FIRST OUT TO BAN FEED ADDITIVES IN 1986 VETERINARY CHALLENGES WITHIN SWEDISH PIG PRODUCTION. PART I: USE OF ANTIMICROBIALS AND RESPIRATORY DISEASES

Final Report
APL Project 2012/2413

July 2013

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SUMMARY

The Swedish pig industry today comprises 130,000 sows and rear 3 million pigs to market weight. Being surrounded by water and employing a restricted import of animals, the health status is favourable.
A ban of so called growth promoters (*i.e.* low dose antibiotics in the feed by routine) was effectuated 1986. Use of antibiotics in therapeutic doses to diseased animals has never been prohibited, but large scale medications shall be preceded by a proper diagnose and a written disease preventing strategy including a last date for the in feed-medication. A doubled incidence of post weaning diarrhoeas and severe problems with swine dysentery followed the ban. Also other diseases were at hand and the mean age at 25 kg body weight was increased with one week at a national level.
Obviously disease preventing measures were mandatory. Today the main part of the pig production takes place in age segregated systems from birth to slaughter, and the productivity is well above that prior to 1986. The antibiotics used in veterinary medicine have degreased with 60 % since the ban and antimicrobial resistance among microbes is uncommon.
This manuscript focus on the use of antibiotics and on efforts made to prevent respiratory diseases

INTRODUCTION

The Swedish pig industry today comprises approximately 130,000 sows and around 3 million pigs are reared annually to market weight. The Swedish pig population has a favourable health status. Sweden is free from all diseases listed by the Office International des Epizooties (OIE), including Aujeszky's disease (AD) and porcine reproductive and respiratory syndrome (PRRS), as well as from porcine endemic diarrhoea (PED) and transmissible gastro-enteritis (TGE). AD was diagnosed in 1963 and eradicated from Sweden in 1996 (Robertsson 1996). PRRS was diagnosed for the first time in 2007 and eradicated the same year (Wallgren et al., 2008). Three individual different incidents have influenced the strategies of veterinary medicine in Sweden significantly.

1) In 1953, 9,000 persons were affected by *Salmonella* emanating from an abattoir, and 90 of these individuals died. Despite that no regulations were written until the 1960ies this actually was the start of the Swedish Salmonella control program, and both Norway and Finland followed Sweden in this work. Today, *Salmonella* is generally diagnosed in less than 5 pig herds per year, but the battle is not yet won and a feed related exposure of *Salmonella cubana* to 77 herds in 2003 out of which 48 became infected is a good reminder of that (Österberg et al, 2006).

2) In 1986, Sweden was the first country to effectuate a ban for growth promoters (low dose antibiotics in feed). During the subsequent years intestinal health problems of recently weaned piglets increased (Robertsson and Lundeheim, 1994), which necessitated improvements in the rearing systems of the Swedish pig herds. Consequently, over 90% of the Swedish pigs are today reared in batch systems based on age-segregation from birth to slaughter (Holmgren and Lundeheim, 2002).

3) In 1986, it became prohibited to include dead carcases in the meat-and-bone-meal production for ethical reasons. The issue was not raised by the veterinarians, but by journalists. Quite soon thereafter meat-and-bone-meal was excluded from the feed to strictly vegetarians, *i.e.* to ruminants. With time these decisions had a great impact on the strategies of the Swedish veterinary medicine, since it remained able to focus on other things than BSE.

A GENERAL COMMENT ON THE USE OF ANTIMICROBIALS

The ban of the feed additives (in pigs mainly 55 ppm olaquindox or 50 ppm carbadox) in itself reduced the use of antimicrobials, but not as much as expected since therapeutic use of such drugs never have been prohibited, and a therapeutic use of *e.g.* olaquindox included 165 ppm in medicated feed. By monitoring prescriptions of in feed medications a regional imbalance was discovered and the Swedish Veterinary Society rather rapidly preferred to publish a policy document on how to carry out in feed medications, which included the necessity to make a laboratory diagnose and to make a written plan on how to combat the actual disease which should include a time point for terminating the in-feed medication (Holmgren el al., 1990).

The overall use of antimicrobials has decreased with 60% since the ban was effectuated even when sales figures are corrected for changes in animal numbers over time (Figures 1), and as seen in the Figure 2 this decrease has mainly been achieved by a decreased use of medications via feed and water (SWEDRES-SVARM 2012).

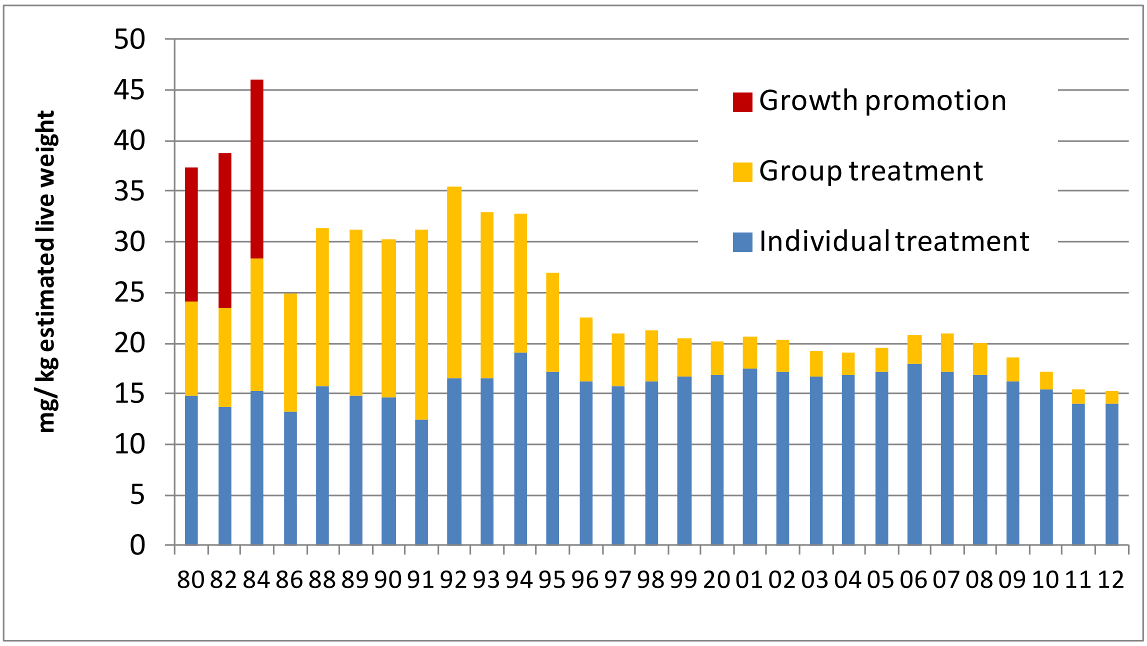

Figure 1. Sales of antimicrobials for animals 1980-2012 expressed as mg/kg estimated liveweight. (Source: SWEDRES-SVARM 2012, www.sva.se).

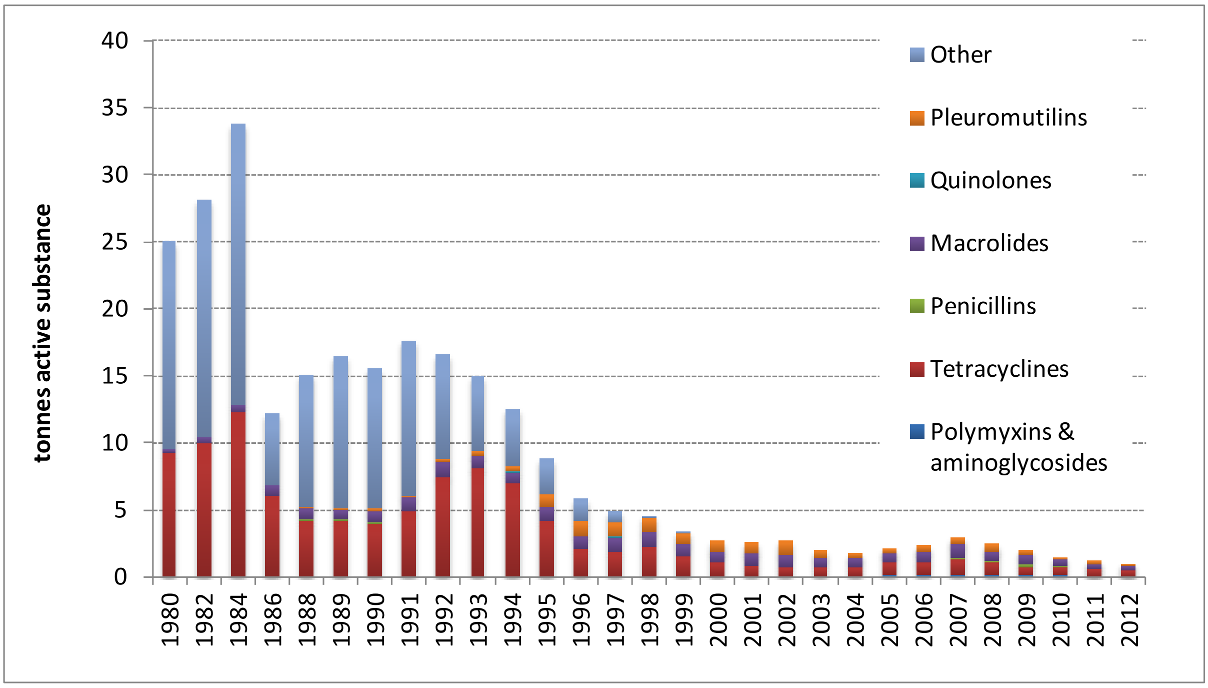

Figure 2. Sales of veterinary antimicrobials for in feed or water medication and of antimicrobial feed additives expressed as tones active substance. Substances grouped as 'others' are the feed additives and other substances that are no longer available on the market (e.g. nitroimidazoles) (Soure: SWEDRES SVARM 2012, www.sva.se).

The low consumption of antimicrobials is companioned with a very favourable situation regarding antimicrobial resistance (SWEDRES-SVARM 2012). In the winter 2011-2012, all nucleus and multiplying herds tested for presence of MRSA. In total, 4,734 pigs in 53 herds were tested and MRSA was not detected in any herd (Ericsson Unnerstad et al., 2012; Table 1).

Table 1. MRSA samplings carried out in Swedish nucleus and multiplying herds in the winter 2011-2012 (Data from Ericsson Unnerstad et al., 2012)

	Individual herds				TOTAL
Herds	1	1	50	1	**53**
Pens per herd	8	14	15	17	**789**
Pigs per herd	48	84	90	102	**4734**
MRSA-pos samples	0	0	0	0	**0**

There has been one cloud on this heaven. In 1992 oxide (ZnO) was introduced to prevent detection of post weaning diarrhoeas, which it also did. Soon an excessive use of ZnO was at hand, which not was favourable for Sweden as a nation since Sweden at that time as a new member of EU fought for keeping the ban of feed additives and the approach to animal feed was "harmonised" within EU. Sweden was correctly blamed for using ZnO instead of low dose antibiotics. Consequently ZnO was only allowed to mix into feed on veterinary prescription and the recommendations of the Swedish Veterinary Society regarding in feed medications were again published and complemented with a recommended use of 2,500 ppm ZnO for a maximal period of 14 days from weaning and restricted to herds with intestinal problems following weaning. By 1998, the use of ZnO decreased to a level corresponding to a treatment incidence for post weaning diarrhoea of 9% - a realistic figure (Odensvik et al., 1999).

RESPIRATORY DISEASES

When the pig production became industrialised, respiratory diseases rapidly became an important issue, as well in Sweden as elsewhere. Sweden was assumed to have exported atrophic rhinitis to both Norway (Braend and Flata, 1954) and United Kingdom (Anonymous, 1954) in the 1950ies, and indeed, the Swedish Animal Health Service was actually established in 1969 with the aim to control respiratory disorders among growers sold from piglet producers to fattening enterprises.

Mycoplasma hyopneumoniae

The late 80ies not only included the ban of low dose antibiotics, it also included the introduction of relevant diagnostic tools to monitor the respiratory disease complex from an epidemiologic perspective. *Mycoplasma hyopneumoniae* appears to be one of the globally most important infections in pigs, infecting practically every pig but in itself killing very few. Still, as *Mycoplasma hyopneumoniae* is calculated to reduce the weight gain with 5% in both Denmark and Sweden based on lost productivity following reinfection with *Mycoplasma hyopneumoniae* solely. The large spread makes the economical impact of this infection significant.

By serology it was concluded that about 100 % percent of the Swedish pigs had antibodies to *Mycoplasma hyopneumoniae* when they reached market weight, despite that "only" 10-15 % of the pigs were registered of having pneumonia at slaughter (Wallgren et al., 1993). As the lesions had to be active and of a certain magnitude to be registered, this discrepancy was explained by the fact that an infection with *Mycoplasma hyopneumoniae* will heal within approximately 10 weeks from seroconversion (Wallgren et al., 1994a). However, if pigs are secondarily infected with e.g. *Pasteurella multocida* the infections will remain active longer and contribute to further animal ill-thrift as well as to economical losses (Figure 3).

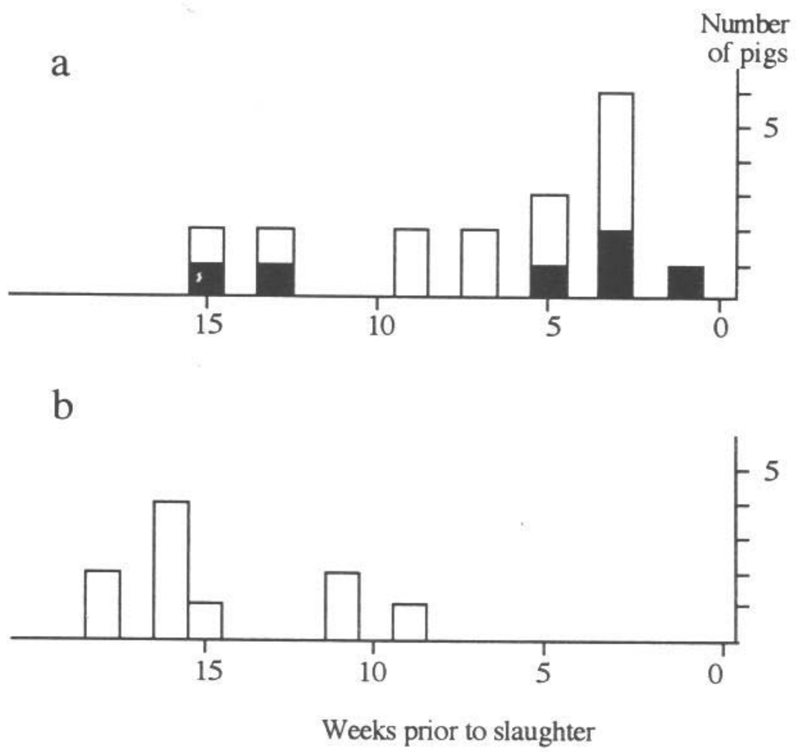

Figure 3. The time point for seroconversion to *Mycoplasma hyopneumoniae* in relation to time for slaughter among 28 pigs. Serum antibodies to *Mycoplasma hyopneumoniae* were detected every fortnight during the entire rearing period. These pigs had ongoing (a) or healed (b) pneumonic lesions at slaughter. Black areas represent pigs with pneumonic lesions also recorded by the official registration. (Data from Wallgren et al., 1994a).

In the late 80ies, fattening enterprises had since long employed batch wise rearing, but piglet producers generally were small at this time and effectuated continuous production systems. Consequently, piglets from many producers were mixed at allocation to fattening enterprises resulting in a heavy mix of viral infections monitored as presence of interferon in serum during the first week after arrival, simultaneously as the immune response of the pigs were decreased due to the stressors induced by the allocation and regrouping (Artursson et al 1989, Wallgren et al., 1993). Since pigs seropositive to and shedding *Mycoplasma hyopneumoniae* always were present at these allocations all growers became exposed to the microbe before reaching market weight (Wallgren et al., 1993).

As the piglet producers became bigger, the ban of regular low-dose antibiotics forced them to introduce age segregated rearing systems. Thereby, the growers generally have been seronegative to *Mycoplasma hyopneumoniae* at allocation since the late 90ies, and many producers now manage to rear pigs to market weight before seroconversion to the slow growing and thereby slow spreading *Mycoplasma hyopneumoniae* take place. Recordings at slaughter of swine enzootic pneumonia (SEP) have decreased to well below 3% (Holmgren and Lundeheim, 2002), reflecting the comparably low load of *Mycoplasma hyopneumoniae* (Figure 4)

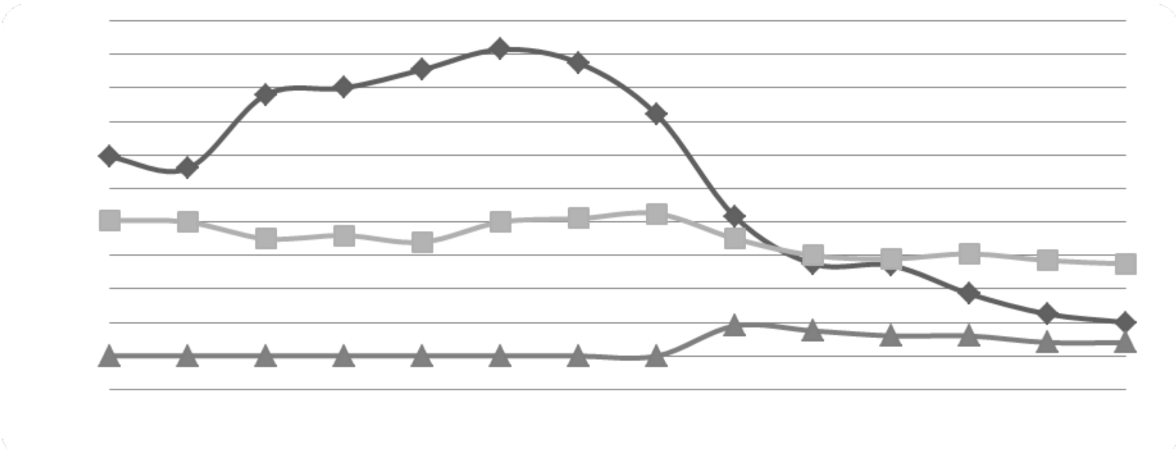

Figure 4. National mean of registrations (%) of pathological lesions in the respiratory tract in Swedish pigs at slaughter. Diamonds represents SEP-like lesions, Triangles represents *Actinobacillus*-like lesions and squares represent pleurits (Data from Holmgren and Lundeheim, 2002).

Thus, when vaccines against *Mycoplasma hyopneumoniae* were introduced, the interest for such vaccinations was limited as batch wise rearing from birth to slaughter generally was performed. However, nucleus and multiplying herds in this matter represented another category of herds since they sold pigs aged 6-10 months to other herds instead of slaughtering them. The slow growing *Mycoplasma hyopneumoniae* risked to become clinically evident just as their pigs were to be merchandised. Consequently strategies to vaccinate growing pigs in these herds were immediately designed aiming to prevent merchandise of contagious breeding stock. These strategies included one single vaccination as late as possible prior to seroconversion to *Mycoplasma hyopneumoniae* aiming to vaccinate as immunologically mature pigs as possible. The "natural infection" then induced a serological response, and was utilizsed as a booster vaccination (Wallgren et al., 1998 and 2000). As vaccinations will decrease the pathogen load of *Mycoplasma hyopneumoniae*, many of these herds have with time also decided to give a booster vaccination prior to merchandise of sexually mature animals with the aim of reducing the risk to deliver contagious animals.

Before Mycoplasma vaccines were available, one way to handle herds that merchandised contagious breeding stock had been to effectuate a strict batch wise production to a certain age and then deliberately mix the pigs with older pigs infected by *Mycoplasma hyopneumoniae* (Wallgren and Schwan, 1994d). This strategy rendered it possible to sell barrows at the age of 10-12 weeks to fattening enterprices and prospective gilts at 14-15 weeks of age as seronegative and non-contagious animals. At the age of 16 weeks, the age segregation was deliberately broken and gilts were mixed with older animals. They became diseased with SEP and were not allowed to be merchandised as unmated gilts at an age of 6-7 months. At that time they were seropositive to *Mycoplasma hyopneumoniae*, but risked to still be contagious. Instead the gilts were mated and sold as pregnant gilts at an age of 10 months. At that time, 26 weeks had passed since they were exposed to *Mycoplasma hyopneumoniae* and the animals have had recovered from the disease (Wallgren et al., 1994a). They were seropositive, non-contagious and immune with respect to SEP and therefore well suited to be sold to other herds that all harboured *Mycoplasma hyopneumoniae* (Table 2).

Table 2. *Mycoplasma hyopneumoniae*-status of pigs at different ages in a multiplying herd deliberately braking the age segregated rearing system as the pigs were aged 16 weeks (Data from Wallgren and Schwan 1994)

Category	**Age**	**Clinic**	**Serology**	**Contagious**	**Merchandise**
10-12 weeks	10-12 weeks	Healthy	---	No	Yes
Prospective gilts	15 weeks	Healthy	---	No	Yes
Mature gilts	**26 weeks**	**Coughing**	**+++**	**Yes**	**No**
Pregnant gilts	40 weeks	Healthy	+++	No	Yes

Actinobacillus pleuropneumoniae

In Sweden, problems with Actinobacillosis have mainly been associated to *Actinobacillus pleuropneumoniae* serotype 2 (Wallgren et al., 2003a). Increased frequencies of pleuritis at slaughter associated to this bacteria has preferable been made in farrow to finish herds with continuous production systems, whereas no correlations between *Actinobacillus pleuropneumoniae* and pleuritis at slaughter have been at hand in fattening herds employing batch wise production (Wallgren et al., 1993). In such herds, the low prevalevences of pleuritis have instead been linked to an early seroconversion to *Mycoplasma hyopneumoniae* (sic!), probably reflecting an influence of secondary invaders such as *Pasteurella multocida* (Holmgren et al., 1999). Also the influence of *Actinobacillus pleuropneumoniae* decreased following the more prompt effectuation of age segregated rearing from birth to slaughter (Holmgren and Lundeheim, 2002; Figure 4).

Despite the clear connection to serotype 2, *Actinobacillus pleuropneumoniae* serotype 5 was isolated from acute (lethal) cases of actinobacillosis in 1999 (Wallgren et al., 2003c). This strain turned out to be atypical and ELISA systems based on the reference strains of serotype 5a and 5b failed to detect antibodies in serum of pigs from the affected herds, leaving no tools available to monitor an eventual spread of the disease. Later, an ELISA-method based on the field isolate of the atypical strain of serotype 5 strain was developed and revealed that the strain had failed to spread despite trade of breeding animals from the affected herds. The conclusion was that this assumed mutation of *Actinobacillus pleuropneumoniae* was highly pathogenic to pigs but luckily also a poor survivor in itself. (Wallgren et al., 2003b). However, in 2007 an atypical variant of serotype 5 was again diagnosed. Again, the ELISA system developed in 2002 managed to detect antibodies to this strain, and by fingerprinting it was concluded that this isolate was identical to the strain isolated in 1999 (Aspàn and Wallgren, 2008).

Despite thought to be under control, *Actinobacillus pleuropneumoniae* at present appears to be re-emerging as a microbe of high significance. Both chronic infections mirrored as pleuritis at slaughter and outbreaks of acute diseases with occasionally high mortality figures are presently increasing in frequency. As fingerprinting has proven that it is the same clones of the microbe that are active today as in the 1970ies (Aspàn and Wallgren, 2008), the steadily increasing herd sizes are suggested to be responsible for this development as also indicated by clinical data. The disease appears to be conserved in herds with more than one unit despite batch wise rearing strategies within each unit. In contrast, affected fattening herds with only one unit that empty themselves completely between batches generally experience no disturbances during the consecutive rearing batch (data not shown).

During the 1990ies a great focus had been attended to *Actinobacillus pleuropneumoniae* and to medical treatment (Wallgren et al., 1999a and b) and to the primary immune responses to the microbe (Wattrang et al., 1998; Fossum et al., 1998; Johansson et al., 2001). As problems related to *Actinobacillus pleuropenumoniae* again have increased during the recent years, this work has been reactivated. Again treatment strategies are scrutinised, but the work now also focus on immune response and resistance to development of disease at repeated exponations to the microbe (Sjölund et al., 2009 and 2011a). In this context, also the concluded relative low protection of vaccinations towards the microbe is documented, and the efficacy of intensified vaccination strategies have been monitored (Sjölund and Wallgren, 2010). Despite the poor protection of vaccines, pigs delivered by dams with high levels of serum antibodies to *Actinobacillus pleuropneumoniae* appeared to be slightly better protected from disease than pigs delivered by dams with low levels of serum antibodies to *Actinobacillus pleuropneumoniae*.(Sjölund et al., 2011b).

Pasteurella multocida

Herd sizes are continuously increasing, which may facilitate for secondary invaders to affect pigs, By developing in-house ELISA systems detecting antibodies to *Pasteurella multocida*, the influence of secondary invaders have been scrutinised in herds with respiratory disease problems and concluded to be of high relevance. However, as *Pasteurella multocida* is an ubiquitarious microbe these studies have to be performed under extreme control. Specific animals are followed by sequential blood samples and at each sampling occasion the antibody level of primary and secondary invaders are compared to the level obtained at the previous sampling occasion (Wallgren et al., 2004). By employing this diagnostic tool, high prevalences of pleuritis have also been demonstrated in herds with low levels of antibodies to *Actinobacillus pleuropneumoniae* (Wallgren et al., 2012).

Apart from being associated to secondarily infected pneumonias, toxin producing strains of *Pasteurella multocida* also is the causative agent of proliferative atrophic rhinitis (PAR; De Jong et al., 1980). The development of ELISA systems detecting the *Pasteurella multocida* toxin (PMT) in nostril samples by DAKO (Copenhagen, Denmark) were clinically evaluated in Sweden (Mattsson and Söderlind, 1990; Matsson et al., 1992). This tool made it possible to view the disease from a herd perspective and to conclude that the pathogen load was highest among older growers, and that it decreased with ageing of the animals (Wallgren et al., 1994b). PMT was demonstrated intermittently in the nostrils of sows in affected herds, and the new method made it possible to identify and remove the few chronically infected sows that were present in each herd and that preserved the disease at herd level. Combined with a batch wise rearing from birth, the establishing of freedom from PMT-carrying animals was possible (Wallgren et al., 1994c). Since 1995 nucleus and multiplying herds are controlled at an annual basis and defined free from PMT-colonisation in the nostrils (Wierup and Wallgren, 2000).

Aujeszky's Disease (AD)

Apart from causing other severe signs of disease, AD may also contribute to severe problems with pneumonias in fatteners. This disease was first diagnosed in Sweden in 1963 (Estola et al., 1963). The first herd was stamped out, and so was the second. However, as new but few cases continuously were identified this strategy was discarded with time. In the early 90ies AD had totally been diagnosed in 100 herds and the figure was steadily increasing. Therefore, a national control program was established and AD was finally eradicated in 1997 (Robertsson, 1996)

Porcine Reproduction and Respiratory Syndrome (PRRS)

Also PRRS is associated to severe pneumonias in growing pigs. PRRS never reached the Scandinavian Peninsula when the European continent was contaminated with a mysterious new disease in the early 90ies. When the causative agent was identified as PRRSV and diagnostic tools became available, screenings for presence of PRRS were immediately initiated and a control program was designed. This control program has been running officially since 1995.

On Thursday the 6th of July in 2007, 16 out of 20 serum collected from a herd within that program were seropositive to PRRS. Measures were immediately undertaken and totally seven herds located into two clusters were identified within 10 days (Figure 5). Measures undertaken in infected herds included stamping out, cleaning, disinfection and a vacancy period of three weeks before repopulation. Still, the follow up-samplings of herds at risk and contacts lasted for almost two months, and confirmation of freedom another four. To confirm freedom from PRRS, serum was collected at abattoirs in the autumn of 2007. In total, almost 16,739 samples were tested negative for PRRS, representing 833 herds and covering over 90% of the production (Wallgren et al., 2008).

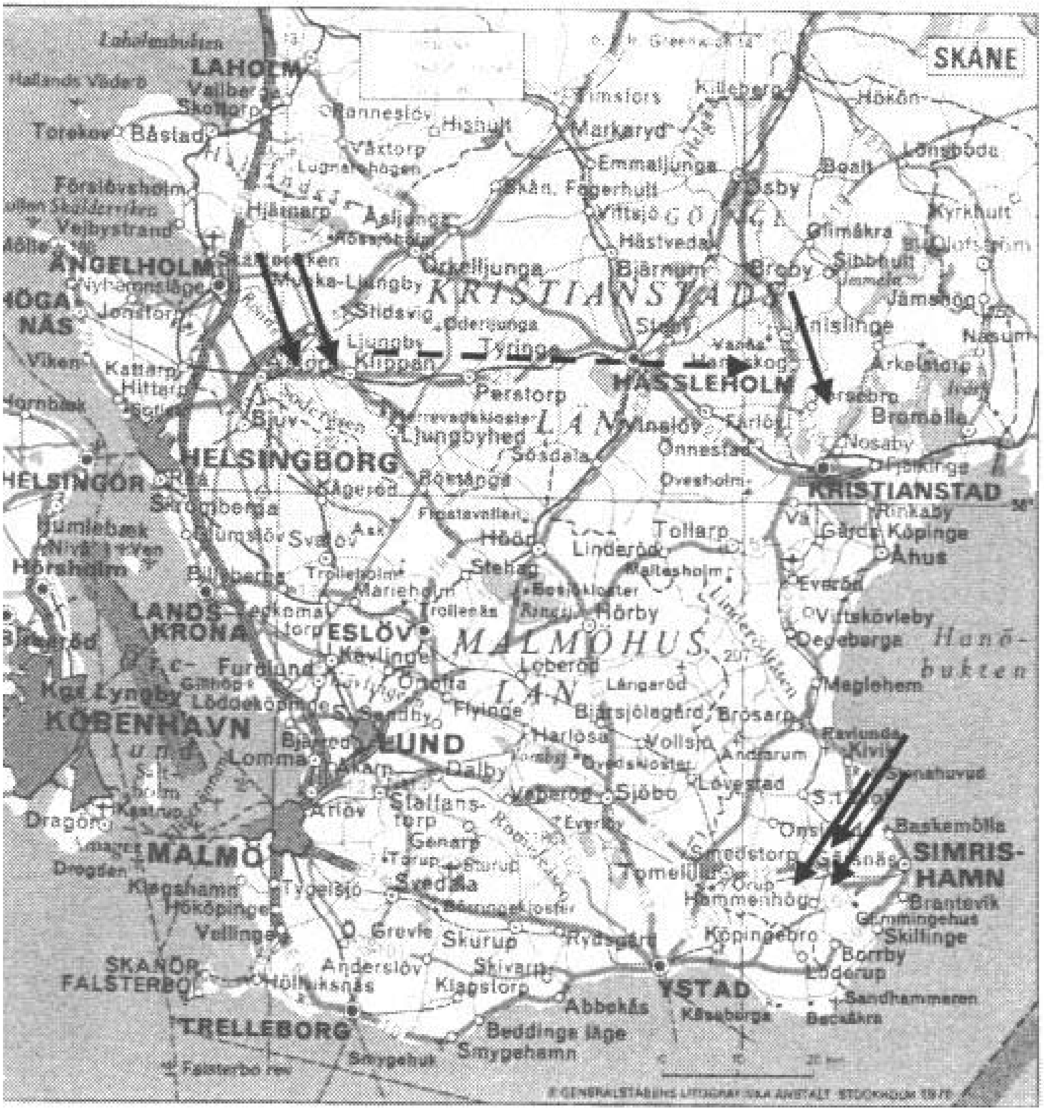

Figure 5. The geographic location of the six herds diagnosed for PRRS and located to two clusters in southern Sweden during the summer 2007 (Data from Wallgren et al., 2008).

During this work, the continuous control of the boar stations since 1995 was extremely valuable because over 95% of the matings ar made by AI. Also the immediate mobilisation was highly beneficial in preventing spread of PRRS. Concurring earlier observations PRRSV was concluded to easily be spread to new herds at direct and indirect contacts (Dee et al., 2002 and 2003), but apparently not by the wind (Trincado et al., 2004).

The source of the outbreak remains unknown. Nucleic acid from the PRRS virus was demonstrated from five of the infected herds and subsequent sequencing has been carried out from 15 different isolates (ORF 5, approx 500 bp). A pattern of two clusters has been identified which corresponds to the clusters mentioned above. Differences between the Swedish isolates were found in twelve positions, whereas the four sequences from the Gene Bank that was closest to the Swedish isolates differed at 39 positions and emanated from 1993. Further sequencing of modern PRRS-isolates from outside Sweden might throw light on the source of the infection.

ACKNOWLEDGEMENTS

This manuscript was written due to the kind invitation to talk at the the Australian Pig Veterinarians conferences in Melbourne in May 2008 on the subject of veterinary challenges following the ban of growth promoters in Sweden, and therefore only has one author. However, the data presented include the merged efforts of authorities, branch organisations, veterinarians and farmers. Not the least skilled producers have been of particular importance, as they have influenced their colleagues in a positive way.

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