; PPV, first demonstrated in Israel in 1996 (11), it is also considered ubiquitous. Leptospirosis is widely distributed in Northern District swine farms but no evidences have been found at Sinclair minipigs and Kibbutz Lahav farms (12). PRRSV2, American or Type 2 strain, was confirmed in Israel in 2017 (13) and it was apparently limited to Northern District farms. PRRSV1, EU or Type 1 strain, was also confirmed in Israel in 2022, and again apparently limited to Northern District Farms (14).

Because the infectious diseases play a very important role in reproductive results, the vaccination plan is a fundamental tool in reproduction health management which should meet the individual needs of each farm.

Vaccines recommendations

PPV, PRRSV, Ery, and Lepto vaccines are used to control reproductive diseases in pigs, preventing or reducing losses as a result of these pathogens. All breeders (gilts, sows, and boars) should be vaccinated. The entire reproductive cycle, from insemination to farrowing, may be affected and therefore must be protected. Apart from PPV, immunity induced by vaccinations is considered of relatively short duration: 3 to 6 months according to antigens/pathogens (6, 10, 12, 13, 14). Young breeders undergo priming and booster vaccinations for each antigen/pathogen before the first insemination time. Thereafter, booster vaccinations, along the whole reproductive career should be carried out, the intensity of which may vary.

Priming and booster vaccination in gilts begins at around 30 weeks of age; the full vaccination cycle should be completed before the first insemination, generally due by week 34-35, at the latest. Subsequently, a booster should be completed at each gestation. Therefore, following farrowing, at the second week of lactation – which means something around 20-22 weeks from the previous vaccinations round

Table 2 B: Breeders

Young Breeders: Boars; Gilts Before AI/NA								
Weeks of Age	**Antigen**	**Modified Live**	**Inactivated**	**Notes**	**Notes**	**Alternative plans**	**FMD**	**CSF**
from 30	PRRSV	V		possible combination	booster pre-AI/NA		basic vacc. priming + booster	priming + booster; only outbreaks
	Mhyo		V					
	PCV2		V					
to 33	Ery		V	possible combination		only Ery + PPV		
	PPV		V					
	Lepto		V					
34	Ery-PPV ± Lepto		V	possible combination	AI/NA			
At Day	**Pregnancy Vaccinations**							
60	*E.coli* F4,F5,F6,LT + *C.perfrigens* β tox		V	only in gilts	toxoid	PRRSV		priming + booster; only outbreaks
	PRRSV	V		6-60 scheme				
from 80 to 90	*E.coli* F4,F5,F6,LT + *C. perfrigens* β tox		V		toxoid		basic vacc.	
100	Mhyo±PCV2		V					
114-116	**Farrowing**							
At Day	**Lactating Period**							
6	PRRSV	V		6-60 scheme				priming + booster; only outbreaks
15	Ery-Parvo ± Lepto		V	possible combination				
28-30	**Weaning**							
≤10 days	**AI/NA; A New Cycle for Pregnancy Vaccinations Begins**							

AI/NA: artificial or natural insemination

– sows are vaccinated again against PPV, Ery, Lepto. This vaccination is aimed at protecting next pregnancy planned to begin in next 3-4 weeks.

Young boars follow the priming and booster vaccination scheme as gilts (week 30 to 33/34) followed by two boosters/year.

The multisystemic diseases (PRRSV and PCV2) require a booster before the first insemination. Within the family *Arteriviridae*, two different species of PRRSV are known: PRRSV1 or EU genotype, and PRRSV2 or USA genotype. Nucleotide sequence of type 1 and 2 differ by around 44%, but intra-type nucleotides sequences may also vary up to 30% in type 1 and ≥20% in type 2. There is no cross-protection between the two different genotypes (13, 14, 15, 16), therefore type 1 or type 2 vaccines should be used in an affected farm according to the field type isolate. Inactivated PRRSV, subunit proteins, and vaccines that do not contain live PRRSV do not induce effective protection against PRRSV (16). Both inter-type and intra-type nucleotide variability affects the immunological response of pigs against PRRSV and the high mutation frequency of PRRSV makes it difficult to limit the disease by vaccination (10), and induction of cross-protective immunity is dependent on specific PRRSV strains vaccines (16).

However, the understanding of the whole mechanism of full protective immunity is still uncomplete. Since the role of

PRRSV increases over time, a special mention is required for positive unstable PRRSV farms that may require a further booster at 60 days of pregnancy, aimed to protect against late abortions and birth of viremic ill piglets. In fact, findings suggest that infection occurs *in utero* or from virus shed in milk (10, 16). A further booster at the 6th day after farrowing is aimed to protect until the first two thirds of next pregnancy, until day 60th, on which day another booster should be carried out. Relative to PCV2 vaccination, following a booster before first insemination in gilts, another booster in pregnant breeders may be carried out at around 80-90 days of pregnancy. The full vaccination plan is detailed in Table 2B.

ENTERIC DISEASES

Background and incidence

Transmissible Gastro Enteritis (TGE) broke out in Israel in 2005-2006 (17), and since then, few samples have been analyzed by the Kimron Veterinary Laboratory. Between 2016-2018, only 8 samples were examined and all of them were PCR positive (18), although there were no records of further outbreaks. The Coronavirus causative agent for TGE is primarily an enteric virus, responsible for destroying enterocytes of the small intestine, causing villous atrophy. Pigs of all ages may be affected, but significant deaths occur mainly in suckling pigs. Almost all the susceptible piglets under 10 days of age die within a few days after exposure but the mortality decreases with age (>10-15 days). Inactivated TGE vaccines were used during the outbreak of 2005-2006, while presently vaccination is no longer in practice since the resolution of the outbreak.

Concerning newborn piglets, *Escherichia coli* and *Clostridium perfringens* type C are mainly responsible of early enteric diseases. Piglets are highly vulnerable to both those pathogens from the first week of age until first weeks after weaning. Specifically, in piglets, pathogenic *E. coli* strains typically display specific types of colonization factors or fimbriae, including F4 (K88), F5 (K99), F6 (P987), F18 and F41. In addition to the colonization/binding factors (F), the pathogenic attributes of *E. coli* is also mediated by the ability to produce enterotoxins and/or *Shigella sp.* – like (Shiga) toxins. The enterotoxins class includes two types of toxins: thermostable (ST-I types a, b) and thermolabile (LT-I; LT-II types) (19).

E. coli are responsible of several clinical symptoms which can be classified according to their pathological patterns in piglets (19):

- Diarrheogenic (DEC) *E. coli* which include: Extraintestinal (ExPEC) shigatoxigenic (STEC), enterohemorrhagic (EHEC), enteropathogenic (EPEC), enterotoxigenic (ETEC), enteroinvasive (EIEC), enteroaggregative (EAggEC), diffusively adherent (DAEC), adherent-invasive (AIEC) and enteroaggregative shigatoxigenic (EAggSTEC).
- Extraintestinal (ExPEC) *E. coli* which includes: uropathogenic (UPEC), neonatal meningitidis (NMEC).

Protective immunity against the different pathotypes of *E. coli* is achieved by anti-F (fimbriae), anti-LT, anti- Stx2e toxin, antibodies (20, 21)

Because of the wide antigenic variability of *E. coli* infections, a universal vaccine is impossible to achieve. Autogenous vaccines may represent a strategy adopted in countries when *E. coli* strains, others than antigens included in commercial vaccines, are involved in clinical cases. Nowadays an oral vaccine against *E. coli* is available in Europe and U.S.A. The novel type of administration combines the easiness of administration and mucosal protection.

Concerning *C. perfringens,* the types *C* and *A* produce two toxins, α and β2, with necrotizing activity on jejunum and ileum. *C. perfringens* infection in suckling piglets is characterized by pasty, creamy, mucoid, pink diarrhea. Mortality of piglets varies but the higher incidence of up to 100% occurs in first farrowing of non-immune young sows. Antibodies to anti-β toxin confer protective immunity against *C. perfringens* (22). The early infection (within first minutes after birth), by DEC *E. coli* and *C. perfringens*, does not allow for active immunization in piglets, and they can be protected only by colostral passive immunity transmitted by immunized sows. The relatively late onset of susceptibility to F18+/Stx2e+ *E. coli* (post-weaning, e.g. from 4th week of age) allows active immunization of piglets against Stx2e toxin.

Vaccines recommendations

Vaccines against *E. coli* and *C. perfringens*, are used to control enteric diseases in neonatal piglets (20, 21, 22). Pregnant breeders are vaccinated in their last third of pregnancy while gilts (first pregnancy breeders) should be vaccinated twice at 60th and 90th days of pregnancy. Vaccination of sows during pregnancy leads to production and secretion

of antigens-specific IgG antibodies in colostrum, rapidly substituted (24 hours after farrowing) by IgA in milk. During a suckling period of 28-30 days, lactogenic IgA antibodies anti-fimbrial adhesins can be transmitted to piglets and protect them against the infections, preventing *E. coli* fimbriae attachment to small intestine receptors. Immunized sows transmit lactogenic, neutralizing antibodies against β toxin of *C. perfringens*. Moreover, vaccines based on Stx2e toxoid are used to control the oedema disease in weaned piglets (21). Specifically, piglets should be vaccinated well before the disease occurrence, at their 1st week of age, and generally a single shot is enough to protect against clinical signs of the disease after weaning. The full vaccination plan is detailed in Table 2B.

RESPIRATORY DISEASES

Background and incidence

M. hyopneumoniae (Mhyo) is a primary respiratory pathogen in pigs and it is considered ubiquitous. It was firstly demonstrated in Israel in 2001 in an epidemiological serology investigation (23). Mhyo is considered prevalent in all pig farms, and from time to time, some farms are serologically checked and found to be positive (2). Piglets may be vertically infected by positive sows during the suckling period and/or horizontally after weaning, when litters intermingle together and infection is allowed to spread. Mhyo does not invade the lung tissue, however *mycoplasma* organisms attach to the cilia of respiratory airways, causing extensive destruction, resulting in reduction of the muco-ciliary clearance; thus, leading to secondary bacterial infections, and as a result Mhyo is considered a "door opener".

A. pleuropneumoniae (App) is also an important primary respiratory pathogen and considered ubiquitous (24). According to capsular polysaccharides (CPS) and cell-wall lipopolysaccharides (LPS) characteristics, at least 15 serotypes of App are recognized, 13 grouped as bio-type I and 2 as bio-type II. App was also firstly serologically demonstrated (serotypes 2, 9) in the above-mentioned serological investigation (23); then it was first isolated in Israel (serotype 13) in 2010 in a Northern District (Galilee) farm (25). App localizes on the alveolar epithelium and resists macrophage phagocytizing activities. Capsular polysaccharides (CPS) and cell-wall lipopolysaccharides (LPS) provide resistance to complement activity (24, 25). When multiplying at the alveolar level, App releases powerful toxins with hemolytic, cytotoxic, cytolytic and edema-inducing activities, which exacerbate the inflammatory response at the lung level. Three different toxins are released by different App strains, in different combinations, having strong hemolytic or cytolytic properties: ApxI; ApxII; ApxIII.

Apx toxins and Outer Membrane Protein (OMP) induce immune response. Circulating toxins/OMP-neutralizing antibodies can be detected 10-14 days following exposure, in surviving animals (24). As for other Gram-negative bacteria *(E. coli; P. multocida TDN+)* immunogenic activity of these toxins is exploited for vaccines formulation (21, 22, 24).

Mhyo induces typical, pathognomonic lesions on the upper/cranial pulmonary lobes, which typically appear consolidated and firm at touch. Coinfections, for example with PCV2, induce an additive effect on lesions, which result in more extensive lesions. Further than facilitating secondary bacterial infections at lung level, Mhyo has been demonstrated to be responsible for growth delay and an increase in the number of runts.

App induces pneumonia in pigs, generally from 10 weeks of age (around 25 to 30 kg body weight) until the finishing period (100 kg body weight and more). Toxins released by App induce severe edema, hemorrhage, and necrosis in peracute and acute cases and alveolar and interlobular edema, intravascular fibrinous thrombosis and necrotizing pleuropneumonia in acute-subacute cases (24, 25). Chronic cases result in necrotic residual areas with intense fibrosis, pleural adherences of various extensions which persist until slaughter (26). Lesions are characteristically located at dorso-caudal lobes. In peracute cases a single lung may be affected. Dorso-caudal lesions are considered pathognomonic of App lesions (24, 25, 26).

Pasteurella multocida (Pm) is a Gram negative bacterium that can cause hemorrhagic septicemia and lower respiratory tract infections in pigs (27). It is widely disseminated in Israeli pig farms, not different from other countries with intensive swine production. OMP and membrane's lipopolysaccharides (LPS), constitute the primary virulence factors for Pm. LPS may significantly show structural variability among different strains.

Vaccines recommendations

Concerning Mhyo, in general, the higher the infective pressure in growing pigs, the earlier the vaccination should be

performed, starting from the first week of age. Some vaccines require priming and booster vaccination; others are "one shot" only. Protection will last for around 22 to 24 weeks after vaccination.

Sows can be vaccinated in the last third of pregnancy; piglets from vaccinated sows are less often colonized by Mhyo at weaning. Serum antibody levels are not correlated with the degree of protection, but specific T-cell populations (Mhyo-specific cytokines-producing T-cells) are transferred from vaccinated sows to their offspring. The role of these transferred cells on immune responses in piglets and their potential protective effect requires further study (28, 29).

Relative to App, piglets are vaccinated on their 6th or 7th week of age, with a booster at 10th weeks of age. Vaccination, performed with toxoid-based vaccines, provides antibodies neutralizing the different Apx toxins, OMP, LPS, which are included in the vaccine. In the course of severe, early outbreaks, affecting very young piglets, as in case of naïve farms, breeders can be vaccinated during their last third of pregnancy (60th and 90th day of pregnancy).

No registered vaccines are available in Israel against *Bordetella bronchiseptica*; this pathogen is therefore not covered in the discussion. Relative to Pm it should be mentioned that autogenous vaccines can be locally produced and be available, as in other countries with extensive swine industries. Use of autogenous vaccines for a variety of bacterial and viral agents is a common practice in swine production (30). They can provide protection only against strains with identical, or very close, LPS antigenic structure (30). Autogenous Pm vaccines should be manufactured from the pathogenic strain involved in the outbreak and mainly, if not exclusively, used in the same source farm. Autogenous authorized vaccines for pigs in Israel are inactivated. The full vaccination plan is detailed in Table 2A.

MULTISYSTEMIC DISEASES

Background and distribution

In pigs, multisystemic diseases are mainly induced by PRRSV and PCV2. PCV2 was firstly demonstrated during 2006-2007 in pig farms from Northern District of Israel (Galilee) (31), since then this form of co-infection has spread to all the other pig farms in Israel. The PRRSV was detected in Israel since 2017 (13, 14), and since then apparently confined to Northern District (Galilee) farms only. PRRSV may affect piglets at their last third of fetal development inducing early farrowing, stillbirth, birth of sick and viremic piglets. In addition, PRRSV induced severe pneumonia with a high percentage of pre-weaning mortality in suckling piglets (13, 14, 15, 16).

PCV2 affects mainly weaned pigs and induces a slow and progressive disease, with a high mortality rate. This virus multiplies in different types of cells (i.e. epithelial, mononuclear, endothelial, fibrocytes) and is associated to different clinical diseases: postweaning multisystemic wasting syndrome (PMWS), lung diseases (interstitial, proliferative, necrotizing pneumonia), reproductive diseases (stillbirth, abortion, mummification), subclinical infections (growth retardation) and (porcine) dermatitis-nephritis syndrome (PDNS); all of these may be present at same time in an affected farm. Clinical signs are usually observed from 6 - 8 weeks of age onwards. Specifically, weaned pigs lose weight and gradually become emaciated, runts, rough-hair coated, with pale or jaundiced skin, until sudden death which often occurs (31).

Vaccines recommendations

Vaccines against PCV2 are used to control post-weaning multisystemic wasting disease PCV2-associated (PMWS), and the Porcine Circovirus – associated diseases (PCVAD). Piglets can be vaccinated as early as first week of age against PCV2; some vaccines require priming and booster vaccinations while others are considered one-shot. Conversely, PRRSV vaccination of piglets requires extreme care, correspondence with field genotype (EU-1 or USA-2), strict coordination with breeders' vaccination and the absence of viremic piglets at birth. The latter situation should ideally persist at least until weaning. Indeed, in viremic piglets, the vaccination with a PRRS-MLV vaccine causes a viral overload and further distress. On the other hand, viremic piglets are almost destined to be lost, so that the only strategy is a strict coordination with breeders' vaccination aimed at obtaining non-viremic piglets at birth and keeping them non-viremic during all the suckling period, therefore allowing their early vaccination. Piglets' vaccination should anticipate the foreseen viremia at post weaning; therefore, it should be ideally carried out before their 3rd week of age.

A novel commercial device has been made available in some countries such as Italy for the simultaneous administration of PCV2 and PRRSV vaccines. This elegant solution

enhances the management of the vaccination plan, which sometimes involves several vaccinations in pigs, both breeders and growers, in a short time-frame (32).

Streptococcus suis (S. suis) causes swine septicemia with typical neurological clinical signs observed worldwide. Thirty-five different serotypes are known, with *S. suis* serotype 2 and 9 playing the major role in the disease. The presence of many serotypes and the complicated measurement of the benefit of vaccination in the field has not allowed the creation of a vaccine that is suitable for all cases, therefore autogenous vaccines often represent the only strategy to overcome this disease.

Haemophilus (Glasserella) parasuis (Hp), is responsible for fibrinous polyserositis (Glasser disease); it is a Gram negative bacteria, of which at least 15 different serotypes are recognized. It is considered a normal component of the respiratory tract, where Hp is able to colonize even in presence of passive colostral antibodies. Dramatic changes in farming conditions (e.g. rapid drop in temperature) and, firstly, other coinfections, contribute to its active multiplication and systemic spread, resulting in severe fibrinous pleuropneumonia, pericarditis, peritonitis and a high incidence of mortality. A strong positive correlation was found between coinfection by Hp with PRRSV and with PCV2 (33). Autogenous vaccines may be used to control Glasser disease, but efficacy can be jeopardized when viral coinfections remain uncontrolled. A vaccination plan should be completed well in advance with respect to age of clinically infected animals, which may vary according to coinfections and predisposing environmental factors as above described. The full vaccination plan is detailed in Table 2A.

CLASSICAL SWINE FEVER (CSF)

Background and distribution

The last outbreak of Classical Swine Fever (CSF) virus occurred on 2009 on a pig farm of (at that time) 425 breeders, located in Israel's Northern District (Fassuta) (2, 34). It most probably resulted from contact with wild boars, a small number of them which were also found dead in the proximity of the farm and proved positive to CSFV. In the outbreak, all categories of pigs were affected: breeders (high fever, cyanosis, recumbency, abortion, mortality; scrotal redness, high fever in boars); weaning, growing and fattening pigs (fever, cyanosis, recumbency, mortality).

In CSFV-free countries, when an outbreak occurs, slaughter of all pigs on affected farms, disposal of carcasses and bedding, surveillance of the infected zone and the surrounding areas apply (35). A mixed strategy of partial culling (clinically sick animals) and vaccination, was implemented during the outbreak occurrence in Israel which resulted in the culling of some hundreds of clinically sick heads and vaccination of the clinically healthy pigs. The application of a culling policy has negative aspects related to high costs and increasing animal welfare/ethical issues (36). Vaccination should be taken into account as the main control measure in future outbreaks.

Vaccines recommendations

CSF vaccines in breeders are used to reduce reproductive losses (abortion, stillbirths) and birth of persistently viremic piglets. Moreover, in fatteners the vaccination reduces the severe losses due to hemorrhagic, necrotic lesions, SNC hyperemia and hyperthermia. Breeders are vaccinated twice within a 4 weeks interval and growing/fattening pigs are vaccinated once, starting at age of day 7.

During the 2009 Israeli CSF outbreak, the C-Strain "Chinese hog cholera Lapinized virus" (HCLV), 100 PD50/dose, was used. This and other CSF – modified live virus (MLV) vaccines have been shown to be safe to the target animals (young pigs and pregnant sows) and to provide early protection in the course of an outbreak, even at one day after a single dose (34, 36). Nevertheless, two main problems have recently arisen with the use of this vaccine and other traditional CSF-MLV vaccines:

1. This vaccine has been in use since the 1950's with high efficacy; but recently a shift in the predominant CSF viral strains circulating, from genotype 1 or 3 to genotype 2, has been seen in the Far East. This genotype 2 has been seen capable of "escaping" the vaccine neutralizing immunity, because of its genetic distance from the vaccine strains. Genotype 2 was demonstrated to be involved in outbreaks in vaccinated pig farms in the Far East (37).
2. This category of CSF-MLV vaccines does not allow differentiation between infected and vaccinated animals. **D**ifferentiating **I**nfected from **V**accinated **A**nimals (DIVA), together with appropriate differentiating laboratory test, is a key concept in eradicating diseases, preventing the economic losses and the serious animal welfare concerns due to culling.

In such a perspective, sub-unit marker CSF vaccines have been developed based on the E2-protein, which is considered the most immunogenic viral protein of CSFV. E2 marker vaccines are considered less powerful than traditional MLV vaccines and need a priming dose and a booster vaccination instead of single shot. They do not provide vertical protection to fetuses in pregnant breeders. The onset of immunity is slower than in MLV and of a shorter duration (6 to 13 months). Their limitation is represented by the fact that, differently from CSF-MLV, they do not replicate in the host; therefore their use in oral baits for wild boar is not feasible (36).

Nevertheless, E2 marker vaccines should be taken into consideration as feasible and animal-welfare acceptable alternative to disease control through mass culling of farm animals. Vaccination can be implemented either on a routine basis in pig farms considered at risk for continuous potential exposure to CSF virus from wild boars, or can be implemented only in emergency cases to stem a CSF outbreak.

CSF-MLV vaccines could anyway be used in baits for CSF control in wild boars (38). The full vaccination plan is detailed in Table 2.

FOOT AND MOUTH DISEASE (FMD)

Background and distribution

Israel is endemic for FMD, with several outbreaks per year in ruminants (2, 18). The last FMD outbreaks in pigs, reported over the last 70 years, occurred in 2015 (39), in a farm located in Fassuta; then in 2022 (Addendum) in two farms located in Afik area of Ibblin, all of them in the Northern District. Type O/ME-SA/PanAsia viral lineage FMD virus, was demonstrated responsible of the outbreaks.

Both FMD outbreaks developed in the farrowing units of the farms, affecting lactating sows and suckling piglets. In 2015 mortality totaled 11.13% as still-born piglets, 59.4% in suckling piglets and only 1 sow (39). In 2015 outbreak, losses were negligible in growing/fattening pigs and other sows (pregnant), probably due to the immediate vaccination on the basis of suspect clinical signs (vesicles on snouts and teats of sows; sudden mortality at high rate in piglets) (39). There is no eradication policy for FMD in Israel, therefore vaccination was implemented in animal populations at risk (39). Table 1 summarizes FMD vaccine availability in Israel for use in pigs. Types of FMD viral antigens included in the vaccine were aligned with epidemiology of FMD in Israel and, therefore, can be adjusted accordingly.

Vaccines recommendations

Pigs vaccination against FMDV is mandatory in Israel, but only for breeders; vaccine distribution is under Veterinary Services control; the vaccination plan is established by The Field Veterinary Services (40). Vaccination indications are vague: "gilts, sows and boars (all the breeders older six months of age) will be vaccinated against FMD" (40); the full vaccination plan is not indicated. The authors believe these recommendations should be more detailed. It is therefore proposed to modify and clearly specify the indications for FMD vaccination in the swine populations according to the following:

Routine vaccination

– Basic vaccination (priming and booster; 3 to 4 weeks apart) in young boars, and in gilts before the first insemination, at 6th to 8th month of age. Biannual vaccination in boars. Biannual vaccination in sows, according to their reproductive cycle: no later than 30-35 days before each farrowing (~80th day of pregnancy).

This plan would guarantee a more uniform coverage in vaccinated animals (all the breeders, all the year round) and the passive protection of piglets until 8 to 12 weeks of age (according to vaccine of choice), due to maternal derived antibodies (MDA). Piglets' passive protection would contribute to population immunity (41).

Growing/fattening pigs, at this stage, would remain at risk, but with less direct economic implications due to lower levels of mortality and losses (39).

Urgency vaccination, in course of a FMD outbreak:

– Prompt vaccination of growing/fattening population of pigs (10 to 26 weeks of age) not included in the routine vaccination plan.

Such a vaccination plan would provide an acceptable level of protection in all the breeders and piglets until 8-12 weeks of age, *at any given time of the year* against FMD virus, with a need of an emergency vaccination in a reduced targeted population and in a less sensitive phase of production. The full vaccination plan for pigs, breeders and growers/fatteners, is detailed in Table 2.

Vaccination techniques in pigs

Vaccinations in pigs can be performed orally (OR), parenterally: intramuscularly (IM), subcutaneous (SC) or intradermally (ID). Oral vaccinations in pigs are mainly used for control of CSF in backyard pigs or wild boars (36, 38), and against *Lawsonia intracellularis*, bacteria responsible for hemorrhagic-proliferative enteritis in affected countries. CSF-MLV strains vaccines are used in baits for disease control in wild boars; their use ensures replication in host and immune stimulation (36, 38).

Oral vaccine against *L.intracellularis* is constituted by a modified live avirulent bacterial strain, available in the lyophilized form, made ready for use after thawing and dilution in drinking water. Thereafter, it is administered either via an oral pump in young piglets (2 ml each, *per os*) or as a drench on feed in heavier pigs. The vaccine bacterial strain is susceptible to several antibiotics belonging to different classes (beta-lactamines, amfenicoles, polypeptides, sulfamidics, macrolydes, etc.), and therefore these should not be used in vaccinated pigs for several days and according to producer's recommendations. Vaccination equipment (oral pumps, drench distributors, etc.) should also be clean from disinfectants. *L.intracellularis* has never been diagnosed in Israel.

In parenteral vaccinations, the antigen is injected through a needle at SC or IM level. In the last two decades "needle-free" devices have been developed, which allow intra-dermal (ID) vaccination against several pathogens without the use of needles.

IM and SC vaccination methods are the most practiced world-wide, including Israel; vaccines should be administered either IM or SC according to producers' recommendations. SC vaccination is performed approximately 2.5 to 7.5 cm (according to age and size of animal) behind the ear on the level of its base (retro-ear dimple); length of needles varies according to age, as in Table 3 below. IM vaccination can be performed in same neck area close to, or as in, SC; length of needle varies according to age, as in Table 3. In SC, IM vaccines the volume injected varies 1ml to 2 ml according to the different commercial vaccines. Figure 1 illustrates SC, IM, vaccination sites in pigs. Figure 2 shows IM and ID vaccination in piglet and an ID "needle-free" vaccination device.

A common mistake in vaccinating pigs, either SC or IM, is represented by vaccinating in the wrong area or using inappropriate needles. Shorter than recommended needles for IM vaccination, vaccinating distant from retro-ear dimple, may lead to vaccine leakage from injection site, or failure to reach muscle tissue for IM vaccines. Figure 4 illustrates an event of vaccine leakages following vaccination with a short needle, and the needles used in the event, with respect to epidermis thickness in a breeder.

ID vaccination "needle-free" is performed without using needles: Vaccine antigen is diluted with special adjuvants at a reduced volume of 0.2 ml/dose, and then it is "shot" at high pressure inside the dermis (32, 42, 43) and muscle tissues. The dermis of pig is rich in Langerhans and dendritic cells, which are activated by antigen uptake, which migrate to the lymph-nodes leading to activation of T-lymphocytes. In addition, macrophage are attracted in the injection area and participate in the immune response. Unlike from SC, IM, the ID vaccination may be performed all over the body of the animal; in large animals (sows, fattening pigs) vaccination in the back area, on the

Table 3: Calibers (in gauge and millimeters) and lengths (in inch and centimeters) of needles for vaccinations (and injections) in pigs

Subcutaneous vaccinations	calibers in gauge	length in inches	caliber in millimeters	length in centimeters
suckling piglets	16 to 18	½	1.2 to 1.6	1.27
growing/finishing	16	¾	1.6	1.9
breeders	14 to 16	⅝ to 1	1.6 to 2	1.5 to 2.54
Intramuscular vaccinations				
suckling piglets	18 to 20	⅝ to ½	0.9 to 1.2	1.27 to 1.5
weaned	16 to 18	¾ to ⅝	1.2 to 1.6	1.5 to 1.9
growing/finishing	16	1	1.6	2.54
breeders	14 to 16	1 to 1½	1.6 to 2	2.54 to 3.8

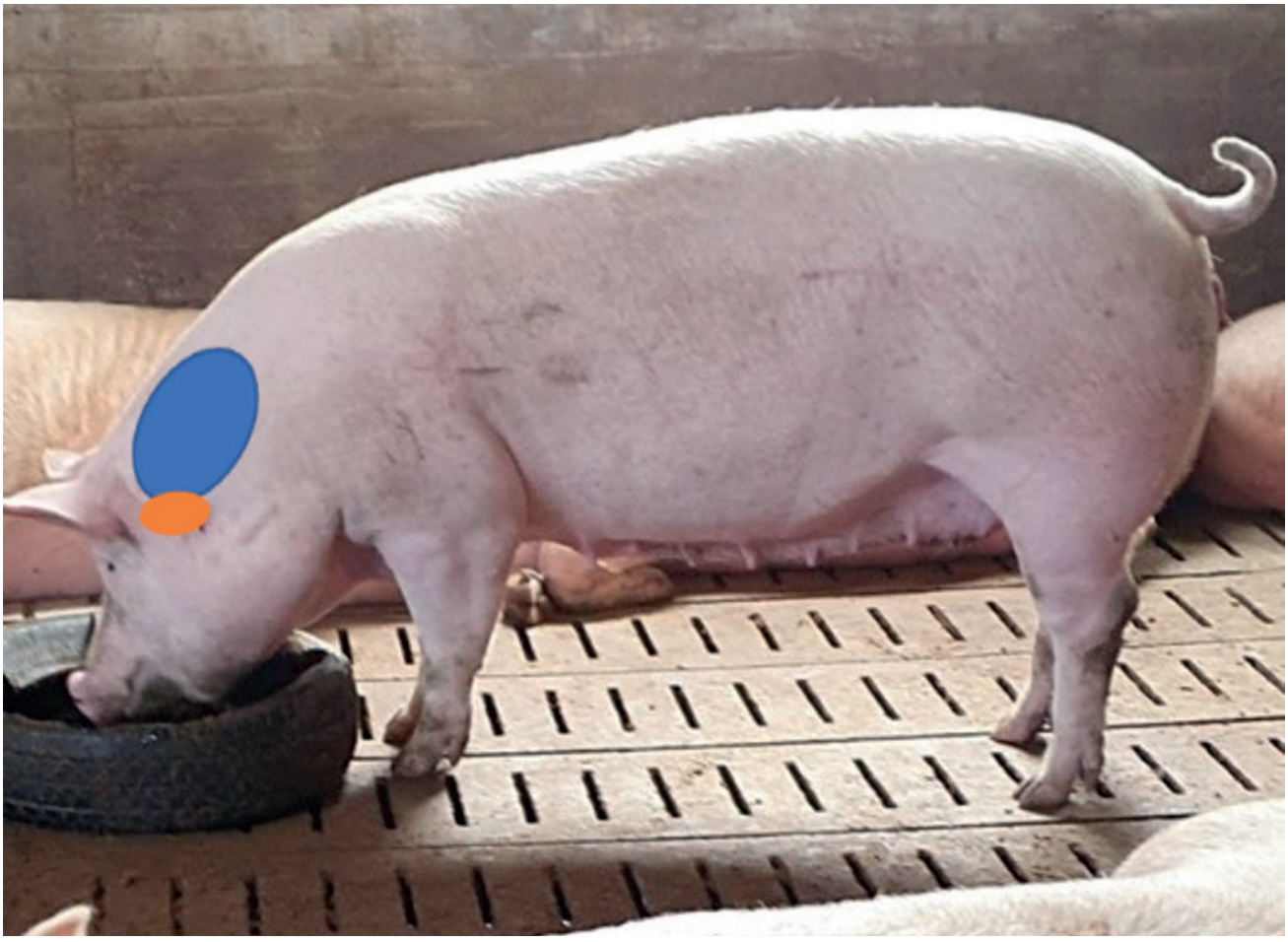

Figure 1: IM and SC sites for vaccination in pig (a breeder in this picture):

intramuscular **subcutaneous**

Figure 2: IM vaccination (left); ID vaccination and ID vaccination device (right); the ID device's tip should be pushed on the body of the animal in order to allow the antigen shot.

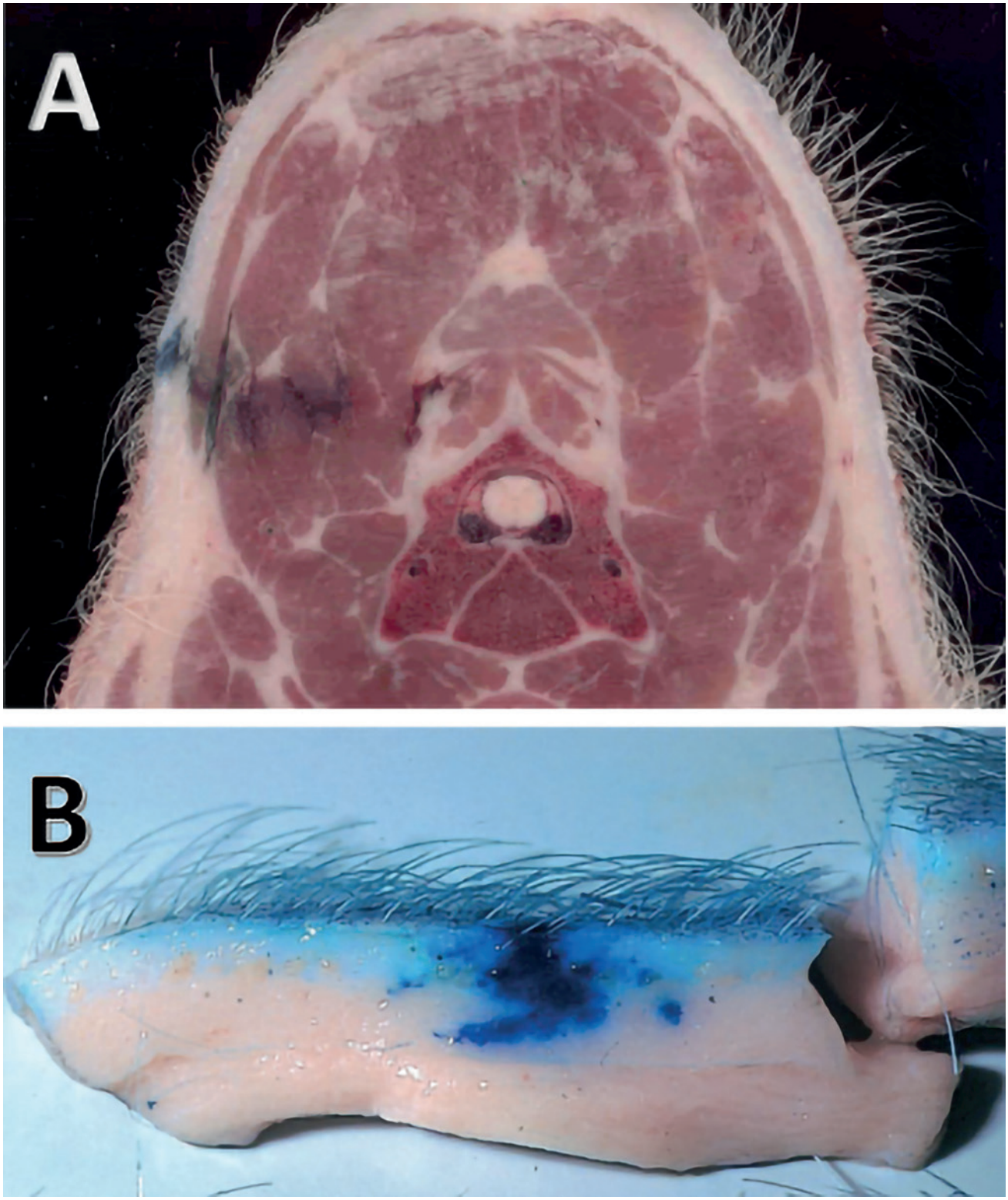

Figure 3: The figure illustrates the ID vaccination and antigen distribution in epidermis and muscle tissues after vaccination.

A: Intra-dermal and intra-muscle distribution of antigen-like (ink) after ID vaccination (courtesy of Ceva Santé Animale, France);
B: Intra-dermal distribution of antigen-like (ink) after ID vaccination (courtesy of MSD/Intervet, USA & courtesy of Pig Progress, The Netherlands) (31)

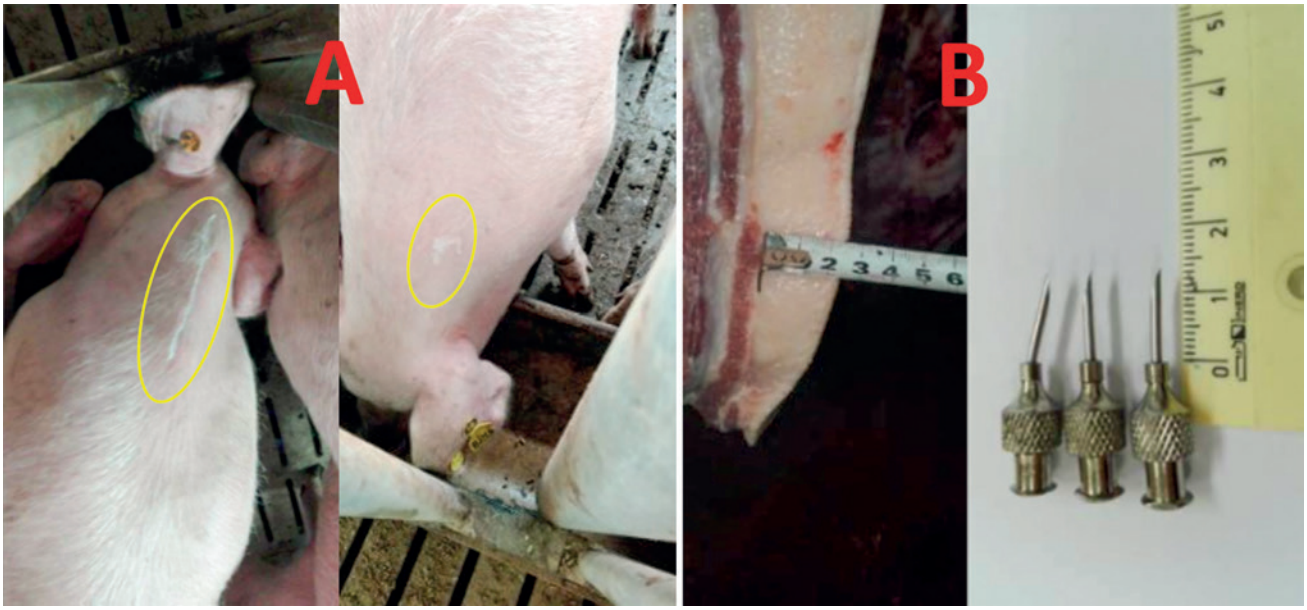

Figure 4: mistakes in SC and IM vaccination in pigs:
A: leakage of vaccine due to use of short needle and vaccination too far from retro-ear dimple.
B: too short needles do not reach the muscle tissue.

thighs, is easy and quick when pigs are all aligned at the feeding trough. ID devices are provided with a pressure sensor at injection point, for which the shot is not released if the device's tip is not pressed at close contact to the body of the animal thus ensuring the actual vaccination of each animal and without leakages. ID vaccination in pigs is mainly used for PCV2, PRRSV, Mhyo; recently, in Far East Countries, also FMD vaccination has been proved efficacious and safe (43).

Safety and welfare implications

Where available, ID vaccination should be preferred rather than IM or SC, both for safety and animal welfare issues.

Safety

Contrarily to companion animals, livestock, including pigs, are generally vaccinated using multi-doses syringes; the syringe is directly filled from vaccine's vial, by drilling the vial's cap with the needle applied to the syringe itself and then sucking the vaccine. A multi-doses syringe may contain up to 50 ml, which means 25 to 50 vaccine doses. Once the syringe is filled, the vaccinations run begins; the same needle is used for all the 25 to 50 doses, which means for 25 to 50 animals. Then the vaccination cycle starts again.

Multiple use makes the needles dull and barbed, even after being used a few times (less than 10 times). Injections with repeatedly used needles create risk of injury and infection at injection site, due to the dragging of infected debris by barbed, dull needle tips. This may result in lesions such as abscesses, fibrosis, and granulomas at injection sites, as illustrated in Figure 5 (43). Drilling a vaccine vial with an already used needle will probably contaminate the vaccine vial itself. Using vaccine vials with a flow infusion set connected to syringe will avoid vial content contamination, but it will not prevent needles dulling and barbing.

Animal welfare

The use of needles is unavoidably painful; pain will increase with dulled, barbed needles; local reactions, inflammatory, abscesses development will induce long-lasting pain. Specific investigations relative to reactions of piglets (which receive multiple vaccinations) revealed that use of ID needle-free devices reduced the behavioral reaction at vaccination, and it did not affect general activity, social and exploratory behavior of the piglets after the injection (44).

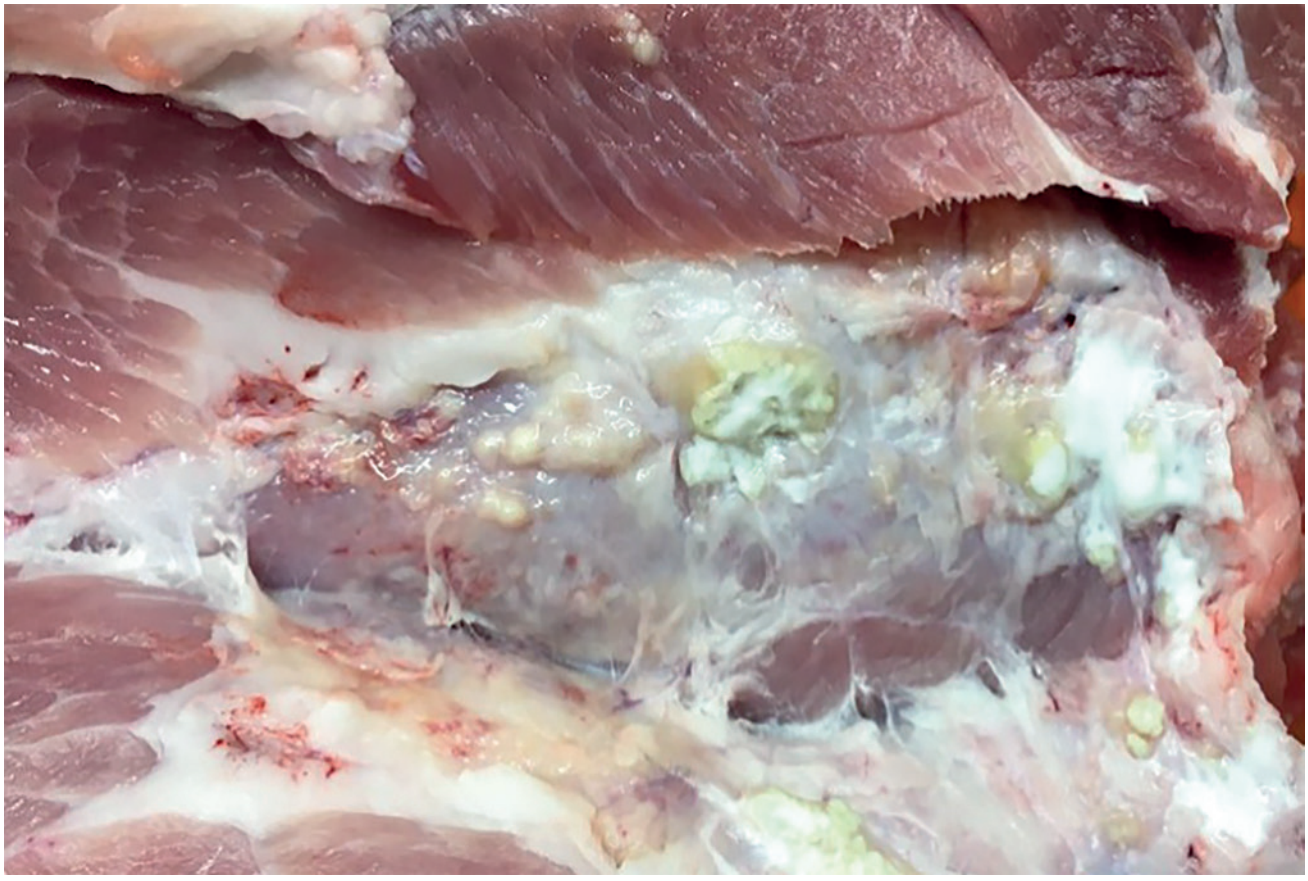

Figure 5: Lesions generated in the muscle and subcutaneous tissue in a pig vaccinated (with a FMD vaccine) using a conventional syringe needle. (Courtesy of: Division of Animal and Dairy Science, Chungnam National University, Daejeon, Korea & Korean Journal for Food Science of Animal Resources) (43).

The use of needle-free technologies may assist in controlling the spread of pathogens, i.e. PRRS virus (16). As in other countries with intensive pig farming, considering the advantages represented by ID vaccination, in terms of safety, meat quality, speed, precision, welfare implications, ID vaccination in pigs should also be promoted in Israel.

CONCLUSIONS

According to Veterinary Services data, apart from few autogenous bacterial vaccines, there is no production of pigs' vaccines in Israel; these are only imported vaccines (2, 18). Pigs' vaccines availability in Israel appears adequate for local epidemiological situation. Vaccination plans in pigs should be tailored not only according to the epidemiological situation of the country and/or of the specific herd, but also according to category and physiological status of pigs: growers/fatteners, breeders, at different reproductive phases. The occurrence of diseases at different ages, gives the opportunity for their prevention and control through active immunization rather than passive, colostral immunity. SC, IM, vaccinations are the only methods practiced, despite the fact that some of registered vaccines may allow ID application. ID application represents a safer and welfare -friendly way of vaccinating pigs, as alternative to injections.

ACKNOWLEDGEMENT

The authors acknowledge Dr. Erez Lubrani of the Israeli Veterinary Services for having provided significant information relative to vaccines registration and availability.

ADDENDUM

Description of 2022 FMD outbreak in Israel will be presented in next issue of the Israel Journal of Veterinary Medicine

REFERENCES

1. Ben-Dov, D., Hadani, Y., Ben-Simchon, A., Alborali, L. and Pozzi, P.S.: Guidelines for Pig Welfare in Israel. Isr. J. Vet. Med. 69:4-15, 2014.
2. Ministry of Agriculture and Rural Development, Veterinary Services, Report of Year 2019.
3. Pozzi, P., Soggiu, A., Bonizzi, L., Elkin, N. and Zecconi, A.: Airborne Coronaviruses: Observations from Veterinary Experience. Pathogens, 10:1-13, 2021.
4. Ramirez, A.: Differential Diagnosis of Diseases; in Disease of Swine, 11th edition. Zimmerman, J., Karriker, L., Ramirez, A., Schwartz, K., Stevenson, G. and Zhang, J. (Eds.), Wiley-Blackwell, Hoboken, NJ, USA, 59-74, 2019.
5. Segalés, J., Allan, G. and Domingo, M.: Circoviruses; in Disease of Swine, 11th edition. Zimmerman, J., Karriker, L., Ramirez, A., Schwartz, K., Stevenson, G. and Zhang, J. (Eds.), Wiley-Blackwell, Hoboken, NJ, USA, 473-487, 2019.
6. Pozzi, P. and Alborali, G.L.: Reproductive diseases in sows (*Sus scrofa domestica*): A Review. Isr. J. Vet. Med. 67: 24-33, 2012.
7. Ballarini, G. and Martelli, P.: Diagnostic of reproductive syndromes, in "Swine clinic" Edagricole, Bologna, (Italy), II.2: 111-149, 1993.
8. Karniychuk, U., Saha, D., Geldhof, M., Vanhee, M., Cornillie, P., Van den Broeck, W. and Nauwynck, H.J.: Porcine reproductive and respiratory syndrome virus (PRRSV) causes apoptosis during its replication in fetal implantation sites. Microbiol. Pathol. 51:194-202, 2011.
9. Arent, Z. and Ellis, W.: Leptospirosis: in Disease of Swine, 11th edition. Zimmerman, J., Karriker, L., Ramirez, A., Schwartz, K., Stevenson, G. and Zhang, J. (Eds), Wiley-Blackwell, Hoboken, NJ, USA, 854-862, 2019.
10. Salogni, C., Lazzaro, M., Giacomini, E., Giovannini, S., Zanoni, M., Giuliani, M., Ruggeri, J., Pozzi, P., Pasquali, P., Boniotti, M. B., and Alborali, G. L.: Infectious agents identified in aborted swine fetuses in a high-density breeding area: a three-year study. J. Vet. Diagn. Invest., 28, 550-554, 2016.
11. Brenner, J., Berenstein, M., Schori, D., Baranover, Y. and Samina, I.: An outbreak of porcine parvovirus infection in a farm in Israel. Isr. J. Vet. Med. 51: 79-81, 1996.
12. Pozzi, P., Alborali G.L., Etinger, M. and Hadani, Y.: Epidemiological investigation of the prevalence of *Leptospira spp.* in pigs in Israel. Isr. J. Vet. Med. 75:14-21, 2020
13. Pozzi, P., Arraf, M., Boniotti, M.B., Barbieri, I., Hadani, Y., Etinger, M. and Alborali, G.L.: First Outbreak of Porcine Reproductive and Respiratory Virus (PRRSV) in Swine Farms in Israel. Isr. J. Vet. Med. 73:15-22, 2018.
14. Pozzi, P., A Barbieri, I., Alborali, G.L., Arraf, M., Hadani, Y., Etinger, M., and Salogni, C.: Porcine Reproductive and Respiratory Virus European Type 1 (PRRSV1) in Swine Farms in Israel. Isr. J. Vet. Med. 77: 72-80, 2022.
15. Choi, K., Park, C., Jeong, J. and Chae, C.: Comparison of protection provided by type 1 and type 2 porcine reproductive and respiratory syndrome field viruses against homologous and heterologous challenge. Vet. Microbiol. 191:72-81, 2016.
16. Zimmerman, J., Dee, S., Holtkamp, D., Murtaugh, M., Stadejek, T., Stevenson, G., Torremorell, M., Yang, H. and Zhang, J.: Porcine Reproductive and Respiratory Syndrome Viruses (Porcine Arteriviruses), in Disease of Swine, 11th edition. Zimmerman, J., Karriker, L., Ramirez, A., Schwartz, K., Stevenson, G., Zhang, J. (Eds), Wiley-Blackwell, Hoboken, NJ, USA, 685-708, 2019.
17. Brenner, J., Yadin, H., Lavi, J., Perl, S., Edery, N., Elad, D., Bargut, A., Pozzi, S., Lavazza A. and Cordioli, P.: Investigation of the first Transmissible Gastro-Enteritis (TGE) epidemics in pigs in Israel. Isr. J. Vet. Med. 59:39-42, 2004.
18. Ministry of Agriculture and Rural Development, Veterinary Services Report of Years 2016-2018.
19. Baldo, V., Salogni. C., Giovannini, S., D'Incau, M., Boniotti, M.B., Birbes, L., Pitozzi, A., Formenti, N., Grassi, A., Pasquali, P. and Alborali, G.L.: Pathogenicity of Shiga Toxin Type 2e Escherichia coli in Pig Colibacillosis. Front. Vet. Sci. 7(545818):1-10, 2020.
20. Van den Broeck, W., Cox, E. and Goddeeris, B. M.: Receptor-dependent immune responses in pigs after oral immunization with F4 fimbriae. Infection and immunity, 67: 520-526, 1999.
21. Fairbrother, J. and Nadeau, E.: Colibacillosis, in: Disease of Swine, 11th edition. Zimmerman, J., Karriker, L., Ramirez, A., Schwartz, K., Stevenson, G., Zhang, J. (Eds), Wiley-Blackwell, Hoboken, NJ, USA, 807-834, 2019.
22. Uzal, F. and Glenn-Songer, J.: Clostridial diseases, in Disease of Swine, 11th edition. Zimmerman, J., Karriker, L., Ramirez, A., Schwartz, K., Stevenson, G., Zhang, J. (Eds), Wiley-Blackwell, Hoboken, NJ, USA, 792-806, 2019.
23. Elad, D., Samina, I., Nankin, M., Barigazzi, G., Foni, E., Guazzetti, S. and Pozzi S.P.: "Serological monitoring towards antigens responsible of respiratory diseases in fattening pigs in Israel", Proc. XXVIII SIPAS, 155-160, 2002.
24. Gottschalk, M., and Broes, A.: Actinobacillosis, in Disease of Swine, 11th edition. Zimmerman, J., Karriker, L., Ramirez, A., Schwartz, K., Stevenson, G., Zhang, J. (Eds), Wiley-Blackwell, Hoboken, NJ, USA, 749-766, 2019.
25. Pozzi, S.P., Dolgkov. I., Rabl-Avidor, M., Hadani, Y. and Aborali, G.L.: Isolation of *Actinobacillus pleuropneumoniae* from pigs in Israel. Isr. J. Vet. Med. 66:29-33, 2011.
26. Merialdi, G., Dottori, M., Bonilauri, P., Luppi, A., Gozio, S., Pozzi, P., Spaggiari, B., and Martelli, P.: Survey of pleuritis and pulmonary lesions in pigs at abattoir with a focus on the extent of the condition and herd risk factors, Vet. J. 193:234-239, 2012.
27. Ross, R.: *Pasteurella multocid*a and its role in porcine pneumonia. Anim. Health. Res. Rev. 7(1-2):13-29, 2006
28. Biebaut, E., Beuckelaere, L., Boyen, F., Haesebrouck, F., Gomez-Duran, C. O., Devriendt, B. and Maes, D.: Transfer of Mycoplasma hyopneumoniae-specific cell mediated immunity to neonatal piglets. Vet. Res. 52:96, 2021.
29. Arsenakis, I., Michiels, A., Schagemann, G., Gomez-Duran, C., Boyen, F., Haesebrouck, F. and Maes, D.: Effects of pre-farrowing sow vaccination against Mycoplasma hyopneumoniae on offspring colonisation and lung lesions. Vet. Rec. 184:222, 2019.
30. Chase, C., and Lunney, J.: Immune system, in Disease of Swine, 11th edition. Zimmerman, J., Karriker, L., Ramirez, A., Schwartz, K., Stevenson, G., Zhang, J. (Eds.), Wiley-Blackwell, Hoboken, NJ, USA, 264-291, 2019.
31. Pozzi, S. P., Yadin, H., Lavi, J., Pacciarini, M. and Alborali, L.:

Porcine circovirus type 2 (pcv2) infection of pigs in Israel: clinical presentation, diagnosis and virus identification. Isr. J. Vet. Med. 63:122-125, 2008.
32. Horsington, J. Witvliet, M. Jacobs, A. and Segers, R.: Efficacy of Simultaneous Intradermal Vaccination of Swine against PCV2, PRRSV, *M. hyopneumoniae* and *L.intracellularis*. Animals, 11: 2225, 2021.
33. Salogni, C., Lazzaro, M., Giovannini, S., Vitale, N., Boniotti, M. B., Pozzi, P., Pasquali, P. and Alborali, G. L.: Causes of swine polyserositis in a high-density breeding area in Italy. J. Vet. Diagn. Invest. 32: 594-597, 2020.
34. David, D., Pozzi, P.S., Ozeri, R., Hadani, Y., Yadin, H., Schmeiser, S., Bashara, R., King, R. and Perl, S.: An outbreak of Classical Swine Fever (CSF) in a closed-cycle unit in Israel. Isr. J. Vet. Med. 67:225-231, 2012.
35. Classical swine fever, in: OIE Terrestrial Manual, 3.8.3, 2019; https://www.oie.int/en/disease/classical-swine-fever/
36. Coronado, L., Perera, C.L., Rios, L., Frías, M.T. and Pérez, L.J.: A critical review about different vaccines against Classical Swine Fever Virus and their repercussions in endemic regions. Vaccines, 9:154, 2021.
37. Yoos. S., Kwon, T., Kang, K., Kim, H., Kang, S., Richt, J. and Lyoo, Y.: Genetic evolution of classical swine fever virus under immune environments conditioned by genotype 1-based modified live virus vaccine. Transb. Emerg. Dis.65: 735-745, 2018.
38. Milicevic, V., Dietze, K., Plavsic, B., Tikvicki, M., Pinto, J. and Depner, K.: Oral vaccination of backyard pigs against classical swine fever, Vet. Microbiol. 163:167-171, 2013.
39. Pozzi, P., Gelman, B., Etinger, M., Pirogov, V., Khinich, E. and Hadani, Y.: Clinical description of an outbreak of Foot and Mouth Disease in a pig close-cycle unit. Isr. J. Vet. Med. 74:93-101, 2019.
40. Ministry of Agriculture and Rural Development; The Veterinary Services and Animal Health; The Field Veterinary Services: "Vaccination of cattle, sheep/goats and pigs against Foot and Mouth Disease (FMD)-2021-2022", 2021.
41. Pozzi, P., Amadori, M., Gelman, B., Hadani, Y. and Alborali, L.: Investigation on results from vaccination of sows against Foot and Mouth Disease (FMD) using different vaccination protocols in Israel. Isr. J. Vet. Med. 74:141-147, 2019.
42. Evans, A.: Intra-dermal vaccination series. Part 2. Original engineering solution. Pig Progress. 22(4):28-30, 2006.
43. Young, K., Jaesung, C., Ho, C., Kyung, J., Hwan, L., Ji, C. and Samooel, J.: Reduction in Lesion Incidence in Pork Carcass Using Transdermal Needle-free Injection of Foot-and-Mouth Disease Vaccine. Korean J. Food Sci. Anim. Resour. 38:1155-1159, 2018.
44. Temple, D., Jiménez, M., Escribano, D., Martín-Valls, G., Díaz, I. and Manteca, X.: Welfare Benefits of Intradermal Vaccination of Piglets. Animals. (10) 1898, 2020.