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Effects of probiotics in swines growth performance: A meta-analysis of randomised controlled trials

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ABSTRACT

The objective of this meta-analysis was to assess effects of probiotics on the growth performance of pigs (Average Daily Gain (ADG) and Feed Efficiency (FE)). Data bases (*i.e.* PubMed, ScienceDirect, and Scopus) were searched from 1980 to 2015 unrestricted by language. The inclusion criteria were: randomised and controlled experiments using pigs without apparent disease and published in peer reviewed journals. Sixty-seven and 60 experiments were included to assess probiotic effects on ADG and FE, respectively. LAB supplementation increased ADG (difference in mean (DM) = 29.930 g/day, 95% confidence interval (CI) 17.617–42.261) and improve feed efficiency (DM = −0.096 kg feed/kg body weight, 95%CI −0.120–0.071), considering the source of heterogeneity. There were no evidence of publication biases. The meta-analysis showed that application of probiotics during the first stage of pig grown and in the finishing period resulted in greater ADG and FE. The effect was not related to the use of mono-strain or multi-strain probiotics, although it may depend on the strain used. The breeds (especially F1 and three-breed-rotational crossbreeding) and the characteristic of these breeds (maternal breeds) included in the experiments had an impact on the outcomes. These results might be used to define the guidelines to standardize the experimental designs of future trials and to include the impact of each covariate on the differences in the estimated effect sizes.

1. Introduction

Intestinal ecosystem management is one of the common strategies used to prevent diarrhea, improve health status, and enhance growth performance in intensive pig farming (Wang et al., 2012; Modesto et al., 2009; Taras et al., 2007). Antimi-

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crobials have been used in feed additives as growth promoters and to preserve health of pigs by reducing the pathogenic bacteria and modifying the microbiota in the gut of animals (Alexopoulos et al., 2004). However, this practice has been associated with the emergence of pathogenic strain resistance with its consequences on public health (Gaggìa et al., 2010).

Therefore, the use of novel additives not only to improve performance and preserve health in animals but also to ensure food safety to protect consumer health has been of growing interest. Probiotics (defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host) appear to be an alternative, safe, and effective feed additive in animal farming (Hill et al., 2014).

Most of the probiotic-addition assays on animal diets show an improvement in the productive performance and health status of different animal species (Signorini et al., 2012; Meng et al., 2010; Mountzouris et al., 2007; Krehbiel et al., 2003). However these positive probioticsí effects were not observed in all the experiments conducted in pigs (Speiser et al., 2015; Veizaj-Delia et al., 2010; Modesto et al., 2009; Harper et al., 1983).

Such disputes and increasing information published on the subject needs to be reviewed and treated with statistical techniques that allow a quantitative assessment of results obtained to date. Therefore, it is of great importance to carry out a meta-analysis. Such reviews can reduce multiple biases inherent in traditional checks and must clearly state the criteria used in the selection and evaluation of scientific papers selected the topic under review.

The objective of this meta-analysis was to assess the effect of probiotic addition on average dairy gain (ADG) and feed efficiency (FE) in intensive pig farming.

2. Materials and methods

2.1. Criteria for study selection

The studies included in the meta-analysis were selected based on the following criteria: randomised and controlled trials and published in peer-reviewed journals, between 1980 and 2015. Probiotics may have been administrated via drinking water or through the feed. Animals must be free of diseases. Studies must have reported ADG and FE with measures of variance. Assorted reviews, duplicate reports, experiments which used non-viable probiotics, and studies which evaluated animals with diseases were excluded. The term "study" refers to a scientific article which can involve one or more experiments (each experiment being a controlled one to compare a particular combination of probiotic-treated and control groups of swines).

2.2. Outcomes and definitions

Supplementation with probiotics was analysed as a tool which may improve ADG and FE in pigs. Average Daily Gain is defined as the rate of weight gain per day over a specified period of time. Feed Efficiency is defined as the amount of feed consumed per unit of weight gain. Data concerning body weight and FE correspond to the whole trial. When the study included more than one probiotic group or different doses of the same probiotic, each probiotic group was compared with the control group separately.

2.3. Data sources

Scopus, PubMed, and ScienceDirect databases were searched for articles unrestricted by language published from 1980 to 2015. Search terms included probiotic* and swine*. The abstracts were assessed and the articles that met the a priori inclusion criteria were selected.

2.4. Data extraction

Information on the study design, methods (diets), treatments (probiotic strains, treatment dose, and duration), number of animals, breed, and outcomes, were extracted from each article. For each study, the methodology used to achieve the results were evaluated. However, no scores were used to exclude studies (Lean et al., 2009).

2.5. Statistical analysis

Statistical analysis was performed used Comprehensive Meta-Analysis version 2.2 (2011). Due to continuous variables being analysed, the effect measure used to present the results was the difference in means (DM) between the probiotic treatment and controls with 95% confidence intervals (CIs) using a random effects model. In this model the true effect could vary from experiment to experiment and between experiment variability (true heterogeneity) as well as sampling error are included (Borenstein et al., 2009). A meta-regression analysis was performed to explore the sources of heterogeneity in the treatment effects. Meta-regression allows assessing the relationship between years of publication, number of pigs included in the experiments, and duration of the studies as covariates, and ADG and FE as outcomes. Furthermore the impact of the number of pigs included in each study was evaluated categorizing them in studies with adequate or inadequate n. The threshold value is established from the formula for calculating the number of experimental units for testing the mean difference from the mean difference and its standard deviation obtained in the meta-analysis with a confidence of 95% and a power of 80%. Additionally, a cumulative meta-analysis was performed to display how the outcomes shift as a function of the year of publication. A priori subgroup analyses were planned depending on factors that could potentially influence the treatment magnitude: (1) Type of probiotic administration (feed *vs.* water), (2) Type of inocula (mono-strain *vs.* multi-strain), (3) Probiotic species strain used as mono-strain inocula (with *Lactobacillus* spp.; with *Saccharomyces* spp.; with *Enterococcus* spp.; with *Bacillus* spp.; *Bifidobacterium* spp., and with *Pediococcus* spp., (4) Study duration considering the typical period of pigs rearing, (5) Different breeds and crossing breeds, (6) Litter form (stainless steel, mesh, plastic, concrete), (7) Temperature (22–25 °C, 25–31 °C), (8) Animal density (0.1–0.7 or >0.7 animals/m^2), and (9) Feed composition (primary and secondary feed ingredients).

Heterogeneity among studies was assessed using the DerSimonian and the Laird test (Qstatistic). The degree of heterogeneity was quantified with the inconsistency index (I^2-statistic; Higgins and Thompson, 2002). A sensitivity analysis was completed to assess the robustness of the meta-analysis results. Sensitivity analyses have also been used to examine effects of studies identified as being aberrant or highly influential on the analysis outcome (Lean et al., 2009). This consists of completing the same analysis, but dropping one study in each iteration.

The presence of publication bias was investigated using funnel plots. An adjusted rank correlation test using the Egger method (Egger et al., 1997) and the Begg's test (Begg and Mazumdar, 1994) was used to assess publication bias. Bias was considered to be present if at least one of the statistical methods was significant ($P < 0.10$). If there was any evidence of publication bias, from either the statistical tests or the funnel plot, the "trim-and-fill" method (Duval and Tweedie, 2000) was used to estimate the quantity and magnitude of missing studies and resultant unbiased effect size.

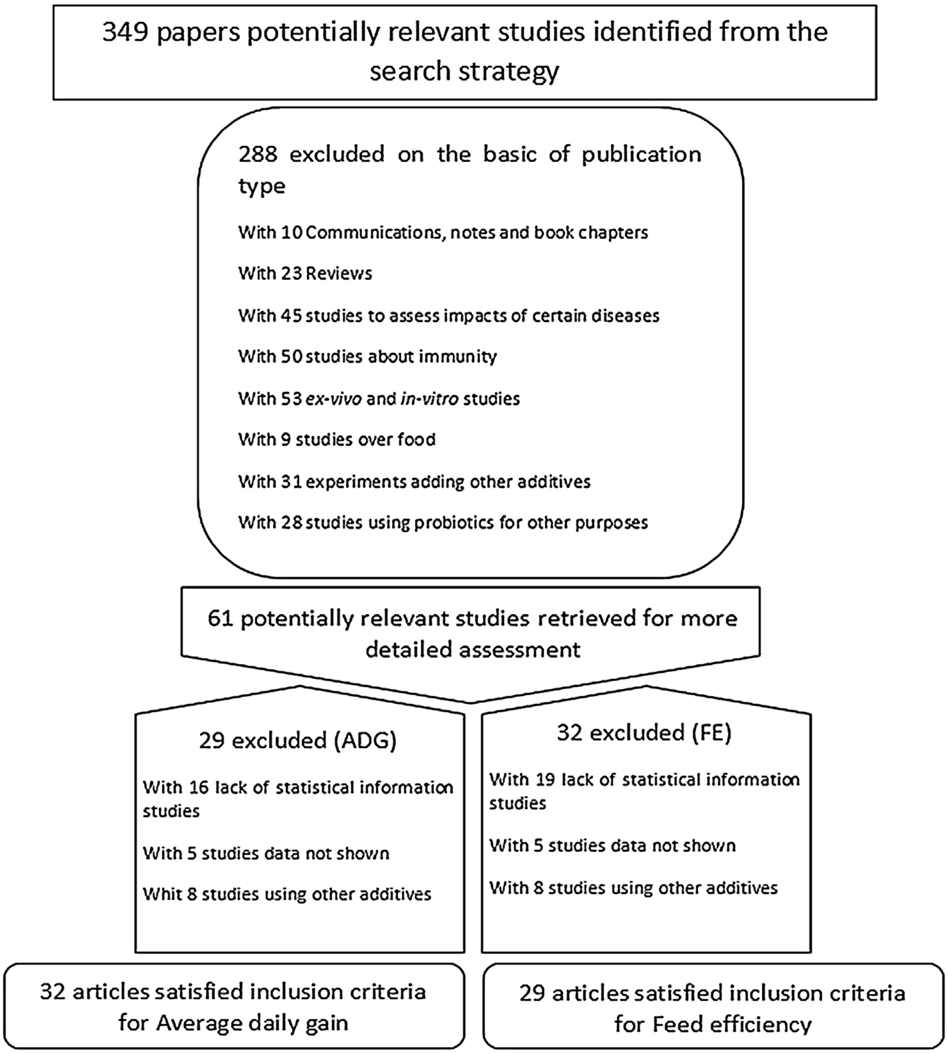

Fig. 1. Study selection flow chart.

3. Results

3.1. Excluded studies

The literature yielded 349 scientific papers using the terms Probiotic* and Swine*. Reviews, articles, experiments conducted to assess impacts of probiotics and prebiotics, or experiments to isolate and select strains with potential probiotic activity without any *in vivo* test to study effects on performance of pigs were excluded (Fig. 1).

3.2. Overview of included studies

Thirty-two of the 349 screened articles met all inclusion criteria to assess the probiotic effect on ADG, while twenty-nine articles were included in the evaluation of the probiotic effect on FE.

Of the studies which assessed the probiotic effect on ADG, fourteen were conducted before 2010 (only two studies were conducted before 2000) and the remaining 18 after 2010. The number of pigs included in the studies was variable: 20 studies included less than 100 animals and 12 studies included more than 100 animals. A total of 11 studies were conducted using multi- strain probiotics and 21 used mono-strain probiotics. Probiotics were given to pigs either added to the feed (28), in water with a syringe (3) or with milk replacer (1). Studies were conducted for ≤90 d (30) or >90 d (2).

On the other hand, a total of 29 studies were included to assess impacts of probiotics on FE, with ten studies conducted before 2010 (two studies conducted before 2000) and 19 after 2010. The number of pigs included in each study was variable, with 19 occasions ≤100 and 10 occasions >100. Nineteen studies used mono-strain probiotics, whereas 10 were conducted using multi-strain probiotics. In most of the experiments the probiotic was administered by the diet (26), two studies provided the probiotic in water with a syringe and one included in milk replacer. Studies were conducted for ≤90 (27) or >90 d (2).

3.3. Average daily gain

Of the 32 studies that met the inclusion criteria, 67 experiments (4122 animals) that combined pigs fed with probiotics and control groups were identified. In the pooled estimate, probiotics increased ADG compared to controls (DM = 29.939 g/day, 95% CI 17.617–42.261 g/day; $P < 0.001$)) in the pooled DM random effect model. Significant heterogeneity was observed across the 67 experiments (Q- statistic: $P < 0.0001$; I^2-statistic = 98.58%, Fig. 2).

Year of publication, number of pigs included in the experiments, the age of pigs, duration of experiment, and duration of the probiotic treatment were associated with the ADG ($P < 0.001$) in the meta-regression analysis. Number of pigs included in the experiments, year of publication and age of pigs explained 26.1%, 21.1%, and 16.02% of the heterogeneity, respectively. However, treatment and experiment duration explained less than 3% of the heterogeneity (Table 1).

Thirty-eight experiments conducted before 2010 were identified, and probiotics increased ADG (DM = 30.706 g/day, 95% CI 12.131–49.280 g/day; Q- statistic: $P < 0.0001$; I^2-statistic = 99.17%). The 29 experiments conducted after 2010 also found a beneficial effect in ADG (DM = 30.646 g/day, 95% CI 18.395–42.897 g/day; Q- statistic: $P < 0.0001$; I^2- statistic = 85.89%). However, there were no difference between both groups of studies ($P = 0.996$).

Table 1
Summary of random weighted meta-regression analysis for independent variables that influenced the effects between probiotic supplementation *versus* no probiotic supplementation in swines.

Co-variable		ADG	FE
Year of publication	Intercept	11555.34	18.84
	P	<0.001	0.005
	Slope	−5.739	−0.009
	P	0.001	0.004
Number of swines included in the experiment	Intercept	81.279	−0.063
	P	<0.001	<0.001
	Slope	−0.111	−0.0003
	P	<0.001	<0.001
Age of the swines	Intercept	−81.96	−0.0733
	P	<0.001	<0.001
	Slope	4.958	−0.00008
	P	<0.001	0.544
Duration of the experiments	Intercept	46.67	−0.052
	P	<0.001	<0.001
	Slope	−0.1662	−0.0004
	P	<0.001	<0.001
Duration of the treatment	Intercept	52.18	−0.0441
	P	<0.001	<0.001
	Slope	−0.363	−0.0007
	P	<0.001	<0.001

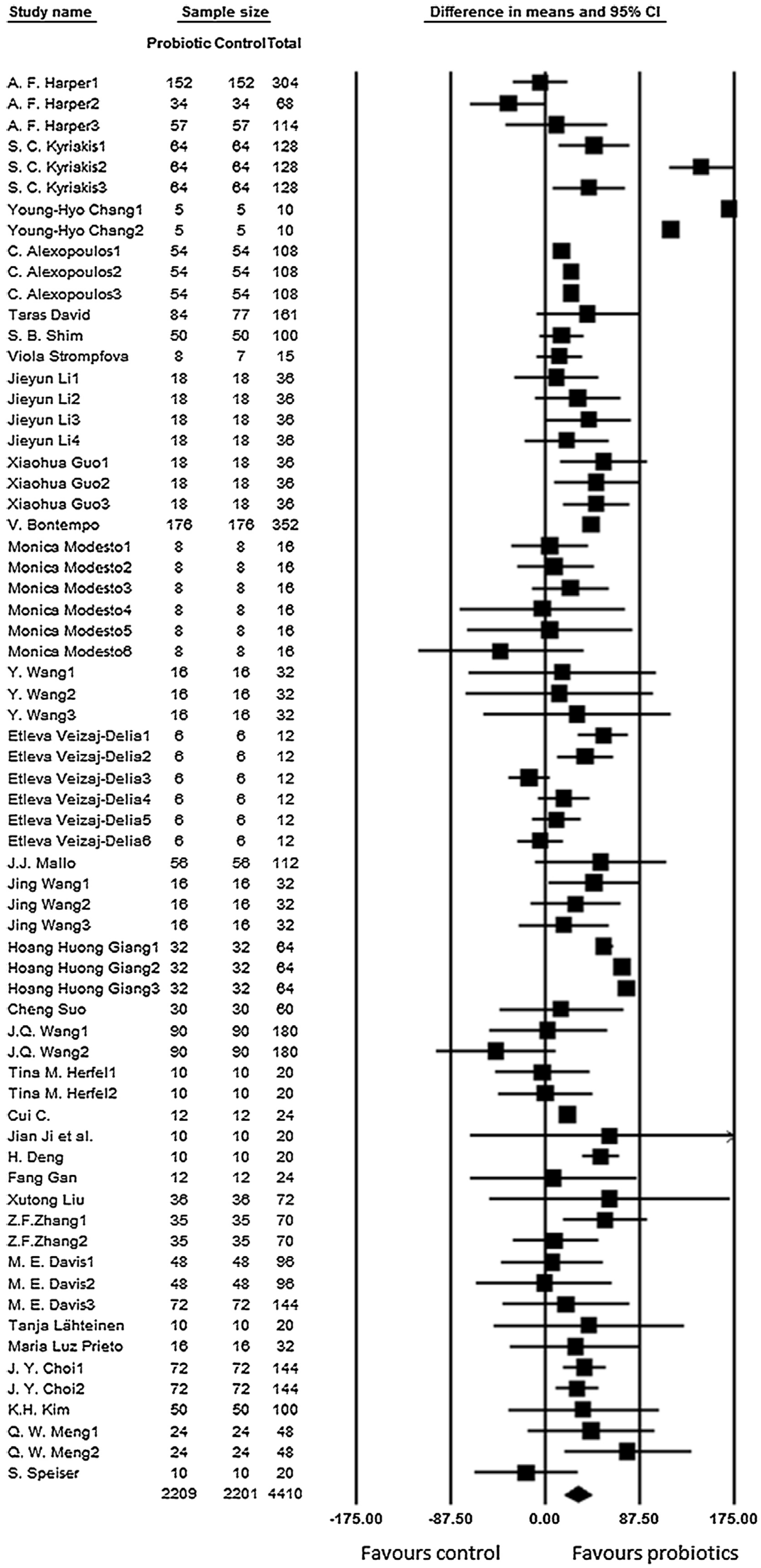

Fig. 2. Forest plot of 67 randomised, controlled trials to study the effect of supplementation with probiotics on average dairy gain (ADG) in swines (Harper et al., 1983; Kyriakis et al., 1999; Chang et al., 2001; Alexopoulos et al., 2004; Taras et al., 2005; Shim et al., 2005; Strompfová et al., 2006; Li et al., 2006; Guo et al., 2006; Bontempo et al., 2006; Modesto et al., 2009; Wang et al., 2009; Veizaj-Delia et al., 2010; Mallo et al., 2010; Wang et al., 2011; Giang et al., 2012; Suo et al., 2012; Wang et al., 2012; Herfel et al., 2013; Cui et al., 2013; Ji et al., 2013; Deng et al., 2014; Gan et al., 2014; Liu et al., 2014; Zhang et al., 2014; Davis et al., 2008; Lähteinen et al., 2014; Prieto et al., 2014; Choi et al., 2011; Kim et al., 2014; Meng et al, 2010; Speiser et al., 2015).

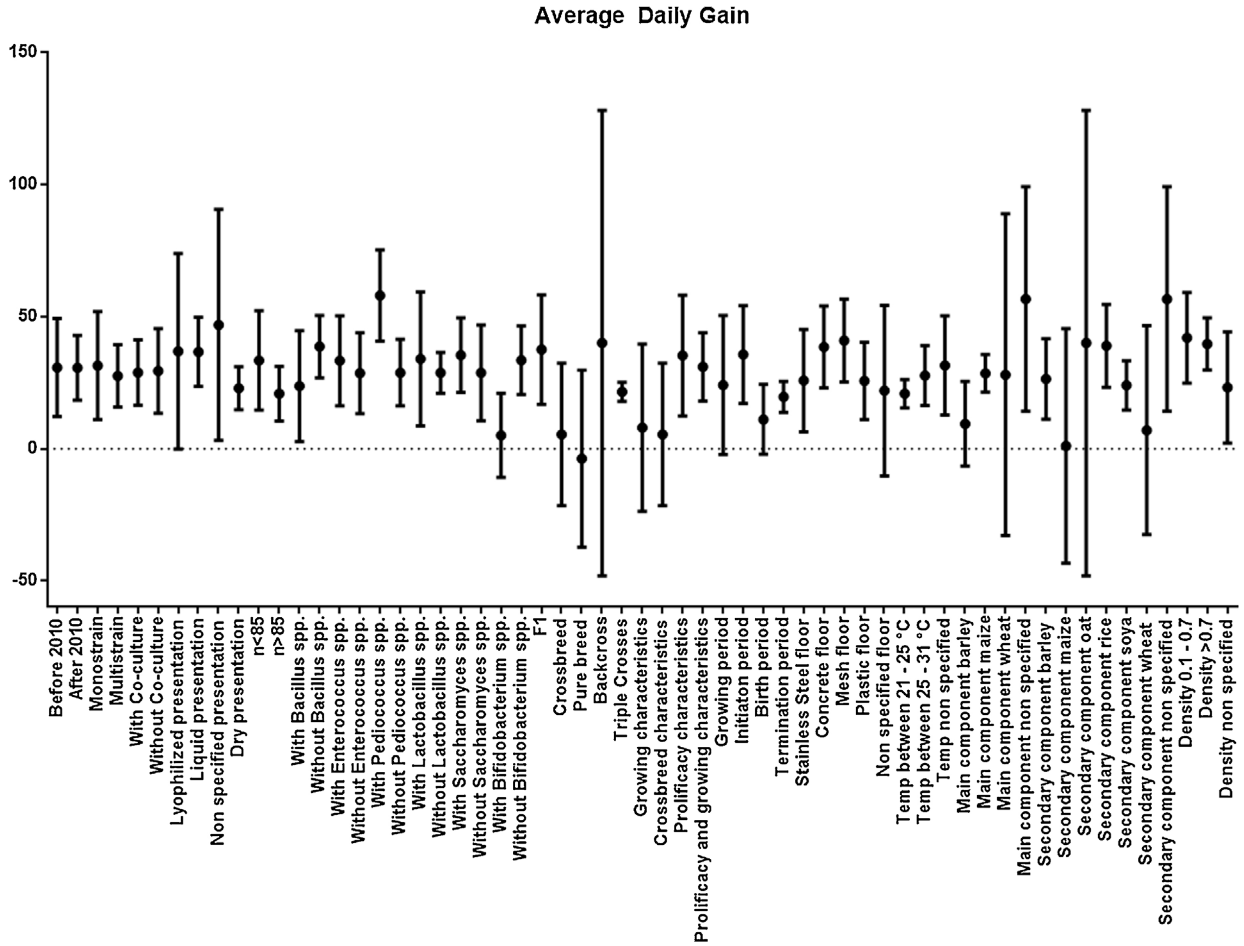

Fig. 3. Subgroup analysis comparing the effect of probiotic supplementation on average dairy gain (ADG) of swines.

The ADG of pigs treated with probiotics and control were 432.89 g/day (SD = 204.75) and 404.27 g/day (SD = 202.32), respectively. Experiments should include at least 85 pigs in each group to identify statistical differences between groups. Experiments which used <85 pigs showed the same ADG than experiments with >85 pigs (P = 0.252). The meta-analysis showed that animals fed with probiotics enhanced ADG in experiments with >85 (n = 17; DM = 20.822 g/day, 95% CI 10.448–31.196 g/day; Q- statistic: P < 0.0001; I^2-statistic = 90.23%), and also the probiotic effect was observed in experiments which used less than 85 pigs (n = 50; DM = 33.401 g/day, 95% CI 14.551–52.252 g/day; Q-statistic: P < 0.0001; I^2-statistic = 98.17%, Fig. 3).

Probiotic supplementation improved ADG in experiments which used mono-strain (n = 41; DM = 31.285 g/day, 95% CI 11.050–51.920 g/day; Q-statistic: P< 0.0001; I^2-statistic = 99.07%) and multi-strain probiotics (n = 26; DM = 27.562 g/day, 95% CI 15.748–39.375 g/day; Q-statistic: P < 0.0001; I^2-statistic = 91.92%) (P = 0.745).

Considering the probiotic species included in the products the probiotic effect remained in those experiments which used *Bacillus* spp. (n = 39; DM = 23.720 g/day, 95% CI 2.697–44.743 g/day), *Enterococcus* spp. (n = 14; DM = 33.323 g/day, 95% CI 16.263–50.382 g/day), *Lactobacillus* spp. (n = 25; DM = 34.020 g/day, 95% CI 8.645–59.395 g/day), and *Sacharomyces* spp. (n = 11; DM = 35.426 g/day, 95% CI 21.288–49.565 g/day). The effect of probiotic supplementation on ADG was higher when *Pediococcus* spp. were included in the formulation (n = 4; DM = 58.018 g/day, 95% CI 40.687–75.348 g/day) than when this species was not included (n = 63; DM = 28.756 g/day, 95% CI 15.167–42.386 g/day) (P = 0.009). However, since the number of experiments that used this microorganism was relatively small, the effect has to be interpreted with caution (Fig. 3). The inclusion of *Bifidobacterium* spp. was not able to induce a positive effect on ADG (n = 8; DM = 5.063 g/day, 95% CI −10.882–21.007 g/day).

Considering the method of administration, the beneficial impact remained in those experiments in which probiotics were included in the drinking water (n = 6; DM = 33.027 g/day, 95% CI 20.239–45.816) or added to the feed (n = 58; DM = 30.818 g/day, 95% CI 16.742–44.895 g/day). The addition of probiotic on milk substitute was not shown a positive impact on ADG (n = 2; DM = −1.500 g/day, 95% CI −32.180–29.180 g/day, Fig. 3).

Table 2
Definition of breeds and crosses used.

	Example
F1: It is the result of crossing a purebred male with a female of other purebred. The progeny can be used for sale or to replace.	• Yorkshire Male × Landrace Female • Duroc Male × Hampshire Female • Large White Male × Big White Female
Triple crosses: It is the result of crossing a pure male with a female F1 consists of two different from the male races. The offspring are used only for sale.	• (Duroc × Landrace) × Yorkshire • (Yorkshire × Landrace) x Duroc • (Yorkshire × Duroc) × Landrace
Backcross: It is the result of crossing a F1 with one of the parental breeds	• F1 (Landrace × Yorkshire) × Landrace • F1 (Duroc × Landrace) × Duroc
Crossbreed: Animal originated by crossing different breeds without applying any selection criteria or hybridization.	

The probiotic effect on ADG was observed when the experiments were conducted from weaning to 18 kg Body Weight (BW) (n = 43; DM = 35.640 g/day, 95% CI 17.066–54.214 g/day) and finishing (>50 kgBW) (n = 12; DM = 19.650 g/day, 95% CI 13.746–25.554 g/day). However, this positive effect on ADG was not observed when the experiments were conducted during the grown period (18 kgBW to ≤50 kgBW) (n = 8; DM = 24.111 g/day, 95% CI −2.210–50.433 g/day) and during the lactation period (n = 4; DM = 11.097 g/day, 95% CI −2.145–24.339 g/day).

Regarding the breeds and crossed animals used in the experiments (The different crosses and breeds used were divided into different categories, whose definitions are in Table 2), the probiotic effect on ADG was observed when were used F1 pigs (n = 39; DM = 37.522 g/day, 95% CI 16.776–58.268 g/day) and three-breed-rotational crossbreeding (n = 16; DM = 21.530 g/day, 95% CI 17.923–25.137 g/day). When crossbreeds, pure breeds, and back-crossing were used in the experiments the probiotic effect on ADG could not be observed (Fig. 3). Considering the production characteristics of different breeds or crosses of pigs, the probiotic effect on ADG could only be observed when there were included in experiments maternal breeds (*e.g.* Chester White, Landrace, Yorkshire) (n = 33; DM = 35.269 g/day, 95% CI 12.443–58.095 g/day) and crossbreeding of prolific and rapid growth breeds (*e.g.* Berkshire, Duroc) (n = 23; DM = 30.986 g/day, 95% CI 17.996–43.976 g/day). Conversely, it was not possible to observe positive effects on ADG when crossbreeds or with grown characteristics were included in the experiments (Fig. 3).

The beneficial effect of probiotic on ADG was observed in all the litters: stainless steel (n = 5; DM = 25.783 g/day, 95% CI 6.406–45.160 g/day), concrete (n = 16; DM = 38.546 g/day, 95% CI 23.066–54.026 g/day), mesh (n = 6; DM = 40.923 g/day, 95% CI 25.219–56.628 g/day), and plastic (n = 18; DM = 25.638 g/day, 95% CI 11.032–40.245 g/day). However, this positive effect on ADG was not observed when the experiments did not specify the litter form (n = 22; DM = 21.989 g/day, 95% CI −10.332–54.311 g/day) (Fig. 3).

The probiotic effect on ADG was observed when the experiments were conducted in pens with controlled temperature at 22–25 °C (n = 5; DM = 20.815 g/day, 95% CI 15.446–26.184 g/day) or 25–31 °C (n = 22; DM = 27.714 g/day, 95% CI 16.353–39.075 g/day) (Fig. 3).

The probiotic effect on ADG was observed when the animal density was 0.1–0.7 pigs/m^2 (n = 11; DM = 41.995 g/day, 95% CI 24.866–59.124 g/day) or >0.7 pigs/m^2 (n = 16; DM = 39.670 g/day, 95% CI 29.781–49.560 g/day) (Fig. 3).

The beneficial effect of probiotic on ADG was observed only when the experiments used maize (n = 45; DM = 28.556 g/day, 95% CI 21.471–35.640 g/day) as the principal feed ingredient. However, when barley (n = 9; DM = 9.40 g/day, 95% CI −6.653–25.453 g/day) or wheat (n = 1; DM = 28.000 g/day, 95% CI −32.910–88.910 g/day) were used, this positive effect on ADG was not observed (Fig. 3). However, since the number of experiments that used these ingredients was relatively small, the effect has to be interpreted with caution. Additionally, the beneficial effect of probiotic on ADG was observed when the experiments used soybean (n = 32; DM = 23.973 g/day, 95% CI 14.640–33.307 g/day) and rice (n = 12; DM = 38.949 g/day, 95% CI 23.264–54.365 g/day) as secondary feed ingredient (Fig. 3).

No publication bias was observed for these 67 experiments, as confirmed by Begg's test (P = 0.075) and Egger's test (P = 0.363). Applying the Duval and Tweedie's trim-and-fill methods none studies were identified trimmed (Fig. 4).

3.4. Feed efficiency

Of the 29 studies that met the inclusion criteria, 60 experiments (4011 animals) that combined pigs fed with probiotics and control groups were identified. In the pooled estimate, probiotics improved FE compared to controls (DM = −0.096 kg feed/kg BW, 95% CI −0.120 to −0.071 kg feed/kg BW; P < 0.001) in the pooled DM random effect model. Significant heterogeneity was observed across the 60 experiments (Q- statistic: P < 0.0001; I^2-statistic = 93.34%, Fig. 5).

Year of publication, number of pigs included in the experiments, duration of the experiment, and duration of the probiotic treatment were associated with the FE (P < 0.001) in the meta-regression analysis. However, these covariates explained only 1.80%, 2.41%, 4.30, and 1.76%, respectively, of the heterogeneity. Age of the pigs was not associated with FE (P = 0.544) in the meta- regression (Table 1).

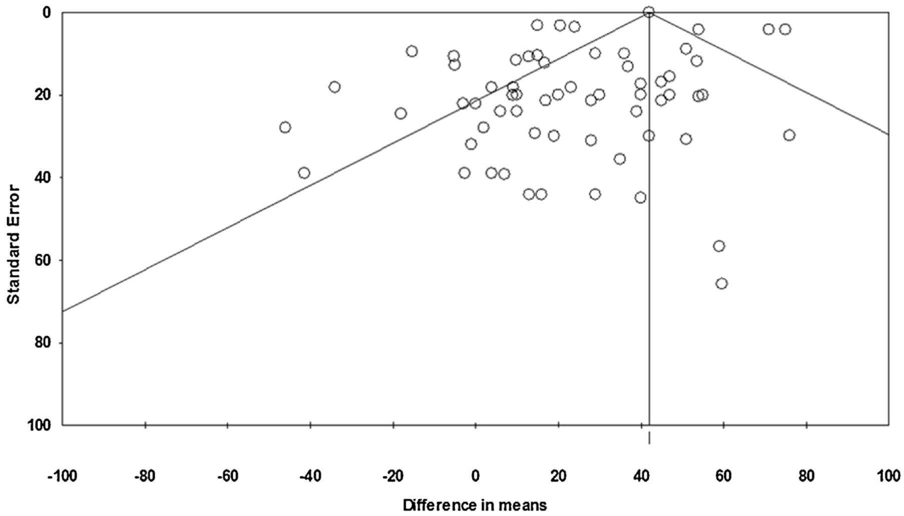

Fig. 4. Funnel plot obtained with the Duval and Tweedie's "Trim-and-Fill" linear random effect model for ADG as an outcome.

Twenty-six experiments conducted before 2010 were identified, and probiotics improved FE (DM = −0.095 kg feed/kg BW, 95% CI −0.132 to −0.058 kg feed/kg BW; Q- statistic: $P < 0.0001$; I^2-statistic = 97.28%). The 34 experiments conducted after 2010 also found a beneficial effect in FE (DM = −0.091 kg feed/kg BW, 95% CI −0.119 to −0.063 kg feed/kg BW; Q-statistic: $P < 0.0001$; I^2- statistic = 72.16%). However, there were no difference between both groups of studies ($P = 0.857$).

The FE of pigs treated with probiotics and control were 1.98 kg feed/kgBW (SD = 0.56 kg feed/kg BW) and 2.11 kg feed/kg BW (SD = 0.60 kg feed/kg BW), respectively. The minimum number of pigs required in an experiment was estimated, considering a 95% CI and a power of 80%. This indicated that experiments should include at least 68 pigs in each group to identify statistical differences between groups. Experiments which used <68 pigs showed the same FE than experiments with >68 pigs ($P = 0.375$). The metaanalysis showed that animals fed with probiotics enhanced FE in experiments with >68 animals (n = 20; DM = −0.084 kg feed/kg BW, 95% CI −0.112 to −0.056 kg feed/kg BW; Q-statistic: $P < 0.0001$; I^2-statistic = 73.19%), and also the probiotic effect was observed in experiments which used less than 68 pigs (n = 40; DM = −0.104 kg feed/kg BW, 95% CI −0.137 to −0.071 kg feed/kg BW; Q-statistic: $P < 0.0001$; I^2-statistic = 95.93%, Fig. 6).

Probiotic supplementation improved FE in experiments which used mono-strain (n = 35; DM = −0.088 kg feed/kg BW, 95% CI −0.119 to −0.056 kg feed/kg BW; Q-statistic: $P < 0.0001$; I^2-statistic = 96.29%) and multi-strain probiotics (n = 25; DM = −0.114 kg feed/kg BW, 95% CI −0.147 to −0.080 kg feed/kg BW; Q-statistic: $P < 0.0001$; I^2-statistic = 74.55%) ($P = 0.265$).

Considering the probiotic species included in the products the probiotic effect remained in those experiments which used *Enterococcus* spp. (n = 14; DM = −0.151 kg feed/kg BW, 95% CI −0.220 to −0.082 kg feed/kg BW), *Pediococcus* spp. (n = 5; DM = −0.147 kg feed/kgBW, 95% CI −0.230 to −0.063 kg feed/kg BW), *Lactobacillus* spp. (n = 23; DM = −0.092 kg feed/kg BW, 95% CI −0.130 to −0.055 kg feed/kg BW), and *Saccharomyces* spp. (n = 10; DM = −0.057 kg feed/kg BW, 95% CI −0.102 to −0.013 kg feed/kg BW). However, in all these cases the absence of these microorganisms also produce a beneficial effect on FE in the probiotic treated groups and there were not significant differences ($P = 0.082$, $P = 0.202$, $P = 0.875$, and $P = 0.079$, respectively). The effect of probiotic supplementation on FE was higher when *Bacillus* spp. were included in the formulation (n = 26; DM = −0.134 kg feed/kg BW, 95% CI −0.184 to −0.085 kg feed/kg BW) than when this species was not included (n = 34; DM = −0.048 kg feed/kg BW, 95% CI −0.073 to −0.024 kg feed/kg BW) ($P = 0.002$). The inclusion of *Bifidobacterium* spp. was not able to induce a positive effect on FE (n = 2; DM = 0.000 kg feed/kg BW, 95% CI −0.039 to 0.039 kg feed/kg BW). However, since the number of experiments that used this microorganism was small, the effect has to be interpreted with caution (Fig. 6).

The probiotic effect on FE was observed when the experiments were conducted during the first stage of the pig grown (from weaning to 18 kg BW) (n = 38; DM = −0.101 kg feed/kg BW, 95% CI −0.138 to −0.068 kg feed/kg BW), during the grown period (18 kgBW to 50 kg BW) (n = 8; DM = −0.116 kg feed/kg BW, 95% CI −0.221 to −0.011 kg feed/kg BW), and finishing (> 50 kgBW) (n = 12; DM = −0.095 kg feed/kg BW, 95% CI −0.131 to −0.060 kg feed/kg BW). However, this positive effect on FE was not observed when the experiments were conducted during the lactation period (n = 2; DM = 0.000 kg feed/kg BW, 95% CI −0.039 to 0.039 kg feed/kg BW).

Regarding the breeds and crossed animals used in the experiments, the probiotic effect on FE was observed when were used F1 pigs (n = 30; DM = −0.149 kg feed/kg BW, 95% CI −0.216 to −0.081 kg feed/kg BW) and three-breed-rotational crossbreeding system (n = 15; DM = −0.095 kg feed/kg BW, 95% CI −0.126 to −0.063 kg feed/kg BW). When crossbreeds and pure breeds were used in the experiments the probiotic effect on FE could not be observed (Fig. 6). Considering the production characteristics of different breeds or crosses of pigs, the probiotic effect on FE could only be observed when there were included in experiments maternal breeds (n = 23; DM = −0.109 kg feed/kg BW, 95% CI −0.139 to −0.079 kg feed/kg BW) and

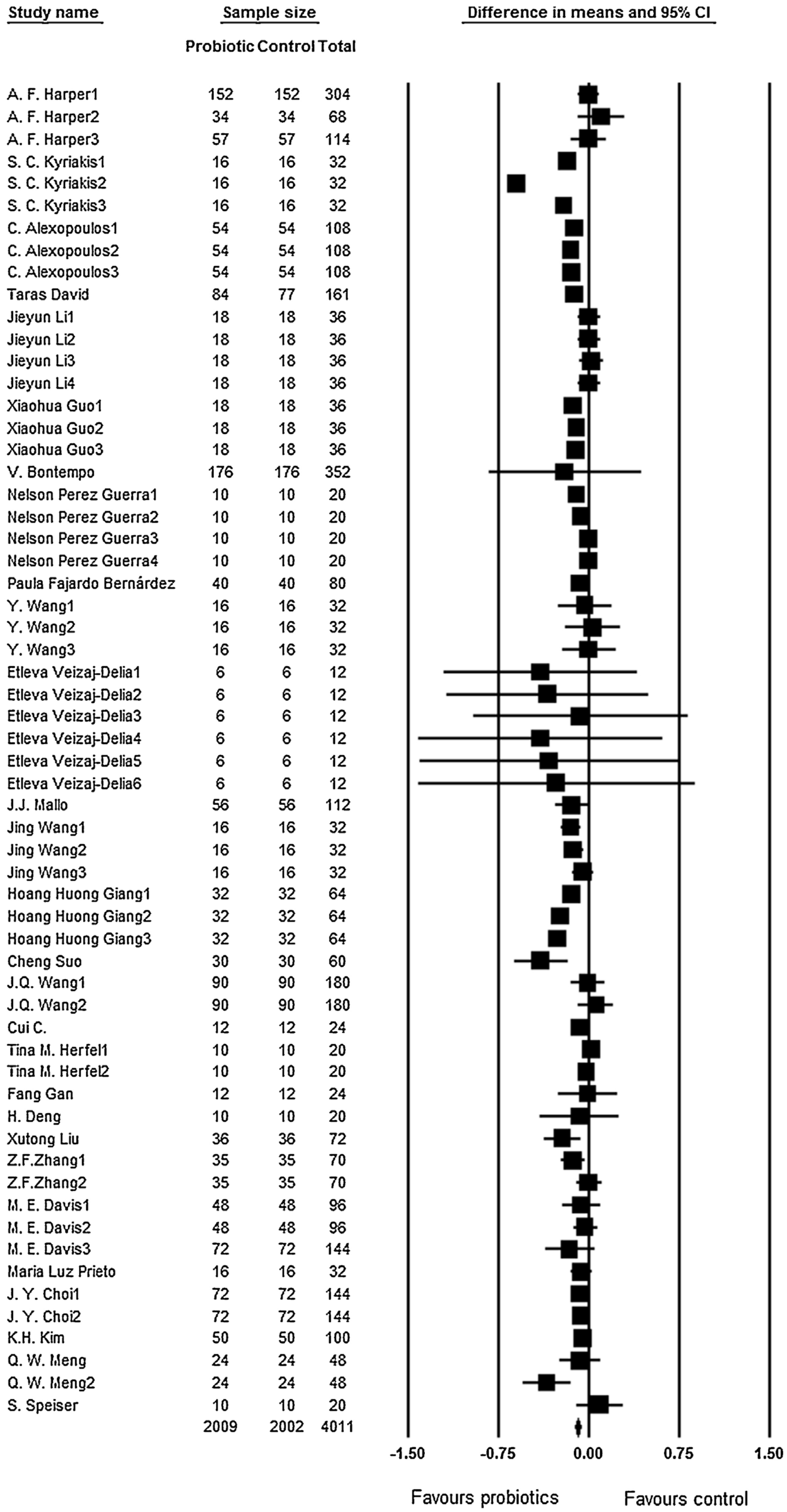

Fig. 5. Forest plot of 60 randomised, controlled trials to study the effect of supplementation with probiotics on feed efficiency (FE) in swines (Harper et al., 1983; Kyriakis et al., 1999; Alexopoulos et al., 2004; Taras et al., 2005; Li et al., 2006; Guo et al., 2006; Bontempo et al., 2006; Guerra et al., 2007; Fajardo-Bernardez et al., 2008; Wang et al., 2009; Veizaj-Delia et al., 2010; Mallo et al., 2010; Wang et al., 2011; Giang et al., 2012; Suo et al., 2012; Wang et al., 2012; Cui et al., 2013; Herfel et al., 2013; Gan et al., 2014; Deng et al., 2014; Liu et al., 2014; Zhang et al., 2014; Davis et al., 2008; Prieto et al., 2014; Choi et al., 2011; Kim et al., 2014; Meng et al, 2010; Speiser et al., 2015).

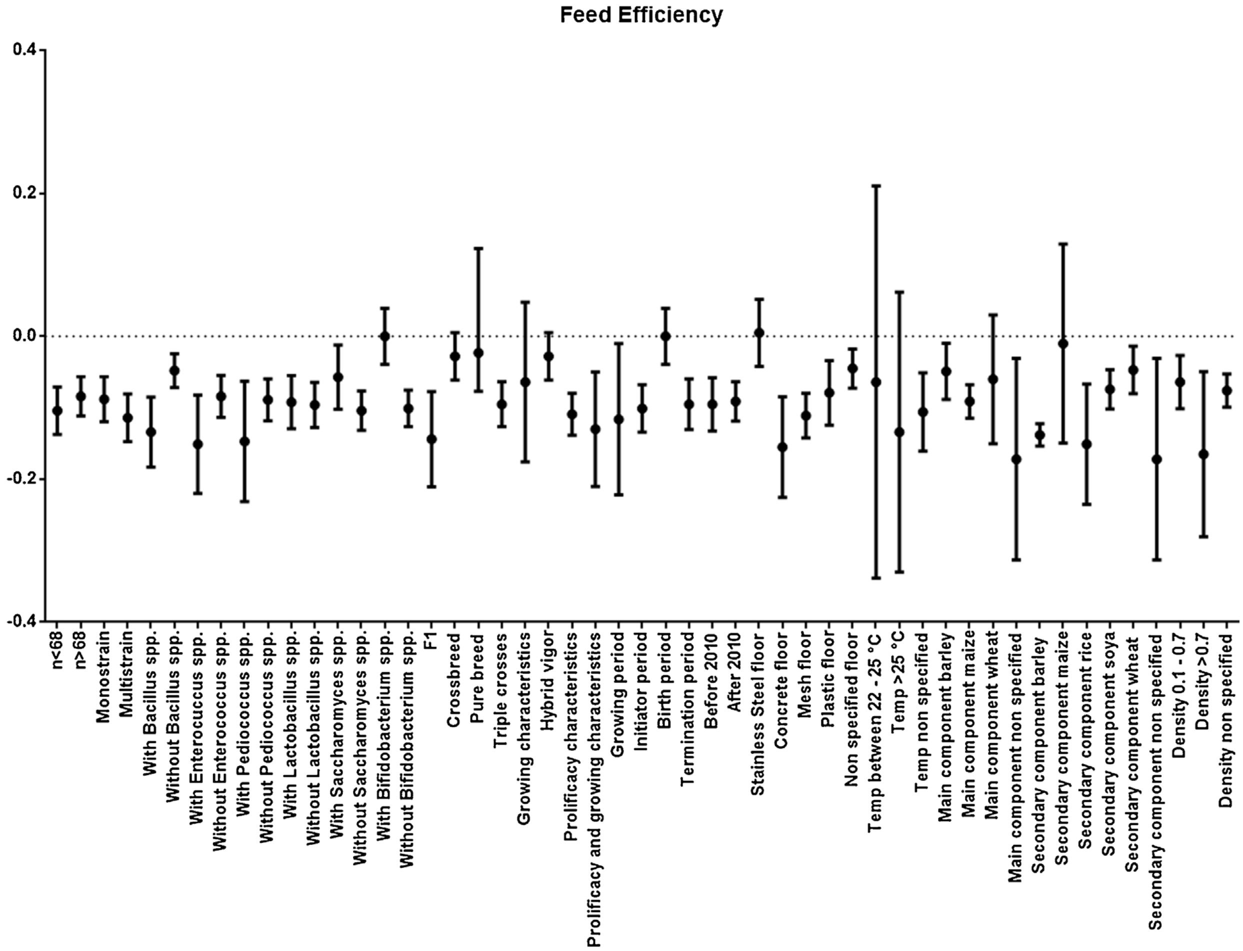

Fig. 6. Subgroup analysis comparing the effect of probiotic supplementation on feed efficiency (FE) of swines.

crosses of maternal breeds and terminal sirebreeds (n = 22; DM = −0.130 kg feed/kg BW, 95% CI −0.209 to −0.050 kg feed/kg BW). Conversely, it was not possible to observe positive effects on FE when crossbreeds or with grown characteristics were included in the experiments (Fig. 6).

The beneficial effect of probiotic on ADG was observed when the litters were from concrete (n = 16; DM = −0.155 kg feed/kg BW, 95% CI −0.226 to −0.083 kg feed/kg BW), mesh (n = 6; DM = −0.111 kg feed/kg BW, 95% CI −0.143 to −0.079 kg feed/kg BW), and plastic (n = 17; DM = −0.079 kg feed/kg BW, 95% CI −0.133 to −0.034 kg feed/kg BW). Conversely, it was not possible to observe positive effects on FE when litters were from stainless stell (Fig. 6).

The probiotic effect on FE was observed when the experiments were conducted in pens with controlled temperature at 22–25 °C (n = 5; DM = −0.134 kg feed/kg BW, 95% CI −0.154 to −0.114 kg feed/kg BW) or 25–31 °C (n = 26; DM = −0.064, 95% CI −0.092 to −0.036 kg feed/kg BW) (Fig. 6).

The probiotic effect on FE was observed when the animal density was 0.1–0.7 pigs/m^2 (n = 12; DM = −0.165 kg feed/kg BW, 95% CI −0.280 to −0.050 kg feed/kg BW) or >0.7 pigs/m^2 (n = 14; DM = −0.064 kg feed/kg BW, 95% CI −0.102 to −0.026 kg feed/kg BW) (Fig. 6).

The beneficial effect of probiotic on FE was observed when the experiments used maize (n = 45; DM = −0.091 kg feed/kg BW, 95% CI −0.115 to −0.066 kg feed/kg BW) or barley (n = 7; DM = −0.049 kg feed/kg BW, 95% CI −0.088 to −0.011 kg feed/kg BW) as the principal feed ingredients. However, when or wheat (n = 1; DM = −0.060 kg feed/kg BW, 95% CI −0.150 to 0.03 kg feed/kg BW) were used, this positive effect on FE was not observed (Fig. 6). However, since the number of experiments that used these ingredients was relatively small, the effect has to be interpreted with caution. Additionally, the beneficial effect of probiotic on FE was observed when the experiments used soybean (n = 32; DM = −0.074, 95% CI −0.101 to −0.046 kg feed/kg BW), wheat (n = 9; DM = −0.047 kg feed/kg BW, 95% CI −0.080 to −0.014 kg feed/kg BW), and rice (n = 6; DM = −0.151 kg feed/kg BW, 95% CI −0.236 to −0.067 kg feed/kg BW) as secondary feed ingredient (Fig. 6).

There was no significant publication bias for these 60 experiments, as confirmed by Begg's test (P = 0.379) and Egger's test (P < 0.136). None studies were identified applying the Duval and Tweedie's trim-and-fill methods (Fig. 7).

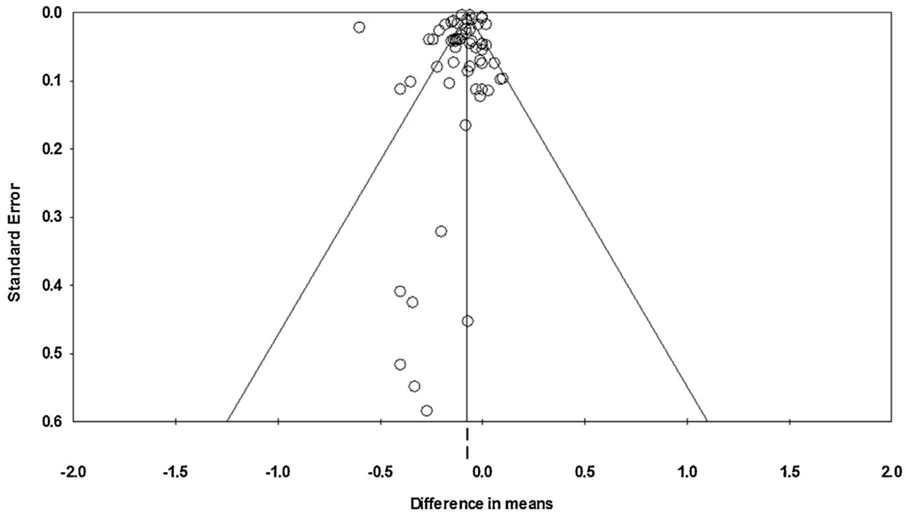

Fig. 7. Funnel plot obtained with the Duval and Tweedie's "Trim-and-Fill" linear random effect model for ADG as an outcome.

4. Discussion

The meta-analysis of data from several randomised controlled experiments showed that probiotics supplementation increased ADG and FE in pigs.

Farm animals raised under intensive methods of management, are extremely susceptible to suffering enteric bacteria imbalance resulting in low digestion and absorption of nutrients and delayed animal growth (Nousiainen and Setälä, 1998). Use of probiotics aims to prevent illnesses and increase productivity (Fuller, 1992).

According with our meta-analysis, the probiotic supplementation had a beneficial effect on ADG (29.939 g) and on FE (−96 g less feed consumed/kg of weight gain). These effects were not modified after the bias adjustment.

Several factors in combination determine the growth performance of the pig between birth and weaning. These factors can be divided into factors related to the herd/sow, the pen, the litter, and the piglet. Piglets are especially susceptible during the first days of life and low piglet weight at weaning implies a loss of income for the farmer (Johanses et al., 2004).

The positive effect of probiotics is achieved through different mechanisms including competition for nutrients, the production of antimicrobial substances (*e.g.*, organic acids, hydrogen peroxide, bacteriocins), host immunomodulation, intestinal adhesion, and competitive exclusion of pathogenic bacteria (Fuller, 1989; Blum et al., 1999; Steer et al., 2000). The results of this Meta – analysis confirm the positive effect of the use of probiotics in piglets according to ADG and FE. However, there is an important heterogeneity between trials, therefore studies should be conducted to identify those factors that could contribute to show positive effect of probiotics addition to the pigs diet.

The number of pigs is a limiting factor in many experiments and this factor may impact directly on the results variability. The number of animals included in a study, affect the probability of finding significant differences when there really is an impact by probiotic supplementation. In this meta-analysis, the probiotic effect on ADG was evident with more or less than 85 pigs. In the case of FE, the probiotic effect was evident with more or less than 65 pigs.

The utilization of mono-strain or multi-strain is another important determinant. The activity of probiotic microorganisms may vary since the functionality of a multi- strain probiotic inoculum could be more effective and consistent than a mono-strain (Timmerman et al., 2005). One of the advantages of a multi-strain inoculum is the possibility of complementary effects of their probiotic properties. Probiotic complex comprising a mixture of lactic acid bacteria was found to be effective in the improving the performance of weaned pigs (Giang et al., 2012). Sanders and Huisin't Veld (1999) suggested that the health effects of probiotics to be genera, species, and strain specific and they further proposed that multistrain and multispecies probiotics to be more effective than monostrain probiotics. However, pigs involved in this meta-analysis that received mono-strain or multi-strain probiotic performed similarly.

In both cases, ADG and FE, the probiotic effect remained in those experiments that included *Lactobacillus* spp., *Enterococcus* spp., and *Saccharomyces* spp. Also, *Bacillus* spp. and *Pediococcus* spp. showed a probiotic effect on ADG and FE, respectively. The inclusion of *Bifidobacterium* spp. was not able to induce a positive effect neither on ADG nor FE.

The effect of probiotic supplementation on ADG was higher when *Pediococcus* spp. were included in the formulation. However, since the number of experiments that used this microorganism was relatively small, the effect has to be interpreted with caution. The inclusion of *Bacillus* spp. shows a higher probiotic effect on the FE. In the gut of the animals, is known, that *Bacillus* spp. enhances the growth and (or) viability of *Lactobacillus* spp., possibly through the production of catalase and subtilisin (Hosoi et al., 2000). Furthermore, *Bacillus* spp. spores resist acid and oxygen, many live spores administered orally may reach the intestine and then affect the microbial community of the feces (Hosoi et al., 1999) (Deng et al., 2013).

With respect to *Pediococcus* spp., it has the potential to exert antagonism against enteric pathogens, primarily through the competition for adhesion sites on the intestinal wall, the stimulation of specific and non-specific immune responses, the suppression of pathogens by competitive exclusion, and the production of lactic acid and secretion of bacteriocins known as pediocins (Daeschel and Klaenhammer, 1985).

Differences in the method of administration of probiotic may be a factor affecting growth performance. Probiotic have enhanced ADG via feed and drinking water, nevertheless the addition on milk replacer was not shown to have a positive impact. The role of colostrum is to provide the piglet with energy and passive immunity during the first days after birth (Le Dividich et al., 2005). This could explain the lack of positive effect in the milk replacer treatment. Regarding to administration of probiotics in drinking water, is generally reported to result in a smaller increase in average daily gain compared with administering them *via* feed (Jin et al., 2000; Kalavethy et al., 2003). However, the studies included regarding to milk replacer and water treatments were few and these results should be taken with caution.

The probiotic effect was evident during the first stage of rearing and finishing in the daily gain. With regard of the feed efficiency the probiotic effect was observed from first stage to finishing, including the growth period. The positive effect was not observed neither in daily gain nor in feed efficiency during lactation period, however, the number of experiments with this results was small, the effect has to be interpreted with caution. Varying results have been reported regarding the effect of probiotics in the different stages of growth. Huang et al. (2004) showed that dietary lactobacilli complex supplementation improved average daily feed intake of piglets from d 0–14. Zhao and Kim (2015) instead not found significant effect on growth performance during the same period. Positive effects on growth performance were observed in the early period after weaning by the addition of lactobacilli complex, but there were no positive effects in later period after weaning (Zhao and Kim, 2015). The efficiency of probiotics should be expected to be higher when the animals are confronted with stress during the early days after weaning. (Zhao and Kim, 2015). Regarding to growing and finishing pigs, the administration of probiotics in high energy and protein density diets is more effective than in low density (Meng et al., 2010; Yan and Kim, 2013). A possible explanation for the benefit after the administration of the probiotic during the growing stage and a short-time at the beginning of the finishing period could be that microbial balance in the gut of these animals is optimized – as is the case in weaners – and a better utilization of nutrients is taking place, thereby leading to faster metabolism and transformation of feed into body mass (ADG, FCR) and transformation into lean meat. However, such an explanation is just a hypothesis, as there is no data available (Alexopoulos et al., 2004)

The utilization of F1 and three-breed-rotational crossbreeding shown beneficial probiotic effect. When crossbreeds and pure breeds were used in the experiments the probiotic effect on ADG and FE could not be observed.

Considering the production characteristics of different breeds or crosses of pigs, the probiotic effect on ADG could only be observed when there were included in experiments maternal breeds and crossbreeding of prolific and rapid growth breeds. On FE, could only be observed when there were included in experiments maternal breeds and crosses of maternal breeds and terminal sirebreeds. It was not possible to observe positive effects when crossbreeds or with grown characteristics were included in the experiments. In the literature review were not found related works to the influence of genetic selection and crossbreeding with the supplementation with probiotics. Robison et al. (2000) found that rates of weight gain was significantly influenced by genetic type, diet, sex, genetic type × diet interaction, and diet × sex interaction. The use of probiotics could help the highest expression of hybrid vigor obtained from crossing different breeds. Studies should be conducted to compare the probiotic effect in piglets obtained from different crosses.

The date on which the experiments were carried did not influence on the outcome variables.

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