



CRITICAL REVIEW OF ON-FARM INTERVENTION STRATEGIES AGAINST *SALMONELLA*

Friendship, R.M.¹, Mouchili, A¹, McEwen, S.¹ Rajić, A.²

¹ Department of Population Medicine, University of Guelph, Ontario Veterinary College, Guelph, Canada N1G 2W1.

² Public Health Agency of Canada, 260 Research Lane, Guelph, Canada N1G 5B2.

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Executive Summary

The purposes of this study are to summarize the available scientific literature on the effectiveness of on-farm interventions against *Salmonella*, to evaluate existing diagnostic tests for *Salmonella*, and to review studies on the cost-benefits of single interventions or *Salmonella* control programs. A summary of the existing scientific evidence associated with antimicrobial resistance and *Salmonella* in swine is also provided.

1. Literature Review of Interventions

A comprehensive and replicable literature search, screening of abstracts for relevance, and evaluation of full articles for quality were conducted using the principles of systematic review methodology.

Among 1,126 potentially relevant references, 173 (15.4%) were relevant; 86 were suitable for quality assessment and data extraction (Sixty references pertained to pre-harvest interventions; the remainder dealt with transport, lairage and contamination at slaughter. The review yielded the following information:

- Vaccination: 15 related references were included; most showed a beneficial effect of vaccine in reducing *Salmonella* shedding or other outcomes.
- Probiotics/Competitive exclusion: 7 related references were included; the results were contradictory and inconsistent.
- Antibiotics: 11 related references were included; (i) four on chlortetracycline, (ii) four on various combinations of two antibiotics that included oxytetracycline, (iii) two on tylosin, and (iv) one each for efrotomycin, flavomycin™, and oxytetracycline. Only three reported beneficial outcomes and two of these were from the 1970's and may not be valid today. In general, antibiotics tend not to be useful and can be detrimental. The use of antibiotics likely promotes the selection for resistant serovars and under certain circumstances might lead to a more severe infection of *S.Typhimurium*.
- Sodium Chlorate: Three related references were included and these reported generally beneficial results.
- Acidification of feed or water. Eight related references were included and the results were generally positive but inconsistent.
- Cleaning and Disinfection. Three related references included in this study evaluated the efficacy of off-site weaning to control *Salmonella* and reported beneficial effects.
- Depopulation / Repopulation. Two related studies suggest that initially *Salmonella* prevalence on a repopulated farm can be reduced, however, the fact that *Salmonella* can persist in the environment and be carried by other animals such as rodents, means that complete eradication is unlikely.
- Management-Related Strategies. A few studies examined various strategies and some reported success, although these were usually conducted in conjunction with other measures (e.g. Danish *Salmonella* Control Program).
- Feed-Related Control. Under the sub-category "type of feed" (meal and pelleted feed), among 14 related studies, 8 assessed the effect of meal over pelleted feed, and 5

reported favourable results. Liquid feed and coarse feed tended to demonstrate positive outcomes

- Novel Strategies. Only a few studies examined the effectiveness of egg-yolk immunoglobulin, spray-dried porcine plasma, prebiotics, essential oils and bacteriophages, and although they tended to show promise in laboratory settings their potential beneficial effects still have to be evaluated in clinical trials and under 'more representative' field conditions.

Overall, the current review of existing scientific evidence, revealed a beneficial effect in controlling *Salmonella* in swine by vaccination, feeding coarse mash feeds or liquid feeding, acidification of feed or water, and potentially by strategic movement of pigs to off-site (or separate) weaning or finishing units along with good hygiene. For interventions such as antibiotics, sodium chlorate, competitive exclusion, the results were less consistent. This review also revealed the lack of studies on some of the factors that have been identified in observational studies as potential risk factors for *Salmonella* infections in swine: limiting visitors to the farm, changing clothes and boots for visitors, the use of footbaths where necessary, pest (e.g. rodents, wild birds and other wildlife species) control, purchasing replacement animals from fewer suppliers, and stocking density. Consequently further investigations are needed not only in these areas, but also in those that showed promising results in controlling *Salmonella* spp. and/or other foodborne pathogens in pigs/pork or species other than pigs (for example, prebiotics, probiotics, and bacteriophage).

It is important to note that there is uncertainty regarding the impact of any type of intervention strategy on an individual commercial farm and that results are likely to be variable from farm to farm.

2. Evaluation of Diagnostic Tests for Salmonella

Although traditional culture methods for isolating *Salmonella* take 3-5 days to complete, this method remains standard for detecting this organism. Furthermore, this is the only method that allows the identification of definitive serovars and antimicrobial resistance profiles of isolated *Salmonella*. The sensitivity of the culture methods may be affected by the phase of the *Salmonella* infection. In acute salmonellosis, large numbers of *Salmonella* are excreted in the feces, whereas a chronically infected or carrier pig may excrete only low numbers of *Salmonella*, and then only intermittently. Therefore, for clinical cases, a direct culture may be sufficient, whereas samples from chronically infected pigs or from the environment will almost always require pre-enrichment and selective enrichment to have reasonable sensitivity.

Two selective enrichment methods dominate most epidemiological investigations for *Salmonella* in. In method 1, 10 g or more of feces are initially diluted in buffered peptone water and incubated at 37°C for 24 hours. In method 2, a 1-g sample of feces is initially diluted in tetrathionate broth and incubated at 37°C for 48 hours. The subsequent procedural steps are identical for both methods. Culturing is the most specific diagnostic technique and can lead to further information including serotype, phage type, antimicrobial resistance pattern, and molecular determinants. However, it may fail to detect *Salmonella* in feces from non-shedding carriers. It is also labour intensive and costly so that culturing large numbers of samples per farm to increase the likelihood of finding a positive sample becomes prohibitively expensive and may not be practical for routine applications, particularly for screening purposes.

Enzyme-linked immunosorbent assays (ELISA) can be used to detect either the organism or a humoral response to the organism. The latter is used more frequently in pigs to demonstrate previous and current exposure to this organism. Over the last decade, serology has been used in research and national surveillance programs to determine the prevalence of *Salmonella* spp. in swine populations. Culture and ELISA tests measure different stages of *Salmonella* infection and therefore cannot be easily compared since at some stages the pigs may not be shedding bacteria but have antibodies to *Salmonella* as a result of a previous exposure. In addition, *Salmonella* infection has been demonstrated to be very dynamic and therefore culture and seroprevalence of *Salmonella* on swine farms may not be constant over time. However, the correlation between serology and *Salmonella* shedding has been demonstrated using experimental trials and in field studies.

Recently, molecular diagnostics, based on the polymerase chain reaction assays and genotyping, have been used for the diagnosis of clinical salmonellosis and sub-clinical infections in pigs. Promising results have been obtained in laboratory studies, however, the ability of PCR for detecting *Salmonella* from naturally infected samples needs to be investigated.

3. Review of Studies on the Cost-Benefits of Single Interventions or *Salmonella* Control Programs.

Among 321 potentially relevant citations, identified using a combination of seven economic, health, and agricultural bibliographical databases, only 17 were relevant. There was generally lack of data on the costs and benefits associated with the implementation of single or multiple interventions or control programs against *Salmonella* in swine. Only 13 studies reported data associated with specific on-farm interventions and four studies evaluated the interventions related to the entire farm-to-abattoir continuum. Only eight studies captured the actual cost of the intervention or control program for reducing *Salmonella* in swine. Only two studies used a cost-effectiveness analysis, and another two studies a cost-benefit analysis. More primary research is needed that investigates the costs and benefits associated with different specific interventions for *Salmonella* in pigs.

One study evaluated the implementation of farm-to-abattoir interventions in the United States and concluded that interventions at the plant level are cheaper than those at the farm level. Another study performed a cost-benefit analysis of *Salmonella* control strategies in Danish pork production and concluded that only hot-water decontamination at the abattoir was “socio-economically profitable”. They drew attention to the fact that the costs of on-farm intervention procedures were borne by the producers, and any benefits went to the consumers. A Dutch study reported that the cost/pig for an acid mixture was 2.49 Euro; and that investment costs would be approximately 0.41 Euro (pump and pipelines). A Danish study reported that the cost of a comprehensive integrated farm-to-abattoir control program in Denmark originally cost the industry and government \$14 million U.S. per year, however, a recent revision to the program resulted in the cost decreasing to \$8.5 million (U.S.) per year solely for the industry.

4. Summary of the Work Associated with Antimicrobial Resistance.

It has been suggested that the use of antimicrobials in food animals may be associated with the increased fecal excretion of gram-negative enteric pathogens such as *Salmonella*, however, a systematic review of several challenge trials conducted in pigs between 1976 and 1988 did not find significant differences in *Salmonella* shedding between groups fed or treated with or without antimicrobials. The emergence and spread of *Salmonella* strains resistant to one or more antimicrobials are of increasing threat to human health and presumably to animal health. An infection with a multi-resistant strain of *S.Typhimurium* PT104 is of particular concern. First reported in cattle in the United Kingdom in 1984, this organism has been subsequently recovered from many other species, including swine. Other serovars containing high levels of resistance have also been recovered from pigs in a number of countries, however the prevalence of resistance is low in many other serovars.

As a result of growing concern over antimicrobial resistance in *Salmonella* and other organisms and its adverse impact on human and animal health, international public health and agri-food agencies have recommended that nations develop or expand existing surveillance programs and research efforts for antimicrobial resistance, both in food-animals and humans. *Salmonella* is a key organism in these programs because of its public health importance. International trends indicate that it is desirable from a food safety perspective to keep levels of resistance in the intestinal flora of food animals low. Thus, on-going monitoring of antimicrobial use and antimicrobial resistance is necessary to evaluate the overall resistance trends and to detect emerging resistance phenotypes in swine and other livestock populations

Objectives

The purposes of this study are to summarize the available scientific literature on the effectiveness of on-farm interventions against *Salmonella* (part one), and to evaluate monitoring and diagnostic techniques (part two), as well as review studies on the cost-benefits of *Salmonella* control programs (part three), and present a summary of the work associated with antimicrobial resistance (part 4).

Part 1

Material and Methods

The review used a multi-stage process, which started with the specification of the question to be answered, followed by the determination of the search strategy, the literature search, the duplication screening, relevance screening, quality assessment of relevant articles, data extraction, and summarization of the results.

Literature search and databases

The literature search was limited to English language publications and was conducted using various strategies that included:

- (i) Online computer searches of four selected electronic databases, Agricola (National Agricultural Library), PubMed (University of Guelph), Scopus, and Current Content. Current Contents covered references published from January 1999; whereas, Agricola, PubMed and Scopus contained references dating from 1960.
- (ii) Hand searches of the table of contents of the *Journal of Swine Health and Production* (from 1990 to 2005) and the proceedings of the *International Symposium on the Epidemiology and Control of Foodborne Pathogens in Pork* (1999, 2001, 2003 and 2005 editions), and the *Opinion of the Scientific Panel on Biological Hazards on the request from the Commission related to "Risk assessment and mitigation options of Salmonella in pig production"* (EFSA, 2006), and the reference lists of 13 recent literature reviews on *Salmonella* control strategies/programs in pork or/and swine: Callaway et al., 2003; Davies et al., 2004; Brooks et al., 2003; Dickson et al., 2003; Mastroeni & Ménager, 2003; Wegener et al., 2003; Lo Fo Wong et al., 2002; Nielsen, 2002; Wray, 2001; Hurd et al., 2005.
- (iii) Simple Internet ("Google") search for topic-related unpublished literature.

Search terms

A list of potential on-farm intervention strategies against *Salmonella* infection was developed and submitted for validation to an expert panel of swine specialists and epidemiologists (N = 6). Two authors conducted a comprehensive literature search, starting with the development of keywords (Table 1). Search terms were categorized into different components: population-based terms, outcome terms, intervention terms, and site-specific terms.

Search terms were combined and entered sequentially in each of the selected electronic databases. Abstracts detected from each of these search strategies were

imported into a reference management software (Reference Manager[®], version 11). Abstracts from simple Internet and manual searches of the *Journal of Swine Health and Production*, the proceedings of the *International Symposium on the Epidemiology and Control of Foodborne Pathogens in Pork*, as well as those that originated from the reference lists of review articles, were manually entered into this database. Duplicated abstracts were identified and deleted. Peer-reviewed articles were preferred when their duplicates were also published in conference proceedings.

Table 1 Categorization of search terms for the systematic review of references on intervention strategies against *Salmonella*

Category	Terms
Population	Pig, pigs, swine, hog, hogs, sow, sows, gilt, gilts, finisher, finishers, piglet, piglets, pork ¹ , & carcass ¹
Outcome	Salmonell* ¹
Common intervention	Effect, effects, control, controls, interven*, eliminat*
General intervention	Sanitation, hygiene, desinf*, disinf*
On-farm	On-farm, farm level, preharvest, pre harvest, feed, vaccin*, Immuniz*, Immunis*, water acidification, acid, acidifier, lactic acid, antibiotic, antibiotics, antimicrobial, antimicrobials, prebiotic, prebiotics, biosecurity, all in all out, housing, probiotic probiotics lactobac* bifidobac* propionibac* Saccharomyces, fermentation, yeast, bacteriocin, bacteriocins, competitive exclusion, dietary supplement, feed

¹ * Asterisk indicates that the electronic reference will look for words beginning with those letters

Relevance and quality assessment screening

The abstracts of the references retained after the duplication screening were assessed for their relevance to the review questions. Studies were classified as relevant if the abstract described primary research on the impact of one or more intervention strategies against *Salmonella* contamination of swine (at the farm level) or pork (abattoir level). References that passed the relevance screening were then subjected to quality assessment for which the inclusion/exclusion criteria included:

- ❑ The article describes an experimental (not an observational) study,
- ❑ Description of the intervention protocol (including the housing conditions of studied subjects) provided,
- ❑ Selection of the appropriate control group(s),
- ❑ Adequate follow-up/monitoring of the control group(s) i.e. similar to that of the treatment group,

- ❑ Description of the statistical analyses (if performed) provided or availability of sufficient data to perform one,
- ❑ Description (or reference) of the diagnostic technique(s) and tissues used for the detection of *Salmonella* organisms provided.

Checklists, in which the above-mentioned criteria for both relevance screening and quality assessment were developed following the guidance elaborated by Sargeant et al. (2006) and pre-tested by two reviewers in a pilot study comprised of 30 randomly selected articles. Results of this independent evaluation suggested perfect agreement ($\kappa = 1.0$) between the reviewers; consequently only one reviewer was assigned to screen the remaining articles for relevance and quality of the study design.

Data extraction

To ensure consistency and transparency, a uniform data extraction form was developed and pre-tested with two reviewers. The data extraction form (available upon request from the 1st author) contained of the following sections:

- ❑ Stage of production at which the intervention was being tested,
- ❑ Characteristics of the population (animals or carcasses) involved,
- ❑ Study design (intervention protocol and outcome of interest),
- ❑ Diagnostic techniques (qualitative and/or quantitative) used,
- ❑ Statistical analyses, which included the effect measured (prevalence, incidence or mean difference of bacterial concentration) and their measure(s) of variability (i.e. *p-value*, standard error or confidence intervals).

Two reviewers performed the data extraction for all the articles that passed the quality assessment. Differences between the reviewers' reports were resolved by consensus.

Results

The literature search of all the above-mentioned databases yielded 1,126 potentially relevant references, from which only 173 (15.4%) were retained after relevance and duplication screening. Assessment of the methodological quality further rejected 87 additional references and retained 60 for pre-harvest interventions. The remainder dealt with transport, lairage and contamination at slaughter.

Vaccination

The review yielded 15 vaccine-related references deemed to be relevant and of acceptable quality (See Table 2). Seven of these references assessed more than one trial, in that they tested the effectiveness of more than one vaccine, or the same vaccine with either different doses or different routes of administration. The test

population was predominantly weaned pigs, however one study examined the effect of vaccinating sows to reduce *Salmonella* shed by suckling pigs (Roesler et al, 2006).

Table 2. Relevant references on vaccination strategies to control *Salmonella*

REFERENCE	STUDY DESIGN	EFFECT
Roesler et al., 2006	Field Trial N=25 vac. sows, and N=37 control sows	Beneficial effect: no shedding in piglets from vaccinated sows vs 47.7% in piglets from antibiotic-treated controls
Roesler et al., 2004	Non-random challenge trial. N = 30 pigs	Beneficial effect: 20-80% reduction in the proportion of weaned pigs shedding <i>Salmonella</i> after vaccination with a Typhimurium-based vaccine.
Springer et al., 2001	Non-random challenge trial N = 36 pigs	Beneficial effect: Ileal/caecal mucosa & ileocecal lymph nodes (ICLN) of vaccinated (with a Typhimurium-based vaccine) grower-finisher pigs less colonized with <i>Salmonella</i> .
Lindner et al., 2001	Field trial ² N = 575 sows + 16356 piglets	Beneficial effect: Vaccination (Typhimurium-based vaccine) was protective against <i>Salmonella</i> infections (over 86% reduction in the ICLN prevalence).
Lumsden et al., 1991	Randomized challenge trial N = 17 pigs	Beneficial effect for the 1 st two weeks: 40% of shedders in the control group against 0% in the vaccinated (Typhimurium-based vaccine)
Letellier et al., 1999b	Randomized challenge trial N = 20 pigs	Negative effect: Endovac™ - Vaccinated pigs were all shedding <i>Salmonella</i> compared to only 10% of the controls at necropsy.
Roof & Doitchinoff, 1995	Randomized challenge trial N = 82 piglets	Beneficial effect: 44-75% reduction in the proportion of weaned pigs shedding <i>Salmonella</i> after vaccination with a Cholerasuis vaccine.
Kramer et al., 1987	Randomized challenge trial N = 34	Beneficial effect: Cholerasuis vaccine (5.5*10 ⁹ via conjunctival sac) responsible of 50-75% reduction of <i>Salmonella</i> -positive MLN in grower-finisher pigs. Second trial given IM had similar results.
Kramer et al., 1992	Randomized challenge trial N = 67 pigs	Beneficial effect: No death and no cases of salmonellosis in SC-54 vaccinated weaned pigs, compared to 3 deaths & 9 cases of acute salmonellosis for the controls.
Hanna et al., 1979	Randomized challenge trial N = 35 pigs	Beneficial (SUGGESTIVE³) effect: SC-54 vaccinated weaned pigs did not shed <i>Salmonella</i> , compared to non-vaccinated pigs.
Kolb et al., 2003	Randomized field trial N _{Study 1} = 420 pigs N _{Study 2} = 420 pigs	Beneficial effect: 50-75% reduction in the proportion ICLN positive for <i>Salmonella</i> in vaccinated (Enterisol®) grower-finisher pigs.

² The effect of the program measured by evaluating the levels of *Salmonella* contamination prior to and after the implementation of the program.

³ SUGGESTIVE because the level of statistical significance of the difference between vaccinated & non-vaccinated pigs was not reported.

REFERENCE	STUDY DESIGN	EFFECT
Groninga et al., 2000	Randomized challenge trial N = 24 pigs	Beneficial cross-protection effect: Overall, about 70% reduction in <i>Salmonella</i> prevalence in vaccinated (Choleraesuis vaccine) pigs (83% vs. 25%) at slaughter.
Gibson et al., 1999	Randomized challenge trial N = 34 pigs	Beneficial cross-protection effect of Argus™ in reducing <i>S. Typhimurium</i> shedding load (not prevalence).
Maes et al., 2001	Randomized field trial N = 655 pigs	Beneficial cross-protection effect of Argus™ against ($p < 0.05$) <i>Salmonella</i> (over 90% reduction in ICLN prevalence).
Charles et al., 2000	Randomized challenge trial N = 20 pigs per study	Beneficial cross-protection effect: (modified-live Choleraesuis vaccine via drinking water) No shedding vs 58% among controls. No beneficial cross-protection effect of a modified-live <i>S. Choleraesuis</i> vaccine (individually administered twice) against <i>S. Typhimurium</i> shedding.

Probiotics

Only two trials were selected for inclusion in this study (Table 3). Theoretically, probiotics should be useful, although its unlikely that on their own they will be the whole answer to controlling *Salmonella* at the farm level. There has been a lack of good scientific method in the application of this technology. There are a number of criteria that potential probiotic strains must meet in order to be considered for use in *Salmonella* control. The screening and selection of a probiotic includes testing, *in-vitro* or *in-vivo* of the following important criteria: be nonpathogenic and nontoxic, and of proven safety for human and animals; proven stability against gastric acid (pH1-4), bile, oxygen and resist degradation by digestive enzymes present in the intestine (e.g lysozymes); adhere to gut epithelial tissue, and be able to persist, albeit for short periods, in the gastrointestinal tract; be isolated from the same species (pig) as its intended host; be able to grow rapidly, retain viability and stability of the desirable characteristics of the strain during commercial production as well as in the final product; be cost effective for use in farm animals. Any proposed probiotic strain must additionally be easy to grow, to freeze-dry and be suitable for inclusion in feed.

Table 3 Relevant references on probiotics to control *Salmonella*

REFERENCE	STUDY DESIGN	EFFECT
Baum & Harris, 2000	Non-randomized challenge trial (N = 24 pigs)	Beneficial effect: Lower prevalence & short duration (2 weeks) of <i>Salmonella</i> shedding in <i>Lactobacillus</i> -treated pigs.
Letellier et al., 1999	Randomized challenge trial (N = 20 pigs)	No beneficial effect: Ferlac-2™ had no significant effect on shedding <i>Salmonella</i> Typhimurium.

Competitive Exclusion

The current review identified five references of acceptable quality for competitive exclusion: Anderson et al. (1999) assessed the effect of three different porcine competitive exclusion cultures in six different non-randomized trials from which only one reported a significant ($P < 0.05$) beneficial effect in reducing *Salmonella* Choleraesuis prevalence in challenged suckling pigs. With the exception of the study of Frana et al. (2004) that reported a non-significant ($P > 0.05$) effect of Microcin-producing *E. coli* on *Salmonella* Typhimurium concentration and prevalence in treated pigs, the remaining three references (Fedorka-Cray et al., 1999a; Nisbet et al., 1999; and Genovese et al., 2003) in this category yielded promising results in controlling *Salmonella* caecal carriage (Table 4).

Table 4. Relevant references on competitive exclusion strategies to control *Salmonella*

REFERENCE	STUDY DESIGN	EFFECT
Fedorka-Cray et al, 1999a	Randomized challenge trial (N = 53 pigs)	Beneficial effect: 68% reduction in the prevalence <i>Salmonella</i> shedding in suckling pigs treated with mucosal competitive exclusion culture.
Genovese et al., 2003	Challenge trial (Expt 1, intranasal) N = 16 pigs (Experiment 2, oral) N = 18 pigs	Beneficial effect: Exp1. 71% (fecal swab) or 82% (caecal contents) reduction in the prevalence <i>Salmonella</i> in suckling pigs treated with porcine competitive exclusion culture (PCF ₁). Exp2. 52.5% reduction in the prevalence <i>Salmonella</i> shedding in suckling pigs treated with PCF ₁ .
Nisbet et al., 1999	Non-randomized challenge trial (N = 15 pigs)	Beneficial (SUGGESTIVE) effect: Over 40% reduction in <i>Salmonella</i> caecal prevalence in suckling pigs treated with CE
Anderson et al., 1999	Non-randomized challenge trial (N = 74 pigs)	Beneficial (SUGGESTIVE) effect: About 65% reduction in <i>Salmonella</i> fecal prevalence in pigs treated with PCF.
Frana et al, 2004	Non-randomized challenge trial (N = 48 pigs)	No beneficial effect: Microcin-producing <i>E. coli</i> had no effect on <i>Salmonella</i> shedding.

Genetic Resistance

Genetic variation in porcine resistance to *Salmonella* infection has been demonstrated (van Diemen et al., 2002). Certain genes such as Natural resistance-associated macrophage protein (Nramp1) have been shown to render greater host resistance to intracellular organisms like *Salmonella*. Porcine Nramp1 has been mapped and cloned, however no observational studies have yet proven an association between the presence of the gene and resistance to infection from *Salmonella*.

Antimicrobials

Eleven antibiotic-related references that reported the findings of a total of 14 randomized and one non-randomized controlled trial were deemed to be relevant and of acceptable methodological quality: (i) four on chlortetracycline, (ii) four on various combinations of two antibiotics that included oxytetracycline, (iii) two on tylosin, and (iv) one each for efrotomycin, flavomycin™, and oxytetracycline. Of these trials, only three reported beneficial outcomes and two of these were from the 1970's and may not be valid today:

- Oxytetracycline / neomycin (Girard et al., 1976) which significantly ($P<0.05$) reduced *Salmonella* Typhimurium concentration and prevalence by at least 50% starting on day-4 post-inoculation until days 21 and 28 when no positive isolation was recorded in treated weaned pigs
- Apramycin / oxytetracycline (Ebner & Mathew, 2000) with similar findings on *Salmonella* prevalence (at least 50% reduction throughout the observation period), but in 50-day old pigs;
- Chlortetracycline (Williams et al., 1978), which showed significant ($P<0.05$) efficiency in reducing the quantity and the prevalence of chlortetracycline-susceptible *Salmonella* Typhimurium but the very opposite result was obtained when resistant *Salmonella* Typhimurium were used in the challenge.

In general, antibiotics tend not to be useful and can be detrimental. The use of antibiotics likely promotes the selection for resistant serovars and under certain circumstances may lead to a more severe infection of *Salmonella*. (See Table 5a)

Table 5a. Relevant references on the use of antibiotics to control *Salmonella*

REFERENCE	STUDY DESIGN	EFFECT
Evangelisti et al., 1975	Randomized challenge trial N = 20 pigs	No beneficial effect of feeding subtherapeutic levels of oxytetracycline in <i>Salmonella</i> Typhimurium prevalence.
Ebner & Mathew, 2000	Randomized challenge trial N = 48 pigs	Beneficial effect: 17-86% reduction in the overall in prevalence of <i>Salmonella</i> shedding in pigs treated with apramycin-oxytetracycline. No effect with carbadox or ceftiofur combined with oxytetracycline.
Girard et al., 1976	Randomized challenge trial N = 20 pigs	Beneficial effect: 40-86% reduction in the overall prevalence of <i>Salmonella</i> Typhimurium shedding in oxytetracycline-neomycin treated pigs (and reduced duration of shedding)
Letellier et al., 1999b	Randomized challenge trial N = 20 pigs	No beneficial effect for flavomycin™ in <i>Salmonella</i> Typhimurium prevalence.
Williams et al., 1978	Randomized challenge trial N = 14 pigs	No beneficial effect: in use of 100g/ton chlortetracycline on <i>Salmonella</i> Typhimurium prevalence.
Shryok et al., 1998	Randomized challenge trial N = 35 pigs	No beneficial effect: of Tylosin (100g/ton) on the fecal prevalence <i>Salmonella</i> Typhimurium.

REFERENCE	STUDY DESIGN	EFFECT
Baggesen et al., 1999	Randomized challenge trial (N = 117 pigs)	No beneficial effect: Subtherapeutic (14.5ppm in feed) tylosin on <i>Salmonella</i> prevalence.
Jacks et al., 1988	Randomized challenge trial (N = 40 pigs)	No beneficial effect: of Efrotomycin (16mg/kg) on the fecal prevalence or concentration of <i>Salmonella</i> Typhimurium.
Delsol et al., 2003	Randomized challenge trial (N = 18 pigs)	No beneficial effect: of a single dose of chlortetracycline on <i>Salmonella</i> Typhimurium DT104 prevalence.
Finlayson & Barnum, 1973	Non-randomized challenge trial (N = 14 pigs)	No beneficial effect: Chlortetracycline (10-40 g/ton) not effective in controlling shedding patterns.
Delsol et al., 2004	Randomized challenge trial (N=36 pigs)	No beneficial effect: Enrofloxacin-treated piglets consistently shed higher numbers of <i>Salmonella</i> Typhimurium DT104 than the untreated control pigs.

Sodium chlorate

Salmonella possess respiratory nitrate reductase activity that catalyzes the intracellular reduction of chlorate to cytotoxic chlorite. Most anaerobic bacteria lack respiratory nitrate reductase, and therefore theoretically, treatment with sodium chlorate should selectively kill *Salmonella* and not harm beneficial gut flora.

The four selected references retained after systematic screening reported generally beneficial results. The effect of sodium chlorate treatment on *Salmonella* concentration/prevalence depended not only on the formulation itself, but also on sampling time (relative to the time of the administration of the last treatment) and the age-group of the pigs on which the treatment was applied (Table 5b).

Table 5b. Relevant references on the use of Sodium Chlorate to control *Salmonella*

REFERENCE	STUDY DESIGN	EFFECT
Anderson et al., 2001	Randomized challenge trial (N = 59 pigs)	Beneficial effect: Single dose of sodium chlorate reduced <i>Salmonella</i> caecal colonization by 1.4-2.7 log ₁₀ in weaned pigs.
Anderson et al., 2004	Randomized challenge trial (N = 60 pigs)	Beneficial effect: 2X ¹ of sodium chlorate reduced (by over 50%) caecal carriage of <i>Salmonella</i> Typhimurium in weaned pigs, but results were not satisfactory in finisher pigs.
Patchanee et al., 2005	Randomized controlled trial (N= 80 pigs)	Beneficial effect: The effect of sodium chlorate on <i>Salmonella</i> shedding depended on age at weaning: among late (at 21 days of age) weaned pigs had a 63% reduction in the prevalence <i>Salmonella</i> shedding due to sodium chlorate treatment. No effect on early-weaned pigs. when topical disinfectant was used, sodium chlorate reduced the prevalence by 79%. No

REFERENCE	STUDY DESIGN	EFFECT
		effect when disinfectant was not used.
Burkey et al., 2004	Randomized challenge trial N = 96 pigs	Beneficial effect: Sodium chlorate-treated pigs had lower <i>Salmonella</i> shedding score than that of non-treated controls.

Acidification of Feed or Water

Eight papers were included in this study. The results were generally positive but inconsistent (see Table 6). Some practical problems are reported such as clogging of drinkers in the case of water acidification and corrosion of equipment. The principle behind this approach is that non-dissociated organic acids can potentially enter bacteria, where they dissociate as a result of the higher pH in the cell. The acids lower the cell pH and disrupt DNA synthesis. The effects of fermented liquid feeding may be related to acidification but liquid feeding is dealt with separately.

Table 6. Relevant references on the use of acidification of feed or water to control *Salmonella*

REFERENCE	STUDY DESIGN	EFFECT
van der Wolf et al., 2001	Randomized controlled trial (N = 280 pigs)	Beneficial effect: water acidification (2ml/L) resulted in a 65% (cut-off OD%>10) or 84% (cut-off OD%>40) reduction in the overall <i>Salmonella</i> sero-prevalence in finisher pigs.
Papenbrock et al., 2005	Randomized challenge trial (N = 20 pigs)	Beneficial effect: Potassium diformate dietary supplement produced over a 30% reduction in <i>Salmonella</i> fecal prevalence.
Jørgensen et al., 2001a	Randomized controlled trial (N = 22 pens)	Marginal ($p = 0.07$) beneficial effect: 43% reduction in pen fecal prevalence following feed acidification.
van der Heijden et al., 2005	Non-randomized control study (N = 36 farms)	Beneficial effect: Water and feed acidification reduced the <i>Salmonella</i> titre of fattening pigs significantly.
Hansen et al., 1999	Randomized controlled trial (N = 685 pigs)	No clear beneficial effect: Addition of formic acid yielded results not consistent across different sections of herd 1, and no effect in herd 2.
Letellier et al., 1999b	Randomized challenge trial (N = 20 pigs)	No beneficial effect: Acidification of drinking water (formic acid) was not efficient in reducing <i>Salmonella</i> infection in swine.
McLaren et al., 2001	Non-randomized controlled trial (N = 1147 pigs)	Negative effect in both weaned and finisher pig: increased <i>Salmonella</i> pen-prevalence after following feed acidification.
Walsh et al., 2003	Non-randomized challenge trial (N = 180 pigs).	No beneficial effect: No effect of organic/inorganic acid dietary treatment on <i>Salmonella</i> shedding in weaned pigs.

Cleaning and Disinfecting

In many studies cleaning and disinfecting is examined in combination with other strategies for example the flow of pigs (all-in/all-out vs continuous flow) and biosecurity. Three reports that have been included in this study evaluated the efficacy of off-site weaning to control *Salmonella* and concluded that this is a useful strategy (see Table 7a)

Table 7a. Relevant references on cleaning and disinfecting-related strategies to control *Salmonella*

OFF-SITE WEANING

REFERENCE	STUDY DESIGN	EFFECT
Fedorka-Cray et al., 1997	Controlled trials (N = 407 pigs)	Beneficial effect: Management practices that include isolated weaning and internal biosecurity led to complete elimination of <i>Salmonella</i> infections, in comparison with the practice of raising weaned pigs on the source farm (12% positive)
Nietfeld et al., 1998	Randomized controlled trial N = 71 pigs	Beneficial effect: No <i>Salmonella</i> isolated from 444 rectal & oropharyngeal swabs from 57 off-site weaned pigs, compared to 46.7% (7/15) in the pigs raised on the source site.
Dahl et al., 1997	Randomized controlled trial N = 293 pigs	Beneficial effect: Strategic movement of pigs at weaning yielded satisfactory ($p < 0.05$) results (sero-prevalence): Herd A: No sero-positive among off-site weaned pig, compared to control pigs (97.4% at week 16 of age); Herd B: No <i>Salmonella</i> -positive culture in pigs raised in the external finishing unit; compared to 11.4% in the internal unit; Herd C: No <i>Salmonella</i> -positive pig detected among finisher pigs raised in a newly built finishing unit, compared to 53.3% among those raised in an old unit.

Likewise studies have examined the effectiveness of depopulation-repopulation as a control strategy. Reports suggest that initially *Salmonella* prevalence on a repopulated farm can be reduced (see Table 7b). The fact that *Salmonella* can persist in the environment and be carried by other animals such as rodents, means that complete eradication is unlikely.

Table 7b. Relevant references on management-related strategies to control *Salmonella*

DEPOPULATION-REPOPULATION

REFERENCE	STUDY DESIGN	EFFECT
Dahl, 1999	Field study (N = 349)	Beneficial effect: Depopulation and repopulation after thorough cleaning & disinfection yielded a 45.6% success

REFERENCE	STUDY DESIGN	EFFECT
	farms)	rate. Of the 349 herds that were enrolled in this program, 183 (56.4%) went back to lower classification (Danish) levels (2 & 3) within the six-month observation period.
Møgelmoose et al., 1999	Field (longitudinal) study (N = 11 farms)	Beneficial effect: Depopulation and repopulation after thorough cleaning and disinfection resulted in the eradication of <i>Salmonella</i> Typhimurium DT 104. Of the 11 herds that were enrolled in the program, eight (82%) claimed success at the initial stage, and the two remaining herds were also about to be declared <i>Salmonella</i> Typhimurium DT 104-free after readjustments.

The results of studies evaluating housing-management interventions are inconsistent. This is a very difficult area to conduct controlled trials, but observational studies suggest this is an important area to investigate (see table 7c).

Table 7c. Relevant references on management-related strategies to control *Salmonella*

OTHER HOUSING-HYGIENE FACTORS

REFERENCE	STUDY DESIGN	EFFECT
Christensen et al., 1999 <i>Danish Salmonella control program</i>	Cross-sectional study (N = 3996 farms)	Beneficial effect: Danish <i>Salmonella</i> control program yielded satisfactory ($p < 0.05$) results (feces at slaughter): both herd and pig-level prevalence dropped by almost 50%.
Davies et al., 1997b <i>Slotted floor vs. Open-flush gutter system</i>	Cross-sectional study (N = 521 pigs)	Beneficial effect for slotted floor barn: Barn with partially slotted floors (9%) protective ($p < 0.05$) against <i>Salmonella</i> in pigs than barn with open-flush gutters (84%)
Oliveira et al., 2002a <i>Presence of dunging gutter system</i>	Cross-sectional study (N = 70 pigs)	No beneficial effect: <i>Salmonella</i> shedding in pigs housed in barns with dunging-gutter system not different ($p > 0.05$) from that in pigs housed in barns without this system.
MLC, 2005a <i>Fully slatted vs. straw-based housing system</i>	Randomized controlled trial N = 4400 pigs (from 4 trials)	No beneficial effect: Fully slatted flooring system was not different ($p > 0.10$) of straw-based system in regard to <i>Salmonella</i> caecal carriage in finisher pigs.
Cook et al., 2003	Randomized controlled trial (N = 22 farms)	No beneficial effect: Biosecurity + Hygiene failed to reduce <i>Salmonella</i> contamination.

REFERENCE	STUDY DESIGN	EFFECT
Roesler et al., 2005	Randomized controlled trial (N = 80 pigs)	No beneficial effect: Hygiene + acidified feed + Fluorquinolone package did not yield success in reducing/controlling <i>Salmonella</i> in a herd.

Feed-related control strategies

Under the sub-category “type of feed” (meal and pelleted feed), fourteen randomized non-challenge trials from four references were identified. Eight of these trials assessed the effect of meal over pelleted feed, five (Jørgensen et al., 1999; 2003; Hansen, 2001) of which reported results indicating a significantly ($P < 0.05$) lower sero-prevalence of *Salmonella* spp. (Danish mix-ELISA) in meal-fed grow-finisher pigs (Table 8a). The comparison of wheat:barley-based meal with the following three types of pelleted feed (5% potato protein concentrate, 0.05% zinc gluconate, and the combination of barley, wheat, and oats) yielded a non-significant ($P > 0.05$) effect on *Salmonella* spp. sero-prevalence at a cut off OD-value of 20% (Hansen, 2001).

Results of the work of Jørgensen and collaborators (Jørgensen et al., 2001b) suggested that the proportion of sero-positive (Danish mix-ELISA cut off OD-value > 20%) grow-finisher pigs was lower (4.9%) in the group fed pelleted feed made of wheat and barley in a ratio of 25:75, followed by those in the group fed wheat:barley pellets at a ratio of 50:50 or 100% barley-based pellets (Table 8a). Also, the findings of another trial from the same authors (Jørgensen et al., 1999) were in agreement with the hypothesis that feeding coarsely ground pelleted feed (compared to finely ground) was protective against *Salmonella* spp. infections (Table 8b).

Table 8a. Relevant references on feed-related strategies to control *Salmonella*

FEED TYPE (Meal versus Pellets)

REFERENCE	STUDY DESIGN	EFFECT
Jørgensen et al., 1999	Randomized controlled study N = 1125 pigs	Beneficial effect: <i>Salmonella</i> sero-prevalence in pigs on meal (2.8%) lower than that of pigs on finely ground feed (9.0%).
Hansen et al., 2001	Randomized controlled trial N = 1224	Beneficial effect: Finisher pigs fed wheat-based meal (10.3%) had lower <i>Salmonella</i> sero-positive than those on wheat-based pellets (30.2%). Finisher pigs fed heat-treated beet pellets (17.5%) had lower <i>Salmonella</i> sero-prevalence than those fed wheat-based pellets (30.2%).
O'Connor et al., 2005	Randomized controlled trial (N = 32 pigs)	Beneficial effect: <i>Salmonella</i> -positive fecal cultures in pigs on mash corn-soy diet (4%) versus pelleted feed (8%).
Lettelier et al., 2003	Field trial ¹ N = 263 pens	Beneficial effect: The proportion of <i>Salmonella</i> -positive pens (21%) was lower when the pigs were fed mash feed vs pelleted feed (64%).
Kjeldsen & Dahl, 1999	Randomized controlled trial (N = 1048 pigs)	Beneficial effect: <i>Salmonella</i> prevalence (OD-value > 20) in grow/finisher pigs fed meal (22.2%) lower than that in pigs on pelleted feed (42.2%).

REFERENCE	STUDY DESIGN	EFFECT
Bysted, 2003	Cross-sectional study (N = 199 sow herds)	Marginal ($p=0.09$) beneficial effect: <i>Salmonella</i> -positive culture from pens housing sows fed home-mixed meal (36%) was lower than that of pens housing sows fed pelleted feed (48%).
Jørgensen et al., 2003	Controlled trial (N = 764 pigs)	Beneficial effect: The proportion of <i>Salmonella</i> sero-positive pigs fed with optimized ¹ wheat-based pellets (34%) lower than those of the pigs on meal or standard pellets (55%)
Jørgensen et al., 2001b	Randomized controlled trial (N = 2304 pigs)	Beneficial effect: lower prevalence of <i>Salmonella</i> in pellet with 25% -100% barley vs 100% wheat.
Jørgensen et al., 2001a	Randomized controlled trial (N = 22 pens)	No beneficial effect: <i>Salmonella</i> prevalence in pens housing weaner pigs fed meal (16.7%) was not significantly different from that of pens housing weaner pigs on pelleted feed (20%).
Kjærsgaard et al., 2001	Randomized controlled trial (N = 406 sows)	No beneficial effect: <i>Salmonella</i> isolation rate in sows (or weaner pigs) fed meal (14%) was not significantly different vs control pigs on pellets (6%).

Table 8b. Relevant references on feed-related strategies to control *Salmonella*
FEED PARTICLE SIZE

REFERENCE	STUDY DESIGN	EFFECT
Jørgensen et al., 1999	Cross-sectional study (N = 1695 pigs)	Beneficial effect: <i>Salmonella</i> sero-prevalence in pigs on coarse feed (5.2%) lower ($p<0.05$) than that of pigs on finely ground feed (12.9%).
Papenbrock et al., 2005 (Trial 2)	Randomized challenge & longitudinal trial (N = 20 pigs)	Beneficial effect: Coarsely ground feed significantly ($p<0.05$) reduced <i>Salmonella</i> excretion in pigs by approximately 49%.
Kjeldsen & Dahl, 1999	Randomized controlled trial N = 612 pigs	Marginal ($p=0.08$) beneficial effect: <i>Salmonella</i> prevalence in pigs on coarse ground feed was 4 (OD-value<20) or 1.3 (OD-value>20) times lower than that of the pigs on finely ground feed

The impact of other types of feed on *Salmonella* spp. prevalence in swine were assessed and variable results were reported. British researchers (MLC, 2004) compared pigs fed liquid feed with those on dry feed and the results suggested that liquid feed significantly ($P<0.05$) reduced the percentage of finisher pigs which tested positive for *Salmonella* at slaughter: 16% versus 35% (sero-prevalence) or 23% versus 39% (caecal carriage). The liquid feed in this study was not fermented but a degree of natural fermentation was recorded during the normal feed processing. When the same authors compared controlled fermentation with the same liquid feeding protocol used in the earlier study there was no significant difference in *Salmonella* levels in the pigs at slaughter (MLC, 2005). In contrast, results from van Winsen et al. (2001) suggested no beneficial effect of fermented feed on *Salmonella* prevalence in grow-finishing pigs (Table 8c).

Table 8c. Relevant references on feed-related strategies to control *Salmonella*
FERMENTED LIQUID FEED

REFERENCE	STUDY DESIGN	EFFECT
MLC, 2004	Controlled trial N = 1056 pigs.	Beneficial effect: The prevalence of <i>Salmonella</i> in pigs fed liquid feed was 2.2 (serology) or 1.7 (caecal culture) times lower ($p < 0.05$) than that in the pigs on dry feed.
Farzan et al., 2005	Cross-sectional study N = 41 farms	Beneficial effect: Only 3 out of 400 fecal samples from liquid-feeding farms were positive for <i>Salmonella</i> , compared to 25 of the 420 from dry-feeding farms. The proportion of <i>Salmonella</i> -positive farms on liquid feed was 2.5 times lower ($p < 0.05$) than that of farms on dry feed.
van Schie & Overgoor, 1987 ¹	Cross-sectional study N = 1860 pigs (40 farms)	Beneficial effect: Whey (19.4%) as the liquid component of fermented feed more protective ($p > 0.05$) against <i>Salmonella</i> excretion (in fattening pigs) than water (64.1%)
van Winsen et al., 2002	Non-randomized controlled trial (N = 998 pigs)	No beneficial effect: Fermented feed had no influence on <i>Salmonella</i> prevalence in finisher pigs.
MLC, 2005 _b <i>Controlled fermentation</i>	Randomized controlled trial (N = 1024 pigs)	No additional effect: No conclusive effects ($p > 0.05$) of the feeding system on caecal carriage of <i>Salmonella</i> : of 685 pigs tested, 13 were positive (9 on the control liquid feeding system, and 4 on the controlled fermented feeding system). Controlled fermentation against liquid feed that was naturally fermenting.
McLaren et al., 2003 ²	Cohort study (N = 1147 pigs).	No beneficial effect: No difference ($p > 0.05$) in the isolation rates of <i>Salmonella</i> in pigs fed fermented feed (8.2%) and those on dry feed (5.2%).

Novel Strategies

Passive immunity. Researchers have vaccinated hens with *Salmonella* and fed egg-yolk immunoglobulin in an attempt to protect pigs from infection. This approach did not significantly ($P > 0.05$) prevent shedding of inoculated *Salmonella* Typhimurium DT104 in early-weaned (12-day old) pigs (Letellier et al., 1999b). It seems unlikely to be an economically feasible approach. The avian egg-yolk antibodies can be destroyed during the milling process, in storage and by gut acidity and enzymes. Spray-dried porcine plasma has been shown to provide a source of gamma globulins to the newly weaned pig and helps protect against enteric infections (Gatnau and Zimmerman, 1990). However this is also an expensive approach and the use of such animal products in livestock feeds has been prohibited in Europe.

Prebiotics. These are non-digestible feed ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of *Bifidobacteria* or lactic acid-producing bacteria already resident in the colon, as these groups of bacteria are claimed to have several beneficial effects on the host. The definition of prebiotic also states an improvement of the host health, through the increase of carbohydrate

fermentation and decreasing protein degradation. Carbohydrate fermentation generally results in harmless or even beneficial end products, whereas protein fermentation results in the production of potential harmful products. However, it is stated that the fermentative advantage cannot solely explain the prebiotic effect; most probably, there are the interactions between different populations of bacteria. Fructooligosaccharides (FOS) are known for their ability to stimulate the growth of *Bifidobacteria* and to inhibit that of potentially pathogenic bacteria such as *Salmonella*. (Simmering and Blaut, 2001; Cumming et al., 2001). Other non-digestible oligosaccharides (NDO) including, xylo-oligosaccharides (XOS), galacto-oligosaccharides (GOS), isomalto-oligosaccharides (IMO), transgalactooligosaccharides (TOS), mannan-oligosaccharides (MOS), soybean oligosaccharides and lactulose have also been tested for their prebiotic effect (Simmering and Blaut, 2001; Roberfroid and Slavin, 2000). Lettelier et al. (1999b) assessed the effect of feeding Ferlac-2™ (probiotic), fructooligosaccharides (FOS) (prebiotic), and the combination of the two; results suggested that only FOS (administered through drinking water) was effective in reducing *Salmonella* Typhimurium shedding in early-weaned 12-day-old pigs. In general there is a lack of clinical trials investigating the use of prebiotics for the control of *Salmonella* in pigs.

Essential oils. Essential oils (EOs) are volatile components of plants. Many EOs are generally recognized as safe and have been used in feeds. *In-vitro* testing has shown that carvacrol, thymol and cinnamaldehyde have excellent activity against *Salmonella* Typhimurium and show potential as feed agents to control *Salmonella* in field situations (Si et al, 2006) but *in-vivo* work is necessary to confirm efficacy.

Bacteriophages: Bacteriophages are viruses that infect bacteria and are commonly found in the same environment as their hosts. Lee and Harris (2001) challenged 21-day-old pigs with *Salmonella* Typhimurium and introduced Felix 0-1 phage (virulent phage that can infect a broad spectrum of *Salmonella*) via water 3 hours following infection. After a further 9 hours the levels of *Salmonella* in the organs and feces of the sacrificed pigs were found to be significantly decreased compared to controls. The results of the study demonstrated the proof-of-principle of phage therapy in controlling *Salmonella* in pigs. However, although bacteriophage therapy has received considerable attention problems associated with immuno-neutralization and poor replication within the host environment are concerns. Host cells can evolve natural resistance to phage infection although this can be addressed through using bacteriophage cocktails at the latter phases of pig production.

Discussion

Overall, the current review revealed a number of trials showing a beneficial effect in controlling *Salmonella* in swine by vaccination, feeding coarse mash feeds or fermented liquid feeding, acidification of feed or water, strategic movement of pigs to off-site (or separate) weaning or finishing units along with good hygiene. For interventions such as antibiotics, sodium chlorate, competitive exclusion, the results were less consistent.

The review presents a number of challenges when trying to summarize the reported outcomes of the trials under the same intervention category; the methods used in performing these trials were rarely comparable because of: (i) the diversity of diagnostic techniques used for detecting *Salmonella* carriers (ii) differences in the type and quantity of the sampled materials, (iii) the heterogeneity of the population of pigs used in the trials, (iv) the diversity of the route of administration (for product-related interventions); (v) the concentrations and serovars of inoculated *Salmonella* which were not always similar (for challenge trials), (vi) and in some cases, the differences in the time-frame from treatment to sampling (for the assessment of the effect of the intervention). The dissimilarities between trials within intervention categories were also apparent in the reported outcomes, which were given either in bacterial concentrations or prevalence. This lack of standardized study design and reporting of the results makes it illogical to produce average quantitative / numerical summaries (from a meta-analysis) for these interventions. In very few cases did we find a considerable number of comparable trials using a given intervention strategy. Nevertheless, the reported information can still be of great use in quantitative risk assessment modeling to assist in the evaluation of the effectiveness of each intervention category on *Salmonella* prevalence. However, the choice of the trials to serve as data sources for this exercise should depend on the explicit definition of the targeted objective, as this will allow the selection of the trials with the appropriate characteristics and optimal conditions applicable to the commercial/field environment. It should also be noted that there might be a bias within the published literature in that there is at least a perception that negative results are less frequently reported than positive results.

This review also revealed the lack of studies on some of the factors that have been identified in observational studies as potential risk factors for *Salmonella* infections in swine: limiting visitors to the farm, changing clothes and boots for visitors, the use of footbaths where necessary, pest (e.g. rodents, wild birds and other wildlife species) control (Barber et al., 2002; Fedorka-Cray et al., 2000), purchasing replacement animals from fewer suppliers (Nielsen, 2002), stocking density (Linton et al., 1970; Funk et al., 2001_b). Consequently further investigations are needed not only in these areas, but in those that showed promising results in controlling *Salmonella* spp. and/or other foodborne pathogens in pigs/pork or species other than pigs (for example, prebiotics, probiotics, and bacteriophage).

Part 2

Diagnosis

In general pigs carrying *Salmonella* show no clinical signs but when pigs do become ill the diagnosis of salmonellosis cannot be made on the basis of clinical signs alone. These signs are shared by several other diseases of swine, for example swine dysentery and porcine proliferative enteropathy caused by *Lawsonia intracellularis* and thus clinical diagnosis needs to be confirmed by microbiological and histological examinations (Schwartz, 1999; Fedorka-Cray et al., 2000). Samples of lung, liver or spleen, and ileum and ileocecal lymph nodes are recommended for recovery of *Salmonella* from septicemic and enterocolitic forms of salmonellosis, respectively (Schwartz, 1999). Although traditional culture methods for isolating *Salmonella* take 3-5 days to complete, this method remains standard for detecting this organism. Furthermore, this is the only method that allows the identification of definitive serovars and antimicrobial resistance profiles of isolated *Salmonella*. The sensitivity of the culture methods may be affected by the phase of the *Salmonella* infection. In acute salmonellosis, large numbers of *Salmonella* are excreted in the feces, whereas a chronically infected or carrier pig may excrete only low numbers of *Salmonella*, and then only intermittently. Therefore, for clinical cases, a direct culture may be sufficient, whereas samples from chronically infected pigs or from the environment will almost always require pre-enrichment and selective enrichment to have reasonable sensitivity (Schwartz, 1999; Fedorka-Cray et al., 2000; Waltman, 2000; Davies et al., 2001; Funk, 2003).

Many different culture media and methods have been developed and used for *Salmonella* recovery (Waltman, 2000). Two selective enrichment methods dominate most epidemiological investigations for *Salmonella* in swine (Davies et al., 2000; Davies et al., 2001; Funk, 2003). In method 1, 10 g or more of feces are initially diluted in buffered peptone water and incubated at 37°C for 24 hours. In method 2, a 1-g sample of feces is initially diluted in tetrathionate broth and incubated at 37°C for 48 hours. The subsequent procedural steps are identical for both methods. The sensitivity of the bacteriological culture may vary between 10-80% depending on utilized sampling and testing protocols (Hurd et al., 2001). Davies et al (2000) showed that recovery of *Salmonella* is improved by using larger amounts of feces, incubating at 42 C vs 37 C, utilizing secondary selective enrichment or delayed enrichment at room temperature. Rostagno et al (2005) used four different *Salmonella* culture methods with pooled swine fecal samples and depending on the culture method, recovered different serovars from the same sample.

Korsak et al. (2004) evaluated VIDAS SLM and VIDAS ICS methods for detection *Salmonella* spp. from naturally infected pig fecal samples. The VIDAS SLM was composed of a double enrichment in Muller-Kauffmann tetrathionate broth and in M broths before processing in a VIDAS device (an enzyme-linked fluorescent immunoassay for the detection of *Salmonella*-antigens). The VIDAS ICS protocol is an immuno-concentration step followed by plating on XLT-4 agar. They concluded that VIDAS SLM significantly improves the recovery of *Salmonella* in naturally contaminated fecal samples.

Culturing is the most specific diagnostic technique and can lead to further information including serotype, phage type, antimicrobial resistance pattern, and molecular determinants. However, it may fail to detect *Salmonella* in feces from non-shedding carriers. It is also labour intensive and costly so that culturing large numbers of samples per farm to increase the likelihood of finding a positive sample becomes prohibitively expensive and may not be practical for routine applications, particularly for screening purposes.

Enzyme-linked immunosorbent assays (ELISA) can be used to detect either the organism or a humoral response to the organism. The latter is used more frequently in pigs to demonstrate previous and current exposure to this organism. Over the last decade, serology has been used in research and national surveillance programs to determine the prevalence of *Salmonella* spp. in swine populations. This test was initially adopted by Denmark and subsequently in other countries for national surveillance programs designed to monitor and control the occurrence of *Salmonella* on the farm and in pork (Nielsen and Wegener, 1997; Schwartz, 1999; Fedorka-Cray et al., 2000; Nielsen, 2002; Harris, 2003). The mixed ELISA, so-called because the antigen is a combination of lipopolysaccharide extractions of serovars Choleraesuis (O antigens 6 and 7) and Typhimurium (O antigens 1, 4, 5, and 12), is used in the Danish program to assess the *Salmonella* status of serum samples collected from live pigs on the farm or meat juice at slaughter (Nielsen et al., 1995; Nielsen et al., 1998; Harris, 2003). Pigs infected with the most prevailing *Salmonella* serovars produce high titres to the O antigen (Fedorka-Cray et al., 2000) and it has been assumed that this test may detect antibodies associated with the most common serovars in swine (Davies and Funk, 1999; van der Wolf et al., 1999; Harris, 2003). This test is usually recommended for screening purposes at the herd level and is considered less suitable as an individual pig test (Schwartz, 1999; Fedorka-Cray et al., 2000; Harris, 2003). More recently, other countries have developed their own serological tests with the goal of increasing the sensitivity of the test using the same antigens or adding antigens from different *Salmonella* serogroups that are more prevalent in their swine populations (van der Heijden, 2001; Harris, 2003).

However, there are issues still concerning the *Salmonella* serological ELISA tests. In an international ring trial, there was variation between 12 laboratories using 'in-house' or commercially available ELISA kits in testing the same samples correctly (van der Heijden, 2001). Also a slight increase in sero-positivity was observed when the samples were tested twice by ELISA (Ekeroth et al., 2003).

The choice of antigens used in coating the ELISA plates is another key component of each ELISA. The antibodies against some *Salmonella* serotypes might not be detected because the related LPS antigens are not coated on the ELISA plates. van Winsen et al. (2001) proved that the *S. Typhimurium* and *S. Brandenburg*, but not *S. Livingstone*, *S. Goldcoast*, and *S. Panama*, could be detected using *Salmonella*-ELISA. The efficient coating of the *Salmonella* LPS antigens on the ELISA microplates is another parameter, which may affect the ability of the test to detect the *Salmonella*-antibodies. Because of amphiphilic structure, LPS may not be coated to the ELISA microplate efficiently. Also LPS from different serovars may not have similar coating capacity. The cross-reactivity between LPSs from gram-negative bacteria due to Lipid A is another problem when coating the whole LPS molecule on microplates. However, to solve these issues and decrease inter- and intra-plate variation and improve the *Salmonella*-ELISA technique, Jauho et al. (2000) developed and used a new ultra-violet irradiation technique to bind covalently the polysaccharides (LPS without lipid A molecule) of *S. Typhimurium* and *S. Choleraesuis* to microtiter plates. Also, a chemiluminescent immunoassay (CLIA) has been developed and found in good agreement with ELISA to measure *Salmonella* antibodies in the swine meat juice samples in that the cross-reaction of *Escherichia coli* and *Yersinia* with *Salmonella* was observed in ELISA but not in CLIA (Zamora and Hartung, 2002).

Culture and ELISA tests measure different stages of *Salmonella* infection and therefore cannot be easily compared (van Winsen et al, 2001) since at some stages the pigs may not be shedding bacteria but have antibodies to *Salmonella* as a result of a previous exposure. In addition, *Salmonella* infection has been demonstrated to be very dynamic and therefore culture and seroprevalence of *Salmonella* on swine

farms may not be constant over time. However, the correlation between serology and *Salmonella* shedding has been demonstrated using experimental trials (Nielsen et al., 1995) and in field studies conducted in the countries where the tests were designed (Sorensen et al., 2004). A commercial *Salmonella* covalent mix-enzyme linked immunosorbent assay (ELISA) was compared with a culture method using a panel of sera tested in 5 laboratories from Europe and North America. The inter-laboratory comparison showed very good agreement between the laboratories to classify the samples correctly (Chow et al., 2004).

In Denmark, one study was performed in three abattoirs to evaluate the correlation between *Salmonella* serology and bacteriology under field conditions. This study showed that *Salmonella* is more likely to be recovered from caecal-content, pharynx, and carcass surface of the pigs harvested on sero-positive farms. However, there was no correlation between recovery of *Salmonella* from caecal lymph nodes and herd serology status (Sorensen et al., 2004). Kranker et al. (2003) indicated an association between serology, on-farm bacteriology, and recovery of *Salmonella* at slaughter in a longitudinal study. However, this study showed that the culture prevalence peaked in the nursery and became undetectable before slaughter compared to the sero-prevalence maximizing about two month after the peak culture-prevalence. Piglets from sero-positive sows were less likely to be a *Salmonella* shedder in this study. Botteldoorn et al. (2003) found a correlation between the isolation of *Salmonella* from carcass at slaughter and the *Salmonella* shedding by the delivered animals. Studies have found a high correlation between bacteriology and serology at the herd level (Lo Fo Wong et al., 2003). In contrast to other studies, Davies et al. (2003) found a significant correlation between the incidence of *Salmonella* in farm pen pooled faeces and the prevalence of *Salmonella* in caeca of slaughter pigs but generally poor correlation between serological and bacteriological results.

In summary, ELISA is a fast and relatively inexpensive technique for monitoring *Salmonella*. Unlike culture, it also determines the previous exposure and is not dependent on whether the pig is shedding at the time of testing. However, the correlation between the serological tests and bacterial culture is still largely unknown and might be affected either by the factors related to animals and biology of *Salmonella* or by the technical issues related to the test per se.

Traditionally, epidemiological investigations for *Salmonella* have been based on phenotypic characteristics. The predominance of certain phenotypes within hosts or locations requires further epidemiological subgrouping. More recently, molecular diagnostics, based on the polymerase chain reaction assays and genotyping, have been used for the diagnosis of clinical salmonellosis and sub-clinical infections in pigs (Liebana, 2002; Gebreyes, 2003).

Rahn et al. first developed the *invA*-based polymerase chain reaction (PCR) assay for the specific detection of *Salmonella* (Rahn et al., 1992). The PCR of the *invA* gene amplification was efficient to detect *Salmonella* in pigs experimentally infected with *S. Typhimurium* DT104 (Arnold et al., 2004).

A high agreement was reported between the API 20E and *invA* PCR to detect *Salmonella* isolates on swine farms. These tests showed higher sensitivity and specificity when using 16S rRNA sequencing as the gold standard compared to when serotyping was the gold standard (Nucera et al., 2006).

One inter-laboratory trial including 15 laboratories from 13 European countries was conducted to evaluate the performance of PCR-based method for the detection of *Salmonella* on experimentally contaminated samples. Samples were inoculated, pre-enriched in the central laboratory in Germany and submitted to the 15 laboratories where the samples tested by a validated *Salmonella*-specific PCR assay. The inter-

laboratory parameters including the personnel, reagents, and thermal cyclers did not affect the performance of the PCR (Malorny et al., 2004).

The modified PCR assay showed a good correlation with culturing technique to identify *Salmonella* in spiked samples over 48 hours (Scholz et al., 2001). Feder et al. tested fecal and water samples from four swine farms for the presence of *Salmonella* by means of different enrichment techniques and PCR. A good agreement was observed between recovery of *Salmonella* pre-enrichment and detection by PCR.

On the other hand, a poor agreement between culture technique without pre-enrichment and PCR was reported (Feder et al., 2001). Therefore, the ability of PCR for detecting *Salmonella* from naturally infected samples needs to be investigated. A positive-PCR test might occur due to presence of dead bacterial cells in the samples. PCR technique similar to ELISA might fail to identify the specific serotypes.

In conclusion, because *Salmonella* may not be uniformly distributed throughout samples, the size of the sample has an impact on the probability of detecting the bacteria by PCR (large samples will increase the likelihood of detection). However, it should be kept in mind that PCR can detect both live and dead organisms in the samples and therefore it may be necessary to use cultural methods coincidentally with PCR to distinguish between dead and live organisms- and to do further tests such as antimicrobial resistance. Nonetheless, animals shedding dead *Salmonella* have the potential to be carrying live *Salmonella* and therefore, the ability of PCR to detect *Salmonella* in cultural negative samples indicates that it can be applied as a useful screening test.

Pulse Field Gel Electrophoresis (PFGE) can identify multiple subtypes from *Salmonella*-positive samples (Wonderling et al., 2003). Gebreyes et al., (2006) have recently evaluated amplified fragment length polymorphism (AFLP), pulsed-field gel electrophoresis (PFGE), and repetitive palindromic extragenic-PCR (Rep-PCR). AFLP had the highest ability to differentiate *Salmonella* isolates in that it could differentiate distinct clones within DT104.

Botteldoorn et al. (2004) used PFGE in combination of serotyping, phage typing and antimicrobial resistance profile to discriminate *Salmonella* strains isolated from carcasses, colons and mesenteric lymph nodes of individual pigs, and from the slaughterhouse environment and found that only a part of the positive carcass was contaminated with the same serotype or genotype found in the corresponding feces or mesenteric lymph nodes. In fact, other positive carcasses were contaminated by genotypes present in the feces or lymph nodes of pigs slaughtered earlier that day or from the environment.

In summary, PFGE is a useful technique to identify different *Salmonella* isolates at the molecular level. It can provide the relatedness among the isolates recovered on farm, at slaughter, and from different sources including environment, feces, carcasses, and internal organs. PFGE can be performed on *Salmonella* isolated at different ages over a period of time. These features make PFGE an outstanding tool to investigate the clonality and spread of *Salmonella*. However, it should be mentioned that PFGE is an expensive technique, particularly because the culture and serotyping need to be done first.

Part 3

Cost -Benefit

A total of 321 potentially relevant citations were identified using a combination of seven economic, health, and agricultural bibliographical databases. Only 17 were relevant. There was generally lack of data on the costs and benefits associated with the implementation of the interventions against *Salmonella* in swine. Thirteen studies investigated or reported data associated with specific on-farm interventions and four studies evaluated the interventions related to the entire farm-to-abattoir continuum. Only eight studies captured the actual cost of the intervention or control program for reducing *Salmonella* in swine. Only two studies used a cost-effectiveness analysis, and another two studies a cost-benefit analysis. More primary research is needed that investigates the costs and benefits associated with different specific interventions or control programs for *Salmonella* in pigs. One difficulty in applying a cost-benefit analysis to intervention strategies is the uncertain outcome of the control measure. It may not be appropriate to extrapolate the findings of a carefully controlled challenge study to the commercial farm situation. It is possible that the results of one intervention strategy may differ from one farm to another.

Miller et al., 2005, evaluated the implementation of farm-to-abattoir interventions in the United States and concluded that interventions at the plant level are cheaper than those at the farm level; all rinses at the plant were estimated to cost under \$0.20/carcass processing, whereas vaccination costs \$0.85/hog. The currency was not specified, but it is assumed that results are reported in U.S. dollars. Goldbach and Alban (2006) performed a cost-benefit analysis of *Salmonella* control strategies in Danish pork production and concluded that only hot-water decontamination at the abattoir was “socio-economically profitable”. They drew attention to the fact that the costs of on-farm intervention procedures were borne by the producers, and any benefits went to the consumers. They specifically looked at acidification and the use of on-farm feed preparation, both resulting in major costs to producers.

In the Netherlands, van der Wolf (2001) reported that the cost/pig for an acid mixture was 2.49 Euro; and that investment costs would be approximately 0.41 Euro (pump and pipelines). Neumann and Kniffen (1999) measured the cost of multiple interventions at the farm level and concluded that the cost/head in U.S. dollars for antibiotic therapy is \$0.30, and for quarantine and biosecurity is \$0.25. Two studies measured the cost of different feed; that the production cost/kg of pork for a 2000 hog-feeding unit was C \$2.19 for liquid feed, and C \$2.30 for dry feed (Dunn, 2005). This study concluded that the capital cost of a liquid system is 12 times that of a dry system. In comparison, another study stated that the additional cost of pelleting compared to meal form diets varies from \$3 – 7/ton of finished feed (Harper, 1998). Gorton et al. summarized on-farm testing control programs, concluding that with a 5% prevalence level, per pig costs range from \$5.37 to \$0.49, with a strong relationship between testing costs per pig and group size. The larger the group size (eg. n = 10, 000 pigs) the cheaper the testing costs.

Wegener et al. (2003) reported that the cost of a comprehensive integrated farm-to-abattoir control program in Denmark originally cost the industry and government \$14 million U.S. per year, however, a recent revision to the program resulted in the cost decreasing to \$8.5 million (U.S.) per year solely for the industry. Thus, the control costs amount to approximately \$0.075 (U.S.)/kg of pork. They also reported that Denmark saved \$25.5 million (U.S.), since the societal costs in absence of control programs would be \$41 million (U.S) per year (Wegener et al., 2003). The authors made an assumption that salmonellosis cases associated with the major sources remained at the pre-control program level. Therefore, this is an estimate of the cost of *Salmonella* in a no-control situation. The costs of an integrated farm-to-abattoir

control program in the Netherlands to reduce the prevalence of *Salmonella* below 2% was estimated to cost at least 4.5 Euro/pig (van der Gaag, 2004). Both research groups concluded that the cost of *Salmonella* in pigs and humans is higher without an intervention or control program in place.

Implications

There is a general lack of data on the costs and benefits associated with the implementation of the interventions against *Salmonella* in swine at the farm level. More studies that include formal economic analyses of interventions or control programs for reducing *Salmonella* in pork or swine are needed. All economic models that evaluate interventions that prevent *Salmonella* shedding but have no impact on pig growth performance are unlikely to show an economic benefit unless the cost is shared by other sectors of the industry in addition to the pork producers.

Part 4

The effect of antimicrobial use on *Salmonella* shedding in swine

It has been suggested that the use of antimicrobials in food animals may be associated with the increased fecal excretion of gram-negative enteric pathogens such as *Salmonella* (Baggesen et al., 1999). Most antimicrobials that are routinely used for growth promotion of pigs are only active against gram-positive organisms and their use may disrupt typical microflora of the gastrointestinal tract, allowing for preferential colonization, growth and excretion of gram-negative organisms. The pigs carrying increased numbers of these pathogens may pose an increased risk for the contamination of pork carcasses and pork (Baggesen et al., 1999; Ebner and Mathew, 2000; Exponent, 2000). However, a systematic review of several challenge trials conducted in pigs between 1976 and 1988, using serovar Typhimurium as a challenge organism and different antimicrobials at sub-therapeutic levels as a treatment, did not find significant differences in *Salmonella* shedding between groups fed or treated with or without antimicrobials (Exponent, 2000). More recent experimental studies have shown that adding tylosin and carbadox to feed as growth promoters in pigs did not have an effect on *Salmonella* Typhimurium shedding (Baggesen et al., 1999; Ebner et al., 2000). Potential association between antimicrobial use in pigs and *Salmonella* herd prevalence has also been investigated in a few observational studies. In the Netherlands, the use of tylosin as a growth promoter in the finishing herd was associated with a higher *Salmonella* seroprevalence in pigs compared to the farms that used other growth promoters in finishing feed (van der Wolf et al., 2001). In Greece, the risk of seropositivity was four times higher in pigs fed a combination of chlortetracycline, procaine penicillin, and sulphamethazine during finishing growth, than in those fed an approved growth promoter or a probiotic (Leontides et al., 2003). Further studies may be needed to investigate this potential public health concern.

Public health concerns about antimicrobial resistance in *Salmonella* from swine

The emergence and spread of *Salmonella* strains resistant to one or more antimicrobials are of increasing threat to human health and presumably to animal health (van den Bogaard and Stobberingh, 1999; McDermott et al., 2002; Threlfall et al., 2000; McEwen and Fedorka-Cray, 2002; Teale, 2002; Carlson et al., 2003). Although, in most cases, antimicrobials are not used to treat enteric *Salmonella* infections in humans, antimicrobial treatment is necessary in immunocompromised populations or if infections become systemic. Furthermore, antimicrobial resistance may increase the risk and severity of *Salmonella* infection in humans (Barza, 2002).

An infection with a multi-resistant strain of *S. Typhimurium* PT104 is of particular concern (Poppe et al., 1998; O'Brien, 2002; Teale, 2002). First reported in cattle in the United Kingdom in 1984, this organism has been subsequently recovered from many other species, including swine (Poppe et al., 1998; Nielsen, 2002). Multi-resistant *S. Typhimurium* PT104 has two properties: antimicrobial resistance, including common resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracyclines; and increased virulence, which differentiates this strain from many other *Salmonella* species (Poppe et al., 1998; Teale, 2002; Carlson et al., 2003). Epidemiological studies indicate that this serovar and phage type may be associated with increased illness and higher death rates in humans (Glynn et al., 1998; Helms et al., 2002; Travers and Barza, 2002). In Denmark, the first case of pig-to-human transmission of *S. Typhimurium* via the food chain was reported in 1999 (Mølbak et al., 1999). The strain involved in this outbreak showed multiple-resistance, including resistance to fluoroquinolones, one of the first-line antimicrobials in the therapy of gram-negative sepsis in humans (Mølbak et al., 1999). More recently the emergence of ciprofloxacin-resistant *S. Choleraesuis* and *Typhimurium* strains have been observed in pig and human populations in Taiwan (Hsueh et al., 2004; Chang et al., 2005). Although some researchers (Hsueh et al., 2004) have suggested that some closely-related ciprofloxacin-resistant *S. Choleraesuis* and *Typhimurium* strains have been disseminated from pigs to humans in Taiwan, others (Chang et al., 2005) have noted that the pathway of resistance dissemination is still debatable. Although the antimicrobial resistance is most commonly associated with *S. Typhimurium* PT104 worldwide, the correlation between resistance and serovars may vary regionally. Multidrug-resistant *S. Muenchen*, (one the top 10 causes of human salmonellosis), was isolated from humans and pigs in North Carolina. However, pulse-field gel electrophoresis showed no relatedness between the human and pig isolates (Gebreyes and Thakur, 2005). The most frequently resistant *Salmonella* serovar isolated from health pigs and the environment on 60 Canadian swine farms was *S. Derby*, with the most frequent resistance against chloramphenicol, ampicillin, kanamycin, sulfamethoxazole, streptomycin, and tetracycline (Rajic et al., 2004). *Salmonella* Ohio, which is normally not associated with multi-resistance, demonstrated resistance to multi-antimicrobial agents in a Spanish study (Agustin et al., 2005). In Brazil, *S. Agona* plays an important role as a causative agent of salmonellosis in food-producing animals (Michael et al., 2006) and a multidrug-resistant *S. Agona* has been isolated from a hospitalized patient in Rio de Janeiro (Michael et al., 2005). A Brazilian study showed the resistance to extended-spectrum penicillin (ampicillin), broad-spectrum cephalosporins (cefotaxime and ceftriaxone), aminoglycosides (streptomycin, neomycin, gentamicin, amikacin, and tobramycin), narrow-spectrum quinolone (nalidixic acid), broad-spectrum quinolone (ciprofloxacin and norfloxacin), tetracycline, trimethoprim, and chloramphenicol among *Salmonella* isolates (Oliveira et al., 2002b). In a study in Taiwan, *S. Derby*, *S. Anatum*, *S. Typhimurium*, and *S. Schwarzengrund* were the most frequent serovars isolated from pork carcasses in a

nationwide screening program (Chen et al., 2006). In this study, the *Salmonella* Typhimurium strains exhibited 17 and 23% resistance to ciprofloxacin and enrofloxacin, respectively. In Thailand, the most frequently isolated serovar from pigs was *S. Rissen* (Padungtod and Kaneene, 2006). Antimicrobial resistance was mostly to tetracycline and nalidixic acid and the level of multi-drug resistant was higher among *Salmonella* isolates from farm workers than among isolates from workers with no animal contact (Padungtod and Kaneene, 2006). However, *Salmonella* Weltevreden was reported as the most common serovar causing human salmonellosis in this country (Bangtrakulnonth et al., 2004) indicating the relatedness between pork consumption and human salmonellosis needs further investigations.

There are a number of factors which impact on studies measuring antimicrobial resistance. For example, one study found a lower proportion of resistant strains isolated from sows compared to fattening pigs (Nollet et al, 2006). In addition this same study found a higher proportion of resistant isolates at the slaughterhouse compared to the farm (Nollet et al, 2006).. In Thailand, the serotypes varied between farm, slaughterhouse and market (Padungtod and Kaneene, 2006). A study of antimicrobial resistance among *Salmonella* isolated from humans, cattle, pigs, and chickens over 10 years in The Netherlands showed that the levels and patterns of resistance differed considerably between *Salmonella* serovars isolated from one host species (van Duijkeren et al, 2003).

The level of antimicrobial resistance may vary by animal origin and bacterial species; between non-pathogenic bacteria and zoonotic bacteria. In a Danish study the level of resistance was higher among indicator bacteria enterococci compared to zoonotic bacteria (*Campylobacter*, *Salmonella*, *Yersinia enterocolitica*) and swine pathogens (*E. coli*, and *Actinobacillus pleuropneumoniae*) (Aarestrup et al., 1998).

Misclassification of the susceptibility for the individual antimicrobials has been reported as high as 25% (Lo Fo Wong et al., 2006). Deviation in classifying resistant and susceptible *Salmonella* isolates has been reported between laboratory, strains, species, and individual antimicrobials (Lo Fo Wong et al, 2006). In general, lack of minimum inhibition concentration (MIC) reference, or a borderline susceptibility of the strains may explain part of this deviation. Overall this may not be an important problem in that one study has shown 92% agreement between 44 laboratories in 35 different countries in classifying resistant and susceptible *Salmonella* isolates correctly (Petersen et al., 2002).

Correlation between serovar and antimicrobial resistance has been found before (Nollet et al, 2006). It has been shown that the member of serogroup B, are more likely to exhibit resistance than other serogroups (Edrington et al., 2001). The level of resistance to streptomycin, sulfisoxazole, ampicillin, and nitrofurantoin was different between the somatic serogroups suggesting a correlation between the *Salmonella* somatic serogroup and the antimicrobial resistance (Edrington et al, 2001).

As a result of growing concern over antimicrobial resistance in *Salmonella* and other organisms and its adverse impact on human and animal health, international public health and agri-food agencies have recommended that nations develop or expand existing surveillance programs and research efforts for antimicrobial resistance, both in food-animals and humans (World Organization for Animal Health, 2001).

Salmonella is a key organism in these programs because of its public health importance. In the USA, Gebreyes et al. (2004) reported that among 858 isolates of 27 *Salmonella* serovars, recovered from 3 independent on-farm and slaughter studies of pigs in North Carolina from 1997-98, more than 80% of the isolates were resistant to at least one antimicrobial. Similarly, a high proportion of resistance was observed in Spain among 155 *Salmonella* isolates obtained from healthy pigs and those suffering from diarrhoea or septicaemia (Mateu et al., 2002). The purposive

selection of sick pigs in the Spanish study may explain these findings, since others reported that *Salmonella* isolates from clinically ill animals were more resistant than isolates from apparently healthy animals (Poppe et al., 2001). Sorensen et al. (2001) reported that among 282 *Salmonella* isolates obtained from Alberta pigs at slaughter, the most frequent resistances detected were to tetracycline (48.9%), streptomycin (36.2%) and sulfamethoxazole (35.8%), while no resistance was detected to amikacin, ceftiofur, ciprofloxacin, nalidixic acid and trimethoprim/sulfamethoxazole. Antimicrobial resistance, including multiple resistance, has been more commonly associated with serovar Typhimurium than other serovars (Poppe et al., 1998; Farrington et al., 2001; Jones et al., 2002; Carlson et al., 2003; Gebreyes et al., 2004).

International trends indicate that low levels of resistance in the intestinal flora of food animals may be considered beneficial from a food safety perspective when compared to higher levels of resistance (van den Bogaard and Stobberingh, 1996). Thus, on-going monitoring of antimicrobial use and antimicrobial resistance is necessary to evaluate the overall resistance trends and to detect emerging resistance phenotypes in swine and other livestock populations.

Recommendations:

1. Vaccination, feeding coarse mash feeds or fermented liquid feeding, acidification of feed or water, strategic movement of pigs to off-site (or separate) weaning or finishing units along with good hygiene are practices that have shown benefits in reducing the prevalence and/ or level of salmonella shedding. These should be considered for use in on-farm *Salmonella* control programs. There are other areas that may have potential but require research to support claims.
2. Support on-going monitoring of antimicrobial use and antimicrobial resistance in pig production.
3. There is a lack of studies on some potential risk factors for *Salmonella* infections in swine: limiting visitors to the farm, changing clothes and boots for visitors, the use of footbaths where necessary, pest (e.g. rodents, wild birds and other wildlife species) control, purchasing replacement animals from fewer suppliers, and stocking density. Consequently further investigations are needed in these areas.
4. There is a general lack of data on the costs and benefits associated with the implementation of the interventions against *Salmonella* in swine at the farm level. More studies that include formal economic analyses of interventions or control programs for reducing *Salmonella* in pork or swine are needed. All economic models that evaluate interventions that prevent *Salmonella* shedding but have no impact on pig growth performance are unlikely to show an economic benefit unless the cost is shared by other sectors of the industry in addition to the pork producers.
5. There is no guarantee of success with the application of any particular intervention on an individual farm and that the impact of wide scale adoption of an intervention strategy is also unpredictable in that no single approach or combination of interventions can be expected to result in 100% success.

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