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SWINE FEVER :
INFLUENCE OF PASSIVE IMMUNITY
ON PIG IMMUNE RESPONSE FOLLOWING VACCINATION
WITH A LIVE VIRUS VACCINE (THIVERVAL STRAIN)

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SUMMARY

The influence of passive immunity on the immune response to swine fever virus (S.F.V.) was investigated in pigs injected with variable amounts of S.F.V. antibodies instead of piglets from immune sows.

The passive immunity suppresses the primary serum antibody response normally observed after vaccination with the Thiverval strain of S.F.V. This inhibition is either partial or complete depending on the amount of injected antibodies.

Whatever the passive immunity intensity, a priming occurred (even in absence of any detectable primary response). This priming was evidenced by the clinical signs and the type of immune response following a virulent challenge.

Two vaccination routes were tested : intramuscular and intranasal : 48 pigs were checked and no significant differences established, concerning protective efficiency.

Intranasal vaccination induced local antibody production in pharyngeal secretions. Even in the absence of any detectable immunoglobulin transudation from serum to these secretions, local antibody synthesis was completely inhibited in passively immunized animals.

INTRODUCTION

Colostrum immunity is a decisive factor in the protection of young piglets against colibacillosis (PORTER and HILL, 1970) transmissible gastroenteritis (BOHL *et al.*, 1972) or Aujeszky disease (FERRAN and DOW, 1973).

But, because of the passive immunity given by colostrum antibodies, piglets born from immune sows are often unsuccessfully protected when injected with foot and mouth disease vaccine (GIRAUD *et al.*, 1974 ; MOWAT, 1974) or swine fever vaccine

within the first weeks of life (LOAN and RODABAUGH, 1966; SASAHARA *et al.*, 1969; LIN *et al.*, 1969; AYNAUD, CORTHIER and LAUDE, 1973; LAUNAIS and AYNAUD, 1975; PRECAUSTA *et al.*, 1975).

For swine fever various approaches have been tested to overcome the passive antibody inhibitory effect :

— AIKEN and BLORE (1964) successfully immunized piglets from immune sows, before first colostral absorption. This method cannot be applied easily in field conditions.

— The second approach was performed by COGGINS (1964). He injected one hundred times the normal vaccine dosage, and an active immunity was induced in piglets still protected by passive maternal immunity.

Till now, all vaccination approaches of piglets (against swine fever virus) born from immune sows were performed taking only into account the animal's age, not antibody level at vaccination time. For a better knowledge of the immunosuppressive effect of antibodies, it is important to test influence of different antibody quantities at vaccination time on pig immune response.

In the present work we have tried to realize such an approach. For a better control of passive immunity intensity we injected (intraperitoneally) anti-swine fever immunoglobulins to pigs without passive immunity against swine fever virus. That is what we call « artificial » passive immunity. Then we vaccinated animals with live virus vaccine (THIVERVAL strain) by different routes. Immune response was determined by study of neutralizing antibody production and challenge resistance.

MATERIAL AND METHODS

1. — *Experimental procedure*

Forty-eight weaned pigs weighing fifteen to twenty kg, from a conventional breeding farm were randomly distributed in four groups. On day zero, every pig received one of the following anti-swine fever virus immunoglobulins (from pig hyperimmune sera) solutions in phosphate buffer saline containing : 400 mg, 200 mg, 50 mg or 0 mg in a single 50 ml intraperitoneal injection and adjusted to 400 mg proteins by adding non-specific immunoglobulins.

At three days post injection, each group composed of 12 randomly distributed pigs, received either:

- intramuscularly : two ml of vaccine (10^4 Plaque forming units per pig : P.F.U./pig) ;
- intranasally : two ml of vaccine (10^5 P.F.U./pig) ;
- no treatment (control) (table 2). During the 146 days of experimentation some pigs died (7/48) of pneumonia or other diseases unrelated to swine fever.

2. — *Immune response analysis method*

The pig immune response was tested in different ways :

a) every week, neutralizing activity of vena cava blood samples was determined and characterized by neutralization index technique using 1/20 serum dilution (LAUNAIS, AYNAUD and CORTHIER, 1972) ;

b) every week pharyngeal mucus was collected on cotton wools swabs. Samples containing blood traces were discarded. Mucus was extracted from cotton wool by compression in a syringe. Neutralizing activity was measured in 1/10 sample dilution to avoid toxic effect on tissue cultures ;

c) at day 125, animals were challenged by intranasal inoculation of virulent Alfort swine fever virus strain (10^6 P.F.U./pig). Animals were kept 3 weeks and blood samples were taken every week.

3. — *Cells and viruses*

Immunofluorescence, tissue culture techniques and swine fever virus strains were previously described (AYNAUD, 1968 ; AYNAUD *et al.*, 1972 ; LAUNAIS, AYNAUD and CORTHER, 1972).

4. — *Immunoglobulin purification*

Unspecific immunoglobulins were obtained from normal pig serum, precipitated by ammonium sulfate (50 p. 100) dialyzed and purified by chromatography on DE 52 Whatman ion exchange column equilibrated on 0.01 M phosphate buffer pH 8.0. In these conditions only immunoglobulin passed unadsorbed through the gel.

The same technique was used to extract immunoglobulins from swine fever virus hyperimmune serum.

Immunoglobulins are kept lyophilized and dissolved when necessary at 8 mg/ml in a hypertonic sterile glucose solution.

RESULTS

1. — *Relationship between quantity of immunoglobulins injected to pigs and acquired serum neutralization index*

By intraperitoneal injection route, piglets received various levels of swine fever virus specific immunoglobulins. The obtained level of artificial passive immunity was measured three days post injection (table 1).

TABLE I

Relationship between injected anti swine fever immunoglobulins quantities and serum neutralizing activity tested 6 days post injection

Relation entre la quantité d'immunoglobulines anti- peste porcine et l'activité neutralisante sérique observée 6 jours après l'injection

Amount of anti-swine fever immunoglobulins injected (mg) <i>(Quantité d'immunoglobulines anti Peste porcine injectées)</i>	Average neutralizing activity tested 6 days post injection (Neutralization index) <i>(Index de neutralisation)¹</i>
0	< 0.1
50	2
200	4.8
400	6.7

Recently (CORTHER, 1976) we have established that a linear relation exists between neutralization index (N.I.) and antibody dilution if N.I. is higher than one. The same relation is observed in this experiment when N.I. is plotted against the amount of immunoglobulin injected (fig. 1).

According to the slope of the regression (the same as previously observed) one can predict that a 50 p. 100 decrease in antibody concentration will correspond to a N.I. value decrease of one unity. This to estimate injected immunoglobulin half life.

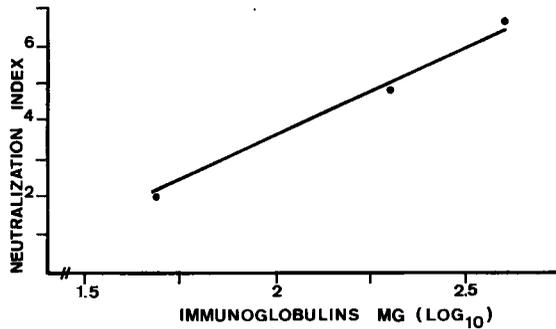


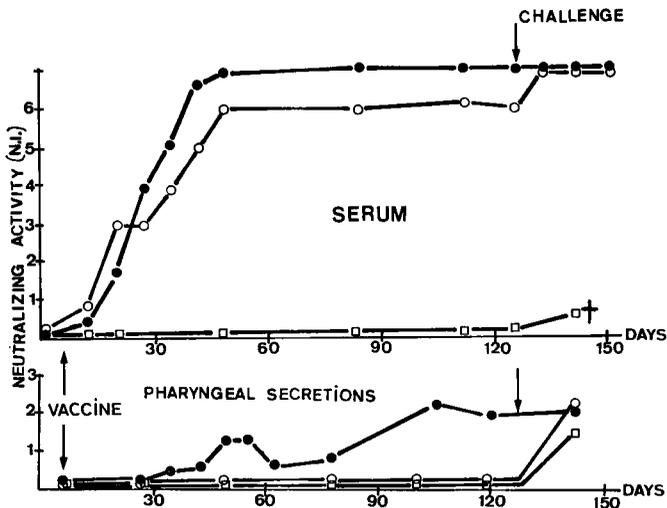
FIG. 1. — Relationship between neutralization index and logarithm of injected immunoglobulin quantity
Relation entre l'index de neutralisation et le logarithme de la quantité d'immunoglobulines injectées

2. — Immune response of passive immunity free piglets

2. I. Immune response induced by vaccination.

2. II. — Serum level.

Neutralizing antibody synthesis was similar to that observed in preceding experiments (LAUNAIS, AYNAUD and CORTHIER, 1972). Irrespective of the route of injection, the antibody production was rapid, high and stable : 50 days post vaccination, the average neutralization index (N.I.) was higher than five (fig. 2).



□ — □ Non vaccinated animals (*animaux non vaccinés*)
● — ● Intranasal vaccination (*vaccination par voie intranasale*)
○ — ○ Intramuscular vaccination (*vaccination par voie intramusculaire*)
Each point represent group neutralization index average (*chaque point représente la moyenne des index de neutralisation du groupe*)

FIG. 2. — Kinetics of neutralizing antibody synthesis following vaccination of pigs without passive immunity

Cinétique d'apparition des anticorps neutralisants après vaccination des porcs sans immunité passive

2. 12. — *Local level.*

Neutralizing antibody production was demonstrated only when the vaccination is performed by intranasal route. In this case, antibody synthesis began at the twentieth day post vaccination and had two intensity peaks : at day 50 and at day 110. Although this synthesis was weak, it was easily measurable (fig. 2).

2. 2. *Immune response to virulent challenge.*

Challenge with the virulent strain, at day 125, can be considered as a booster because virulent and attenuated strains are antigenically related (CORTIER *et al.*, 1974).

2. 21. — *Neutralizing Antibody production in serum.*

At the time of the intranasal challenge, the serum neutralizing activity was too high (N.I. = 7) to permit any detection of an increase in antibody neutralization index in our system.

TABLE 2
Experimental procedure
Protocole expérimental

Day : 0 (Jour)	Day : 3 (Jour)	Day : 125 (Jour)	Results (Résultats)
Anti swine fever Ig injection (<i>Injection d'Ig anti Peste porcine</i>) (mg)	Route of vaccination with Thiverval-strain (<i>Voie de vaccination : souche Thiverval</i>)	Virulent challenge (Alfort-strain) (<i>Épreuve virulente : souche Alfort</i>)	Immune pigs number ⁽¹⁾ Total pigs number <i>Nombre d'immunisés</i> <i>Nombre total</i>
0	● I. Muscular ● I. Nasal ● Control	● ● ●	5/5 3/3 0/4
50	● I. Muscular ● I. Nasal ● Control	● ● ●	3/3 1/2 0/3
200	● I. Muscular ● I. Nasal ● Control	● ● ●	3/4 3/4 0/4
400	● I. Muscular ● I. Nasal ● Control	● ● ●	2/2 2/3 0/4

⁽¹⁾ Pigs are considered as immunized when they resist to virulent challenge without any detectable viremia and when neutralizing antibody increase of vaccinated animals tested one week after challenge is higher (N.I. ≥ 2.5) than antibody increase of control animals (N.I. ≤ 0.5).

⁽¹⁾ *Sont considérés comme immunisés les porcs ayant résisté à l'épreuve virulente, sans virémie ou hyperthermie, et dont l'activité anticorps sept jours après l'épreuve est plus élevée (index $\geq 2,5$) que celle des témoins non vaccinés (index $\leq 0,5$).*

At the local level, no anamnestic response was detected and the neutralization index remained unchanged (N.I. = 2).

2. 22. — *Resistance to virulent challenge.*

All vaccinated pigs were resistant to virulent challenge. The classical clinical signs were observed on non-vaccinated control animals which died two weeks post-challenge (fig. 2 and table 2),

3. — *Immune response of passively immunized pigs*

3. 1. *Local immune response.*

Irrespective of the antibody concentration or the route of vaccination, the local immune response was completely inhibited by passive immunity (fig. 3, 4 and 5).

3. 2. *Humoral immune response of pigs injected with specific immunoglobulin low dose (50 mg).*

3. 2.1. — *Immune response induced by vaccination.*

Primary antibody synthesis was partly inhibited by a low passive immunity. When compared to control animals, antibody production was delayed and weak (100 days post vaccination N.I. = 4). One of the intranasally vaccinated pigs did not develop any antibody production before the virulent challenge.

3. 2.2. — *Immune response to virulent challenge.*

After challenge, a secondary immune response occurred which was rapid and high when compared to control animals : 7 days post challenge N.I. is comprised between 3 and 6 for vaccinated pigs instead of 0.5 for control animals (fig. 3 and table 2). Only vaccinated animals were resistant to virulent challenge.

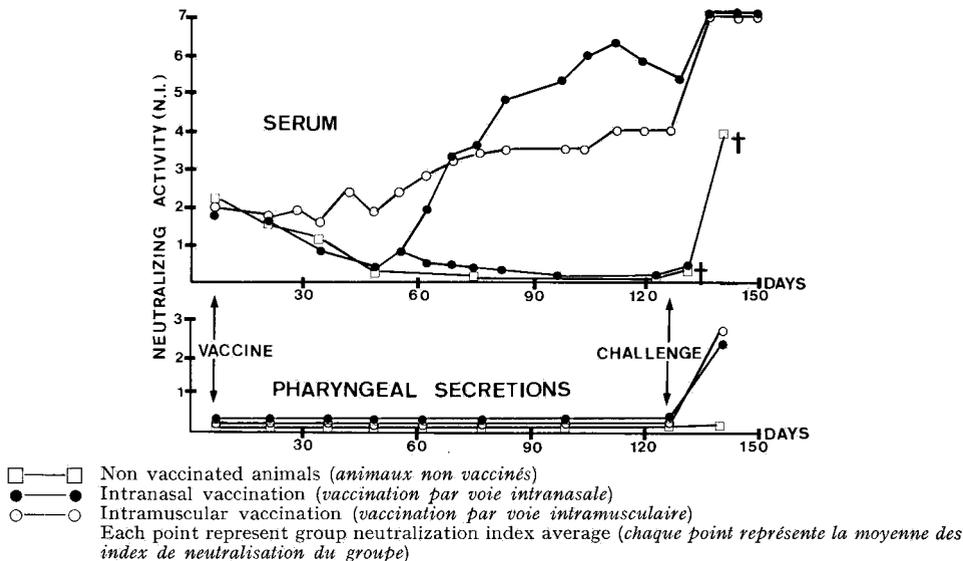


FIG. 3. — Kinetics of neutralizing antibody synthesis following vaccination of pigs injected with 50 mg of anti Swine fever immunoglobulins

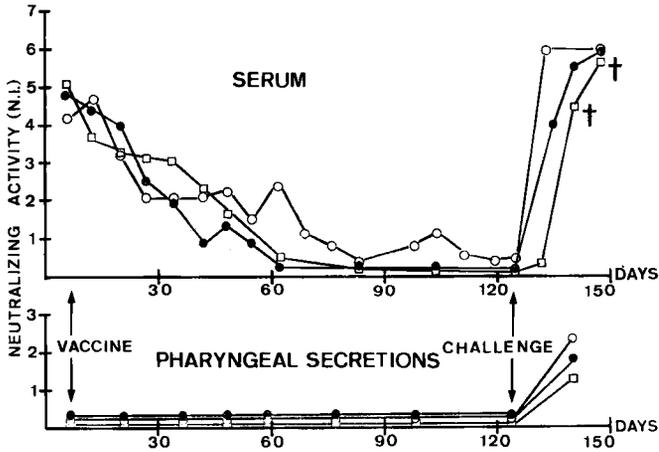
Cinétique d'apparition des anticorps neutralisants après vaccination des porcs ayant reçu 50 mg d'immunoglobulines anti Peste porcine

3. 3. *Humoral immune response of pigs injected with specific immunoglobulin high doses (200 mg and 400 mg).*

3. 3I. — *Immune response induced by vaccination.*

High passive immunity (N.I. = 4.8 and 6.7) apparently suppress all neutralizing antibody production following vaccination. Neutralizing antibody half live are the same (around 12 days) in vaccinated and in control animals (fig. 4 and 5).

No immunoglobulin transudation seemed to occur from the circulatory to the local immune system. Even with 400 mg injection of anti swine fever virus immunoglobulins, no neutralizing activity could be detected in pharyngeal mucus.



□—□ Non vaccinated animals (*animaux non vaccinés*)
 ●—● Intranasal vaccination (*vaccination par voie intranasale*)
 ○—○ Intramuscular vaccination (*vaccination par voie intramusculaire*)
 Each point represent group neutralization index average (*chaque point représente la moyenne des index de neutralisation du groupe*)

FIG. 4. — *Kinetics of neutralizing antibody synthesis following vaccination of pigs injected with 200 mg of anti Swine fever immunoglobulins*
Cinétique d'apparition des anticorps neutralisants après vaccination des porcs ayant reçu 200 mg d'immunoglobulines anti Peste porcine

3. 32. — *Immune response to virulent challenge.*

3. 32I. — *Resistance to virulent challenge.*

Before challenge, traces of passive immunity still remain (average N.I. = 0.5) : 3 of the 4 unvaccinated animals injected with 400 mg of anti-swine fever immunoglobulins resisted to challenge (results not shown). Hence the serum immune response should be studied to identify actively immunized animals.

3. 322. — *Serum neutralizing antibody production.*

In the vaccinated animal group, although no primary antibody synthesis was observed before challenge, priming of the immune system occurred. This priming can be characterized by typical secondary immune response following challenge : average N.I. of resistant vaccinated pigs was 4.4 seven days post challenge, whereas for the control animals the N.I. remained below 0.5 (table 2, fig. 4 and 5).

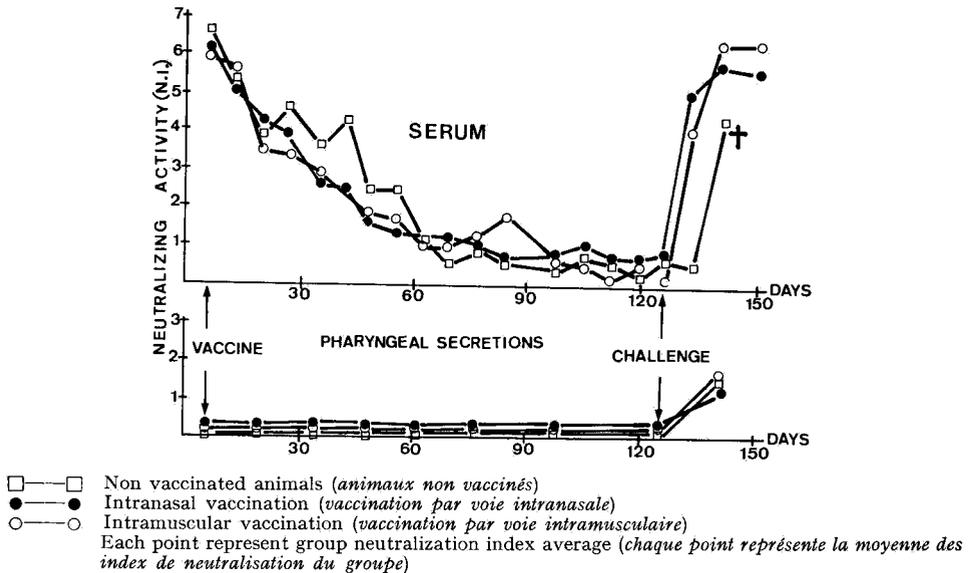


FIG. 5. — Kinetics of neutralizing antibody synthesis following vaccination of pigs injected with 400 mg of anti Swine fever immunoglobulins
Cinétique d'apparition des anticorps neutralisants après vaccination des porcs ayant reçu 400 mg d'immunoglobulines anti Peste porcine

DISCUSSION

I. — Analogies between « artificial » and « natural » passive immunity

According to YABIKI, KASHIWAZAKI and NAMIOKA (1974), the type of immunoglobulin transfer has no influence on passively transferred immunity : subcutaneous injection of immunoglobulin or normal immunoglobulin absorption in colostrum deprived piglets will lead to a passive immunity identical to that normally transferred by the sow. Thus at the serum level, the « artificial passive immunization » provides piglets similar to those normally obtained from an immune sow. However artificially, passively immunized pigs received only IgG instead of a mixture of the three immunoglobulin classes contained in colostrum. But we assumed that, in one month old piglets (see analogy with field experiment), IgA and IgM do not play an important role in an active immunity inhibition mediated by passive antibodies :

1° Serum IgA and IgM catabolism is very high (respectively half lives are equal to 2.6 days and 5 days) when compared to IgG (half life = 14 days) (CURTIS and BOURNE, 1973) ; if vaccination of young piglets is performed when they are one month old (LAUNAIS, CORTHIER, AYNAUD, 1976) :

IgA quantity is 1 p. 1 000 of initial amount and,

IgM quantity is 3 p. 100 of initial amount.

2° At the colostrum and serum levels the quantitative ratio of IgA to IgG and IgM to IgG is very low : approximately 0.1 (CURTIS and BOURNE, 1971).

3° In field conditions, the main interest is to study piglets born from sows vaccinated at least 6 months before parturition (at this moment neutralizing antibody titer is maximum and remain the same during more than 4 years). In such animals, the serum of the sow contains mostly antibodies of the IgG class, and a low level of IgM antibodies. This has been experimentally confirmed in piglets with « natural » passive immunity (COGGINS, 1964) or « artificial » passive immunity (ROUZE, 1974 ; ROUZE, HOUDAYER and METZGER, 1975) ; they established that the half life of both antibody activity and IgG were similar.

Although « artificial » and « natural » passive immunities give similar results in the serum, they differ as far as the intestinal tract's local immunity is concerned. Artificially immunized piglets did not receive any immune milk, and BOHL *et al.* (1972) had shown the important role played by milk IgA in local intestine protection. However in this experiment we assume that such intestinal protection has no influence on swine fever virus vaccination performed intranasally because of the absence of intestinal tract tropism of the virus.

Then, as intestinal local immunity is not concerned, the swine fever virus active immunization can be studied using artificially passively immunized piglets instead of piglets from immune sows. The main advantage of this method is that passive immune intensity can be monitored.

2. — *Influence of passive immunity on active immunization*

a) Intensity of primary response measured in serum depends on the passive immunity level at the time of vaccination :

- low passive immunity (N.I. = 2) partly inhibits the primary response ;
- no primary response occurs when passive immunity is too high (N.I. = 4.8 and 6.7).

These results with a live virus vaccine are in accordance with those previously obtained with an inert antigen (ROUZE, 1974).

b) Although no primary response was observed in the heavily passively immunized group, priming of the immune system occurred. It cannot be tested by resistance to virulent challenge, because at this moment there is a superposition of resistance due to priming and resistance due to passive immunity.

However, if we consider the challenge as a booster, the serum immune response could be used to identify actively immunized animals. Unprimed animals develop a serum primary response : there is no antibody production before the second week, post challenge. Conversely, had a priming occurred, a secondary response would be observed by high antibody production one week following challenge. Using this criterion we can reasonably assert that active immunity had been induced in a large number of passively immunized pigs : 6/8 and 4/5 for animals injected with 200 mg and 400 mg respectively of swine fever specific immunoglobulins.

To conclude, when active anti-swine fever virus vaccination is performed on passively immunized animals, the primary serum response is inhibited, the extent of inhibition is depending on antibody level.

However, a priming of the immune system can occur even in the absence of any detectable serum antibody synthesis following vaccination. The results are in agree-

ment with those obtained with killed or inert antigens in different animal species : guinea pigs (UHR and BAUMANN, 1961) rats, mice (ROWLEY and FITCH, 1964 ; UHR and MOLLER, 1968) and pigs (ROUZE, 1974).

3. — *The influence of vaccination route*

In these experiments with a limited number of animals (48), active immunity was induced irrespective of the vaccination route (intramuscular or intranasal). However, in field conditions, using a large number of passively immunized animals, LAUNAIS and AYNAUD (1975) showed that the intranasal route does not give such good results as the intramuscular route. This situation differs from that observed with rinderpest in bovine (PROVOST and BORREDON, 1972). In this case active immunization of calves from immune cow can be induced by an intranasal vaccination.

The failure of intranasal vaccination route in active immunization of passively protected pigs can be explained in two different ways :

1° Swine fever virus produces septicemia and did not have any mucous tropism.

However, even with a pig respiratory virus (*i. e.* influenza) immunosuppression by colostral antibodies cannot be overcome by intranasal vaccination (RENSHAW, 1975).

2° Immunoglobulin transudation from blood to local system can occur and prevent virus multiplication. Although this passage has been observed in pigs and in lambs during the first hours of life (BRADLEY, BOURNE and BROWN, 1975 ; WELLS *et al.*, 1975) nothing is known yet on immunoglobulin transudation in adult animals. In this experiment, transudation does not seem to have occurred following passive antibody injection. Its intensity is perhaps below the detection level of our technique.

4. — *Analogy with field experiment*

This theoretical study shows that passive immunity suppresses partly, and sometimes completely, the primary response to vaccination. However under our conditions we observed a priming of the immune system. So, criteria which can be applied to detect active immunity induction are :

- primary antibody response if there is one ;
- secondary antibody response after a virulent challenge ;
- resistance to virulent challenge.

Using such criteria, the active immunity induction in piglets born from immune sows has been studied (LAUNAIS and AYNAUD, 1975 ; LAUNAIS, CORTHIER and AYNAUD, 1976) : Immunosuppression is related to serum antibody titer and priming of the immune system occurred (after vaccination) when neutralization index is under 5. This value is slightly different from that obtained in the present experiment (around 6).

In field conditions, with piglets born from sows vaccinated at least one year before parturition, the passive immunity level allowing efficient vaccination is obtained when animals are one month old.

In conditions of artificial or natural passive immunity, works are in progress for studying if it is possible by different ways (double vaccination, adjuvants) to perform efficient vaccinations, leading to priming of immune system, earlier in piglet's life, that is to say when neutralization index is much higher than 6.

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RÉSUMÉ

FIÈVRE PORCINE : INFLUENCE DE L'IMMUNITÉ PASSIVE
SUR LA RÉPONSE IMMUNITAIRE DU PORC OBSERVÉE APRÈS VACCINATION

L'influence de l'immunité passive sur la réponse immunitaire du porc au virus de la Peste porcine a été étudiée. Nous avons utilisé au lieu de porcelets nés de mère immune des porcs (nés de mères non immunes) auxquels on a injecté des quantités variables d'immunoglobulines anti Peste porcine.

Au niveau sérique, l'immunité passive supprime la synthèse primaire d'anticorps normalement observée après vaccination. Cette inhibition peut être partielle ou complète selon la quantité d'anticorps injectée au porc avant la vaccination.

Quelle que soit l'intensité de l'immunité passive, on observe un enregistrement du stimulus antigénique (même en absence de toute synthèse *de novo* d'anticorps). Ce phénomène a été mis en évidence au moyen de l'étude des signes cliniques et du type de réponse immunitaire observée après une injection virulente d'épreuve.

Deux voies de vaccination ont été étudiées : la voie intranasale et la voie intramusculaire.

L'expérience a porté sur 48 animaux et aucune différence significative entre les deux procédés de vaccination n'a pu être établie en ce qui concerne l'efficacité de la protection.

La vaccination par voie intranasale induit une synthèse locale d'anticorps dans les sécrétions bucco pharyngées. Aucune transudation du sérum vers ces sécrétions n'a pu être détectée. Cependant la présence d'anticorps « passifs » dans le sérum inhibe toute synthèse locale d'anticorps après vaccination par voie intranasale des animaux.

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