Harm Voets

Global efficacy and economics of Enterisol® Ileitis; a meta-analysis

Horst Gaumann, Stefan Wesselmann, Frank Gottschalk

Experiences with Enterisol® Ileitis under field circumstances in the North, South and East of Germany

Harm Voets DVM
Boehringer Ingelheim Animal Health GmbH | Ingelheim am Rhein, Germany

Horst Gaumann
Praxis Am Bergweg | Lohne, Germany

Stefan Wesselmann
Tierärztliche Gemeinschaftspraxis Schork & Wesselmann | Wallhausen, Germany

Dr. Frank Gottschalk
Praktizierender Tierarzt | Weimar, Germany
1. Global efficacy and economics of Enterisol® Ileitis; a meta-analysis
Harm Voets

Introduction
Porcine proliferative enteropathy (PPE), also known as ileitis, is an enteric disease of pigs worldwide. The disease is caused by the obligate intracellular micro-organism *Lawsonia intracellularis*. (Lawson and Gebhart, 2000).

A recent diagnostic survey revealed that more than 90% of European pig herds are infected with *Lawsonia intracellularis*, and within these infected herds, 5% to 20% of pigs may be clinically affected (Hardge et al. 2005). Most pigs are infected sub-clinically i.e. without obvious diarrhoea or sudden deaths as is seen in the clinical form of the disease. It is recognised that these sub-clinical infections negatively affect farm economics as a result of poor weight gain and increased body weight variation at slaughter. The economic impact of clinical and sub-clinical forms of the disease is estimated to cost between €1.3 and €18.5 per affected pig depending on the severity and duration of disease (McOrist et al. 1997; Veenhuizen et al. 1998).

Boehringer Ingelheim has developed a vaccine to control PPE in pigs. Data from negative controlled blinded field studies in Denmark, Germany (two studies), Switzerland and The Philippines were collected to investigate the efficacy and economics of Enterisol® Ileitis.

Material and Methods
From five studies spread across the world, data at entry and exit of fattening where collected for a meta-analysis. The studies were conducted to further confirm the efficacy of the oral, modified live vaccine Enterisol® Ileitis in pigs three weeks of age and older. All sows and pigs on the farms are animals of commercial breed. The studies were designed as negative controlled blinded field studies with a standard commercial dose of Enterisol® Ileitis. Conduct of studies was done under typical swine management and housing conditions in Denmark, Germany (two studies), Switzerland and The Philippines.

Description of study sites
Site 1:
In Denmark, the selected herd of animal origin comprises 420 breeding sows. The routine management was a 5 week rhythm in the farrowing unit, with about 800 piglets weaned every 5 weeks. It was a multi-site farm with an all in / all out system in the farrowing unit and the weaning to slaughter unit. In total 646 piglets were included in the study, 335 of the animals received at an age of 4 weeks at the day of weaning Enterisol® Ileitis, whereas the 311 control animals where treated at the same day with a placebo.

The herd had a disease history of Proliferative Enteritis caused by *Lawsonia intracellularis*. Clinically apparent infection was reported to occur when the animals entered the fattening unit and the feed was changed. The positive *Lawsonia intracellularis* status was confirmed by serology (IFAT), immunohistochemistry (IHC) or polymerase chain reaction (PCR) prior to initiation of the study.

Site 2 and 3:
In Germany, two sites where selected. The first site consisted of a commercial single-site sow herd of 6,000 sows. Two weaning units, on two consecutive weeks, were included. From a total of 694 clinical healthy piglets 463 were vaccinated at seven weeks of age (± 5 days) whereas 231 control animals received at the same day a placebo. Although the owner expressed that ileitis was not seen as a problem on his farm, pigs in the middle of fattening demonstrated a strong variance in growth development which is typically for pigs suffering from PPE. Additionally, the presence of *Lawsonia intracellularis* specific antibodies and PCR positive faeces samples obtained from samples taken from different age groups indicated *Lawsonia intracellularis* presence in the pig herd. The second site was a commercial single-site herd of 1,500 sows. A total of 685 pigs were included in this study. Distributed over four week groups 453 animals received the vaccine and 232 received at the same day as vaccination took place a
placebo. A latent ileitis was present on the farm preceding the start of the trial. Detection of *Lawsonia intracellularis* antibodies and positive PCR results from faecal samples led to the conclusion that subclinical ileitis was present at the farm.

**Site 4:**
In the Philippines a commercial farrow-to-finish farm of 2,500 sows vaccinated one week group of 565 pigs at 7 weeks of age, whereas from the same week group 260 pigs in the control group received a placebo at the same day. The farm suffered from both chronic and acute clinical symptoms of ileitis. This was confirmed by autopsy, PCR and ELISA. The profile of the farm demonstrated an increase of positive animals at 12 weeks of age.

**Figure 1.1:** Percentage of positive pigs (%)

**Site 5:**
In Switzerland a single-site herd with 350 sows encountered already for a long time problems with the chronic clinical form of ileitis at 3 weeks after entry of the fattening units. The farm is operated in a 3-week rhythm and distributed over two week groups, 285 pigs where included in the trial. 135 animals received vaccine at 3 weeks of age; 150 animals received a placebo at the same day. The farm is free from PRRS, *Mycoplasma hyopneumoniae*, *Brachyspira hyodysenteriae* and *Brachyspira pilosicoli*. An infection with *Lawsonia intra-

*cellularis* was confirmed by faecal PCR and *Lawsonia* specific antibodies detected by an ELISA. The seroprofile of the farm indicated an onset of infection at entry of the fattening houses.

**Figure 1.2: ELISA PI-Value**

---

**Statistical analysis**
A combined analysis of the animal performance data from all five studies were performed by using analysis of variance procedure with the following General Linear Model (Statistica, version 7.1):

\[ Y_{ijk} = \mu + F_i + V_j + T*V_k + e_{ijk} \]

In this model, \( F_i \) is the effect of the trial farm, \( V_j \) the treatment effect, \( T*V_k \) the interaction between farm and treatment and \( e_{ijk} \) the residual error. The results are presented as Least Square Means (LS Mean) of the five trials included in the meta-analysis.

**Results**
Vaccinated pigs showed a significant better growth than the non-vaccinated controls (Table 1.1). The Average Daily Weight Gain (ADWG) in fattening was increased by +26 g and the total body weight gain by +3.0 kg. In individual trials, differ-
ences in ADWG where seen up to +39 grams. The total weight gain ranged from +1.51 kg to +3.99 kg in the different trials. The average difference in end weight was +3.9 kg (+1.95 kg till +6.0 kg in single trials) between the trial groups. Although there was a significant better feed conversion in some of the trials, the combined results of the meta-analysis did only show numerically better feed conversion in vaccinated pigs. No significant differences where seen between the trial groups on Mortality with a numerically lower mortality in the control group. Here it should be kept in mind that at the time of vaccination 2 of the 5 trials were conducted in sub-clinically infected farms where differences in mortality due to a reduction in clinical signs cannot be expected.

Table 1.1: LS Means of the growth performance in pigs vaccinated with Enterisol® Ileitis versus non-vaccinated controls

<table>
<thead>
<tr>
<th></th>
<th>Vaccination</th>
<th>Control</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs (n)</td>
<td>1952</td>
<td>1184</td>
<td></td>
</tr>
<tr>
<td>ADWG (g)</td>
<td>769&lt;sup&gt;a&lt;/sup&gt;</td>
<td>743&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+26</td>
</tr>
<tr>
<td>Feed conversion (kg/kg)</td>
<td>2.75</td>
<td>2.78</td>
<td>-0.03</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>74.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+3.0</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>5.15</td>
<td>6.33</td>
<td>-1.18</td>
</tr>
<tr>
<td>Start weight (kg)</td>
<td>22.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+0.85</td>
</tr>
<tr>
<td>End weight (kg)</td>
<td>97.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>93.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+3.9</td>
</tr>
<tr>
<td>Slaughter weight (kg)</td>
<td>75.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+3.2</td>
</tr>
</tbody>
</table>

Different letters indicate significant differences between the respective groups (p < 0.01).

An appropriate way to indicate the benefit of a vaccination is by calculation of the Gross Margin which considers the sales at slaughter minus the total direct costs. This meta-analysis demonstrated that vaccinated animals had on average a significant higher gross margin of +4.29 € over the control animals (Table 1.2). This is accountable to the increase in growth and therefore a higher intake of feed with a feed conversion that showed no differences between the groups.

Table 1.2: Economic gross margin in pigs vaccinated with Enterisol® Ileitis versus non-vaccinated controls

<table>
<thead>
<tr>
<th>Economic trait/group</th>
<th>Vaccination</th>
<th>Control</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial returns:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sales (slaughterhouse) (€/pig)</td>
<td>102.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+6.07</td>
</tr>
<tr>
<td>Costs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piglets (€/pig)</td>
<td>43.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>42.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.89</td>
</tr>
<tr>
<td>Feed (€/pig)</td>
<td>35.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-1.16</td>
</tr>
<tr>
<td>Mortality (€/pig)</td>
<td>2.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+0.28</td>
</tr>
<tr>
<td>Costs (€/pig)</td>
<td>80.80&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-1.77</td>
</tr>
<tr>
<td>Gross margin (€/pig)</td>
<td>21.49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17.20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+4.29</td>
</tr>
</tbody>
</table>

Different letters indicate significant differences between the respective groups (p < 0.01).

Assumptions: € 1.40 per kg slaughtered weight; carcase grading grid for all 5 trials adapted to 80% inclusion of slaughter weights in optimal weight window; € 17.50 per ton feed; 2.80 kg/kg feed conversion for the Swiss, German trial No. 1 and Philippine trial whereas for German trial No. 2 and the Danish trial actual feed conversion was used.

Conclusion

This combined analysis of data from five vaccination trials shows clearly that vaccination with Enterisol® Ileitis is profitable. On average pigs have an increased ADWG of +26 gram and a higher Slaughter Weight of +3.2 kg. The higher biological performance of vaccinated pigs is the basis of the higher Gross Margin of vaccinated pigs (+4.29 €) compared to the control. The resulting Return of Investment can be as high as 2.5:1 to 3.3:1 depending on farm specific cost to price relationships.

The consistent efficacy of Enterisol® Ileitis in farms from different parts of Europe and from Asia confirmed that Lawsonia is a global cause of economic losses in the pig industry and that vaccination is effective against isolates from different origin. This has recently been confirmed by a laboratory study of Kroll et al. (2004).

In summary, vaccination can prevent losses due to a Lawsonia intracellularis infection and makes producing pigs a profitable enterprise.
2.a Experiences with Enterisol® Ileitis under field circumstances in the North of Germany

Horst Gaumann

“Prevention is better than treatment” is a basic rule that more and more reaches into the economical boundaries of farm management in the light of new vaccine development. A uniform and complete vaccine concept for all farms is due to the costs, which have an impact on the production results, not feasible anymore. Therefore, in the face of this economical pressure on all our clients, a good insight and evaluation in these matters is often more important than finding the optimal medical solution for the problems these farmers are facing. Moreover, we should ask our selves at any point in time and on any problem whether an improvement in management, an antibiotic therapy and metaphylaxis or a vaccine prophylaxis is the best suiting solution to generate the best economical results for these farms.

Taking all of this in mind, we where very cautiously in vaccinating herds with Enterisol® Ileitis. This is partially, because it is not easy to access losses due to subclinical ileitis and partially because Tylosin is available at a low price for therapy and metaphylaxis.

Enterisol® Ileitis was used in three farrow-to-finish farms under close observation.

On all the farms that where selected for vaccination, massive clinical problems with *Lawsonia intracellularis* in the finishing units and partially at the end of the flatdeck where present despite the fact that all of them where using Tylosinphosphate (*Klatolan feed*) for three weeks or more. On one farm clinical problems remained despite the use of Tylosinphosphate at 200 ppm.

The timing of vaccination was in all three farms in the first week after weaning. The piglets where vaccinated 3 to 4 days after weaning. Metaphylaxis with antibiotics for E.Coli and Streptococcus Suis was started at day 8 after weaning. In some other farms that started to vaccinate, vaccination was carried out in the second week after weaning, to ensure that a metaphylaxis with antibiotics against E.Coli was performed and a three day antibiotic-free-window was guaranteed before vaccination.

The selection for the method of vaccine application was dependent on safety issued by the applicant and the technical prerequisites of the farm.

The vaccination was performed by the veterinarians by drench (1 farm) and by through (2 farms). The easiest and nonetheless most reliable methode seems to be the through application. On most farms, bowls are present to initiate feed-uptake after weaning and are often used due to the positive impact on feed-intake. If the piglets are fed from weaning onwards with tasty pre-starters or milk containing wet-feed, a problem-free uptake of the vaccine by all the animals takes place within one hour. The best way to control this is a 1:1 ratio of animals and feeding places. The application through a proportioner is up to now not performed by our veterinary practice due to fear for residues which can harm the vaccine and troublesome means of control over correct uptake of the vaccine.

Undesirable effects related to the vaccination where not seen on any of the three test farms. Diarrhoea due to E. Coli was seen in one other farm where the metaphylaxis with antibiotics was halted. The timing of vaccination was therefore changed to a later point in time.

The efficacy of the vaccination was very good in all three farms. Therapeutic use of antibiotics for the prevention of diarrhoea was ceased completely in the finishing units of all three farms. This is something that should be extrapolated carefully to other farms which start to vaccinate with Enterisol® Ileitis, to prevent over-expectation of the vaccine considering the ability to reduce antibiotics. At the same time the groups showed a reduction in variability and the total days of fattening where reduced.

An unexpected side-effect was the statement of all the farm managers that the animals where more “stabile”. This was demonstrated by the fact that reduction in total costs for
antibiotics was much higher than expected based on the absence of PIA-therapy.

The number of respiratory diseased animals went down. Therefore, the impact of the gut on the total body and its immune system should be taken more into consideration, and should be better analysed and quantified.

Summary
Based on our experiences up to now with the ileitis-vaccine we can conclude that:

- The vaccine creates an effective immunity against the clinical form of ileitis (PIA)
- The vaccine improves the production, even when compared to antibiotics in clinical ileitis
- The vaccine showed no undesirable effects
- Animals that have been vaccinated seem to have fewer problems with other diseases (especially respiratory diseases) whereas the overall antibiotic usage has dropped

To find out whether the use of the vaccine is profitable in incidental cases or subclinical ileitis is something for the future that needs more investigation.

In any case, the use of Enterisol® Ileitis on farms with endemic clinical PIA showed that prevention is better than treatment – this is also true for the benefit of the farmer.

2.b Experiences with Enterisol® Ileitis under field circumstances in the South of Germany
Stefan Wesselmann

We have started to vaccinate with Enterisol® Ileitis on some of our customer’s farms in December 2004, after Boehringer Ingelheim launched the product for the German market. Extensive diagnostic investigations where performed on these farms before vaccination took place.

The results was that on all of the selected farms, which are between 100 and 270 sows in size, *Lawsonia intracellularis* was repeatedly detected by PCR from faecal samples and from organ samples after necropsy and through serology. The clinical symptoms of ileitis where mainly present in nursery animals of seven to eight weeks of age. Typical signs where wasting, runt- ing, pale animals with grey-black diarrhoea resulting in a high mortality rate. The losses due to mortality in the nursery varied between five and twelve percent. Furthermore, other causes of these clinical symptoms where investigated and among which PRRS, PCV2 and Haemophilus parasuis where detected.

The percentage of diseased animals and incidence of clinical symptoms dropped soon after we have started to vaccinate with Enterisol® Ileitis in these farms, whereas mortality decreased massive to only one to two percent.

The animals in the nursery demonstrate beside the reduction of clinical symptoms a better uniformity than ever before which leads to clearly visible improvement of the results in the finishing barns.

2.c Experiences with Enterisol® Ileitis under field circumstances in the East of Germany
Frank Gottschalk

A cooperation of farmers that operates a multiplier unit consisting of 1,600 sows and a finishing unit with 12,000 finishing places, suffered from frequent problems with diarrhoea in the last third part of finishing during the year 2004. As much as 80% of all animals suffered from enteritis, a percentage which even increased at the time of sorting the first animals out for slaughter.

Serology from growers and finishers performed at the “Landeslabor Neumünster”, and faecal sample investigations done at the “Justus-Liebig-Universität Gießen” (Prof. Baljer), confirmed the overall presence of *Lawsonia intracellularis* and incidental *Brachyspira pilosicoli*. Salmonellosis, E.Coli infections and Swine Dysentery where ruled out as causative...
of the diarrhoea problems. Taken the clinical symptoms into consideration combined with the laboratory results, a diagnosis was made definite for PPE/PIA. It should be noticed that the acute form of ileitis (PHE) was of no real concern, which can explain why no changes in mortality rate where seen between 2003 and 2005.

Treatments targeted for ileitis in the affected groups of finishing pigs at the time of onset of symptoms has led to various results. Neither the prophylactic „Danish Model“ at entry of the finishing units (CTC plus Lincospectin), nor Tylan orally administered and dosed at various levels and at various points in time, neither Tylosin injections in individual animals could overall satisfy the farmers.

In December 2004 Enterisol® Ileitis was introduced into the sow herd, vaccinating piglets at 22 days of age. The vaccine was administered to the animals in a four hour time frame thru a proportioner, whereas in this time frame 100 liter water was easily and completely taken-up by 500 piglets weighing on average 6 to 8 kg.

Up to the 30th of August 2005, 25,500 piglets where vaccinated of whom 12,500 animals entered the adjacent finishing units and 4,800 of these animals are at this moment in the critical phase of finishing in which normally PIA would appear (80 – 110 kg). About 5,000 animals, vaccinated with Enterisol® Ileitis have already been slaughtered.

Table 2.1: Results after vaccination with Enterisol® Ileitis in 2005 versus antibiotic prophylaxis against ileitis in 2004

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy</td>
<td>No ileitis problems</td>
<td>Antibiotics</td>
<td>Enterisol® Ileitis</td>
</tr>
<tr>
<td>Animals included (n)</td>
<td>±4800</td>
<td>±4650</td>
<td>±5000</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>2.8</td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td>ADWG (g/d)</td>
<td>745</td>
<td>689</td>
<td>748</td>
</tr>
<tr>
<td>Fattening days (d)</td>
<td>124</td>
<td>127</td>
<td>124</td>
</tr>
<tr>
<td>Cull animals (%)</td>
<td>ca. 15</td>
<td>ca. 24</td>
<td>ca. 10</td>
</tr>
<tr>
<td>Morbidity (%)</td>
<td>≈ 0</td>
<td>80 – 90</td>
<td>≈ 0</td>
</tr>
</tbody>
</table>

Summary

Based on clinical evaluation in the finishing units and on the production data, the following statements can be made towards the effect of vaccination:

1) Since the introduction of Enterisol® Ileitis on these farms diarrhoea and PIA related enteritis is seen only in rare, mild and individual cases.

2) An increase in uniformity in weight improvement within the finishing groups is seen, and slaughter weight variability is significantly reduced within and amongst the groups.

3) The decrease in Average Daily Weight Gain to 689 g/day in 2004 due to the ileitis problems was fully recovered to an ADWG of 748 g/day in the vaccinated animals. (ADWG in 2003 was 745 g/day).

4) The number of fattening days until slaughter was reduced from 127 days to 124 days.

References


