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Sarah H. Ison [a,b,*], Susan Jarvis [a,b], Cheryl J. Ashworth [c], and Kenneth M. D. Rutherford [a]

[a] SRUC (Scotland's Rural College), Animal Behaviour & Welfare, Animal & Veterinary Sciences Group, West Mains Road, Edinburgh EH9 3JG, UK

[b] Royal (Dick) School of Veterinary Studies, The University of Edinburgh, Easter Bush Veterinary Centre, Roslin, Midlothian, EH25 9RG, UK

[c] The Roslin Institute and Royal (Dick) School of Veterinary Studies, The University of Edinburgh, Easter Bush Veterinary Centre, Roslin, Midlothian, EH25 9RG, UK

[*] Corresponding author present address: Animal Behavior and Welfare, Department of Animal Science, Michigan State University, 474 S. Shaw Lane, East Lansing, Michigan, 48824, USA

Email: shison@msu.edu

Tel: +1 517 488 278

Abstract

Farrowing is a critical time for sows and piglets. Poor post-farrowing sow recovery, and piglet mortality represent a welfare concern, as well as an economic loss to the pig industry. Providing a non-steroidal anti-inflammatory drug (NSAID) to the sow post-farrowing may improve sow welfare and productivity and thereby improve health status and welfare of the piglets, which would be of economic benefit to pig producers. This study investigated the production effects of providing the NSAID ketoprofen post-farrowing, to 24 primiparous (gilts) and 32 multiparous (sows) breeding pigs, in a randomised, blinded, placebo-controlled trial. Gilts and sows were allocated to receive ketoprofen (treated) or the equivalent volume of saline (control) by intramuscular injection 1.5 hours after the last piglet birth. Data collected included sow feed intake, immune transfer (colostrum and piglet serum immunoglobulin-G (IgG)), nursing behaviour and piglet weight, and mortality. An additional factor in this study was that 13 individuals required additional treatment in the days after farrowing for post-farrowing illness. Therefore, data were analysed using mixed models, including treatment (treated or control), parity group (gilt or sow), and additional treatment (yes or no) as fixed factors. Stepwise binomial logistic regression was used to analyse the association between the experimental factors (treatment, additional treatment, gilt or sow), along with other gilt/sow, litter, and piglet-based measures, with piglet death before weaning. Few treatment effects were seen, with parameters being more affected by whether gilts and sows were treated for illness, or between gilts and sows. The only variable to differ by treatment was suckle grunt duration, which was greater for control compared with treated dams ($P = 0.05$). Feed consumption was greater for sows compared with gilts on days 6 and 7 post-farrowing, and serum IgG was greater in piglets from sows than gilts ($P < 0.05$). Feed consumption was reduced in dams needing additional treatment, from days 2-7 post-farrowing, and those developing illness consumed less feed overall ($P = 0.004$). The best regression model for predicting the odds of a

piglet dying before weaning included number born alive (P = 0.03), requiring additional treatment (P = 0.006), being male (P = 0.0005), and pre-farrowing gilt/sow back-fat (P < 0.0001), which increased the log-odds of death, whereas, piglet body weight decreased the log-odds of death (P < 0.0001). This study did not demonstrate clear benefits to ketoprofen, however, high individual variation in piglet mortality, indicates potential for targeted NSAID use.

Keywords: farrowing; ketoprofen; nursing behaviour; pain; performance; sow

Introduction

Farrowing is a critical time in pig production. A common feature of modern pig production is increased litter size, and as the sow must produce enough milk to feed the litter, feed volume and composition must adjust to cope with the increased demand (Theil, 2015). Further, each piglet must have access to a functioning teat as soon as possible after birth to consume colostrum, followed by milk in order to survive (Baxter et al., 2013). Therefore, the sow must recover quickly following farrowing, including feeding and drinking. However, at that time the immunocompetence of the sow is impaired and as parturition is physically demanding, the vulnerability to illness in early lactation is increased (Friendship and O'Sullivan, 2015).

Post-partum dysgalactia syndrome (PPDS) describes any condition that affects milk production in the sow, including infections of the uterine tract (metritis) and udder (mastitis), but milk production can also decline with no obvious signs of infection (Klopfenstein et al., 2006). A number of non-infectious causes of PPDS have been discussed (Klopfenstein et al., 2006) and pain experienced by the sow could contribute to a decreased interest in the piglets

and a reduction in milk let down (Peltoniemi and Oliviero, 2015). This has resulted in recent research administering non-steroidal anti-inflammatory drugs (NSAIDs) post-farrowing and measuring the benefits to health, welfare and productivity (Homedes et al., 2014; Mainau et al., 2016, 2012; Sabaté et al., 2012; Tenbergen et al., 2014; Viitasaari et al., 2014, 2013).

A previous study, involving 15 commercial farms, investigated the production benefits of providing the NSAID ketoprofen post-farrowing to all sows, and demonstrated a reduction in piglet mortality and a greater number of piglets weaned (Homedes et al., 2014). Another study found no piglet performance benefits of administering ketoprofen, but did identify other sow health and welfare benefits including a reduced loss in back-fat, body condition and constipation, less severe shoulder sores, and a delay in feed refusal (Viitasaari et al., 2013). Two studies in which meloxicam was administered after farrowing found no mortality differences but did show an increased average daily weight gain of low birth weight piglets (Mainau et al., 2012) and a tendency for increased piglet weight gain of litters of 11 to 13 piglets (Tenbergen et al., 2014). Another study using oral meloxicam, demonstrated improvements in piglet weaning weight, average daily gain, and plasma IgG concentrations measured on day 1 and 2 post-farrowing (Mainau et al., 2016). The administration of NSAIDs in addition to antibiotics has also been shown to aid in treatment of infectious causes of PPDS (e.g. Hirsch et al., 2003; Tummaruk and Sang-Gassanee, 2013) and on a farm with a high incidence of PPDS, piglet mortality was reduced and the number of piglets weaned increased in sows given ketoprofen and antibiotics (Sabaté et al., 2012).

Ketoprofen is an NSAID with anti-inflammatory, analgesic, and antipyretic properties, which was shown to reach maximum levels approximately one hour after intramuscular (IM) injection in pigs (Raekallio et al., 2008), and reduced nociceptive thresholds in piglets with kaolin-induced inflammation up to 24 hours after IM injection (Fosse et al., 2011). This study investigated the use of ketoprofen after farrowing for primiparous (hereafter referred to as gilts)

and multiparous (referred to as sows) breeding pigs. The aim was to evaluate the benefits of post-farrowing ketoprofen in terms of: i) gilt/sow feed intake; ii) immune transfer using IgG from colostrum and piglet serum; iii) piglet performance including growth and mortality; and iv) nursing behaviour. Based on previous studies, our hypothesis was that prompt post-farrowing treatment with ketoprofen improves sow recovery, including feed intake, and piglet performance through immune transfer and nursing behaviour.

Materials and Methods

This experiment was carried out under UK Home Office Licence, in compliance with EU Directive 2010/63/EU and following approval from the SRUC Animal Welfare and Ethical Review Body (AWERB).

Animal housing and husbandry

Thirty-two Large White × Landrace multiparous (mean parity 4.63 ± 0.43) and 24 primiparous sows were used in this study. The study was carried out at the SRUC pig research farm (Midlothian, UK), with gilts and sows farrowing in nine batches between February and October 2014. No more than five days before the expected farrowing date, gilts and sows were moved into individual farrowing crates (1.8 × 0.5 m), with solid concrete flooring (1.8 × 1.5 m), a small slatted area at the back (0.5 × 0.5 m) and a water and feed trough at the front. Piglets had access to a heated creep area (1.5 × 0.65 m) in front of the water and feed trough. Gilts and sows were fed a standard pelleted lactation diet twice daily at 0745 and 1530 and had continuous access to fresh water. Gilt and sow crates were cleaned daily at the morning feed, and they were provided with fresh, long-stemmed straw. Additional straw was added and manure removed at the afternoon feed in the days preceding farrowing. Lights were switched on immediately before the morning feed, turned off at 1630 and an additional night-light was provided in the centre of each room of crates.

During the experiment and only after the six hour post-injection data collection, cross-fostering was conducted where necessary to even up litter sizes to maximise piglet survival as per normal farm practice. Cross fostering was conducted regardless of experimental treatments. When litter sizes were uneven, the largest piglet(s) were removed and placed on a gilt or sow with a smaller litter. Beyond the time of cross-fostering, data for individual foster piglets was then recorded against the foster sow. Piglets received an intramuscular injection of iron on day 3 post-farrowing, and on the fourth week after farrowing (mean age 26.39 ± 0.20), weaning took place. At weaning, piglets were ear tagged and vaccinated (CircoFLEX) as per farm practice.

Blinding and treatments

This study was a randomised, blinded, placebo controlled trial, with gilts and sows allocated to receive a single intra-muscular (IM) injection of ketoprofen (Ketofen; Merial Animal Health Limited, Harlow, Essex, UK) or the equivalent volume of saline, 90 minutes following the birth of the last piglet. Gilts and sows in each batch were randomly allocated to receive either ketoprofen (**treated**; 3 mg per kg bodyweight or 1 ml per 33 kg pre-farrowing bodyweight rounded down to the nearest 0.5 ml) or the equivalent volume of saline as a placebo control (**control**). The 56 individuals were balanced as much as possible across batches and for parity over the two treatment groups, however, an error in the treatment allocation, resulted in unbalanced groups for gilts (gilts: treated, n = 11, control, n = 13; sows: parity 2 to 4; treated, n = 9, control, n = 8; parity 5 to 7; treated, n = 5, control, n = 6; parity 8+; treated, n = 2, control, n = 2). One experimenter allocated individuals to the two treatment groups and a second added the ketoprofen or saline to individual brown medicine bottles, sealed with rubber stoppers (Adelphi Healthcare Packaging, Haywards Heath, West Sussex, UK), which were labelled only with the individual gilt or sow ear tag for identification. Ketofen contains the active ingredient

ketoprofen at 100 mg/ml contained in a solution of l arginine, benzyl alcohol (10 mg/ml), citric acid monohydrate and water. It is a clear colourless solution, with low viscosity, making it indistinguishable from the saline placebo to the third experimenter administering the injection, who was unaware of the treatment.

Individuals were closely monitored for signs of farrowing, by observation at twice daily feeding and through remote monitoring using a CCTV digital surveillance system around the clock. Once the piglet expulsion phase began, the time of each piglet birth was recorded; and 90 minutes after the last piglet birth and the gilt or sow appeared to have finished farrowing, ketoprofen or saline was administered by intra-muscular injection. Ketoprofen or saline were injected into the neck muscle, just behind the ear using an 18 gauge, 1.5 inch needle attached to a PVC extension tube and using a 10 or 20 ml syringe (Henry Schein Animal Health, Dumfries, Dumfries and Galloway, UK). Following treatment administration, individuals were left undisturbed.

Piglet measurements

Six hours after the treatment administration, the litters were processed and three piglets per litter were blood sampled. All piglets were collected and shut into the heated creep area during processing. Each piglet was weighed, crown-rump length measured (from the tail base to the top of the crown, in between the ears) and were labelled numerically on the back with a permanent marker. Three piglets per litter were selected to be blood sampled for immunoglobulin-G (IgG), based on weight: one less than 1.3 kg, one between 1.31 and 1.63 kg and one greater than 1.64 kg, balanced across litters for sex. If piglets at all weight ranges were not available, alternatives were selected as close as possible, and very weak piglets were avoided.

158 Selected piglets then had a topical local anaesthetic cream (EMLA) applied to their
159 right ear. Each piglet was then held, while cotton wool soaked in hot water was applied to the
160 right ear to promote vasodilation. A general purpose surgical steel lancet (Hawksley*Vet*,
161 Lancing, Sussex, UK) was used to make a small incision in the most prominent ear vein. Blood
162 was allowed to pool briefly and collected into at least five 50 µl plain capillary tubes
163 (Hawksley*Vet*, Lancing, Sussex, UK). Blood was left to coagulate in the tubes for one hour at
164 room temperature, before being sealed at one end using Cristaseal wax plates (Hawksley*Vet*,
165 Lancing, Sussex, UK), and then placed into a micro haemocrit centrifuge (Hawksley*Vet*,
166 Lancing, Sussex, UK) for 1.5 minutes at 13,000 g. The end of the tube containing the
167 condensed cells was cut off and the serum was pushed out of the remaining section of tube
168 using a clean needle and syringe into a clean, pre-labelled 1.5 ml tube. Samples were then
169 stored at -70 ^{o}C to be assayed at a later date.

170 On day three post-farrowing, piglets were weighed when they were given a routine iron
171 injection. At weaning, piglets were weighed and their crown-rump distance measured. All
172 piglet deaths from birth to weaning were recorded and the cause of death identified by visual
173 examination, and from video recording, including: still birth, crushing by the sow, low
174 viability, starvation, savaged, 'greasy pig' (exudative epidermatis) and 'other' (unidentified
175 causes). During the experiment, several litters were affected by exudative epidermatis, a
176 bacterial skin infection, which was unrelated to the study, and was treated with long-acting
177 antibiotics (amoxicillin).

178 <u>Gilt and sow measurements</u>

179 On moving in before farrowing and out at weaning, all gilts and sows were weighed,
180 body condition scored (1 = very thin, 2 = thin, 3 = not too thin, not too fat, 4 = fat, 5 = very fat)

and had their back-fat depth measured at the P2 position (Piglog 105; Carometec Food Technology, Smørum, Denmark).

At six hours after the treatment during piglet processing, a colostrum sample was collected from the dams. This was done by gently rubbing the udder, to ensure the dam was calm, then expressing colostrum from as many different teats as possible into a clean 30 ml plastic tube. Approximately 5 ml of colostrum was collected in the tube before pipetting into three 1.5 ml pre-labelled tubes, which were stored at -20^{o}C to be assayed for IgG at a later date.

Gilt and sow feed intake was recorded on the day of farrowing, until seven days post-farrowing. Individuals were fed a standard pelleted lactation diet consisting of 16.4% crude protein, 6.8 % crude oils and fats, 4.0% crude fibre, 5.8% crude ash, 13.8% moisture, 0.8% calcium, 0.94% lysine, 0.25% methionine, 0.51% phosphorus and 0.22% sodium. Gilts and sows were fed, based on a feed chart, which was adjusted slightly according to the size, body condition and appetite of the individual (e.g. gilts were fed slightly less than sows and a reduced body condition score was given slightly more feed). Feed intake was restricted, and increased gradually from day 0 to day 7. The amount fed was marked on the feed chart (in kg) and the amount left over from the previous feed was removed, weighed and recorded at the next feeding time.

Behaviour

Closed-circuit television (CCTV) cameras (LL20, infra-red cameras, FR concepts, Ireland) were mounted above each farrowing crate and were connected to a computer to record behaviour using GeoVision Digital Surveillance System software (ezCCTV ltd, Herts, UK). This surveillance system was also set up to enable remote monitoring of individuals. Digital video footage was collected and stored to be observed later using The Observer XT 11.0 (Noldus Information Technology, Wageningen, The Netherlands). Three hour observations

were made for suckling behaviour between 15 and 18 hours after the last piglet was born, to coincide with a regular pattern of milk let down and udder massage by the piglets, (Castren et al., 1989) which enabled obvious nursing bouts to be recognised on video. The frequencies and duration of suckle grunting (rapid flank movements indicating suckle grunting), whether more than 50% of piglets were active at the udder (performing udder massage/rapid suckling movements), as well as gilt and sow posture (stand, sit, kneel, lie lateral, lie ventral) and drinking behaviour (snout in the drinking trough with head movements indicating drinking behaviour) were recorded.

Analysis of Immunoglobulin G (IgG) concentrations

Sow colostrum and piglet serum samples were assayed for IgG using an enzyme linked immunosorbent assay (ELISA) kit (Bethyl Laboratories, Inc., Montgomery, Texas, USA). Colostrum and serum samples were removed from the freezer and allowed to thaw gradually at 4 ^{o}C overnight before the assay. On the day of the assay, samples were removed from the fridge, placed at room temperature for 30 minutes before further preparation.

Colostrum samples were centrifuged twice at 16,249 g for 2 minutes, removing the fat layer after each spin. Serum samples were centrifuged for one minute at 865 g. Assays were then conducted according to the manufacturer's instructions, with samples tested in duplicate. A test assay was run, indicating that a 1:500,000 dilution was best for both sample types. This dilution was created using serial dilution in, un-coated V-bottomed 96-well plates.

Quality control (QCs) samples were created using pooled colostrum samples to run across and between plates to measure drift within and between plates. To avoid drift in the time taken to add the samples to the coated plate, 130 µl of standards, blanks, samples and QCs were added to an uncoated 96-well plate according to the plate layout, before using a multi-channel pipette to transfer into the coated plate. The plate was read using a Multiskan^{TM} FC Microplate

Photometer plate reader and results calculated using a 5 point logistic regression curve using Thermo Scientific SkanIt™ for Multiskan™ FC software (version 2.5.1) (Thermo Fisher Scientific Inc, Waltham, Massachusetts, USA). Samples were spread across nine assay runs, balanced as much as possible for treatment, sample type (colostrum or serum), for gilts and sows and between farrowing batches. Duplicate samples with a coefficient of variation (CV) above 10% were repeated and those that failed to reach a CV% of less than 10% were left as missing values. The assay range was 1.37 – 1000 ng/ml.

The lower and upper detectable limits of the samples analysed were 4.76 and 77.37 ng/ml respectively. The average intra-assay CV was 6.66% (7.79, 6.91, 4.51, 6.69, 9.35, 6.17, 6.58, 9.07 and 2.82 for assay runs 1 to 9 respectively) and the inter-assay CV was 8.69%.

Data analysis

Unless stated at the start of each results section, data were available for all individuals. Due to an error in the treatment allocation for gilts, there were 11 gilts and 16 sows in the ketoprofen treated group and 13 gilts and 16 sows in the saline control group. An additional factor in this study was that 13 individuals; 5 gilts (4 treated and 1 control treatment) and 8 sows (4 treated and 4 control treatments) required additional treatment in the days after farrowing for PPDS. Therefore, data were analysed by treatment (treated vs. control), parity group at the level of gilt vs. sow and whether additional treatment was needed (yes vs. no). All data were analysed and descriptive statistics calculated using R version 3.3.1 (R core team, 2013). All figures were plotted using the ggplot2 function, and any correlations were conducted using the spearman.test function. Results were considered statistically significant at $P < 0.05$.

Feed intake

Feed consumed was analysed with linear mixed models, using the lmer function, with dam identity and batch in the random model. Initially, total feed consumed was analysed with treatment (treated or control), parity group (gilt or sow) and additional treatment (yes or no) and their interactions as fixed factors. Then each of the factor interactions with day was tested (0, 1, 2, 3, 4, 5, 6, and 7), including: day × treatment, day × gilt/sow and day × additional treatment. Post hoc analyses were conducted using the lsmeans function.

Immunoglobulin-G (IgG)

Colostrum IgG concentrations (mg/ml) were analysed using linear mixed models with the lmer function, with batch in the random model. Treatment (treated or control), parity group (gilt or sow) and additional treatment (yes or no), and their interactions, and the number of piglets born alive were added as fixed factors. Piglet serum IgG was also analysed using the lmer function, with dam identity and batch in the random model, also with treatment (treated or control), parity group (gilt or sow) and additional treatment (yes or no) and their interactions, and piglets born alive as fixed factors. A Spearman's rank correlation coefficient was calculated between piglet weight (kg) and IgG concentration (mg/ml), resulting in no significant correlation (rho = 0.039, $P = 0.64$), therefore piglet weight was not included in the model.

Production data

The frequency of piglets born alive, still born, and number weaned, as well as live-born pre-weaning deaths were analysed at the litter level with a generalized linear mixed model, using the glmer function, using a Poisson distribution and log link function. Sow weights, bat-fat thickness, and piglet weights and crown rump distances were analysed using linear mixed

models with the lmer function. The number of piglets born alive was included as a random variable in the piglet mortality model. Gilt/sow identity and batch were included in the random model for the piglet measures, and batch for the sow measures. Treatment, additional treatment, gilt or sow and the interactions as fixed factors in all models. No piglets were fostered before the 6 hour post-injection sampling, therefore fostered piglets were analysed with their birth dam for the 6 hour post-injection measures, and with their foster dam for the other piglet measures. Sow weight and back-fat thickness was then analysed with moving in or post-weaning as a fixed factor, also with batch and ID in the random model. Body condition scores were analysed with ordinal logistic regression models using the polr function, with treatment, additional treatment, gilt or sow and the interactions, and batch as fixed factors, and with moving-in or post-weaning, and batch as fixed factors.

Piglets that were born alive were allocated as dead (yes) or alive (no) by weaning. A stepwise binomial logistic regression was conducted using the glm and AIC.step functions, to analyse associations between variables, and whether piglets died before weaning (yes or no). Variables included: treatment (treated or control), additional treatment (yes or no), gilt or sow, batch, litter size at birth, piglet gender, piglet post 6 hour weight, and whether the piglet was fostered (yes or no), as well as sow back-fat, body condition score, farrowing duration (previously obtained from video footage), and lie lateral duration from behavioural observations. Variables were chosen, based on available data, and including known risk factors for piglet mortality (e.g. Baxter and Edwards, 2015).

Behaviour

Postures (stand, sit, kneel, lie lateral, lie ventral), suckle grunting and the duration when there were more than 50 % of piglets active at the udder, were converted to percentages of the three hour observation duration. The frequency of posture changes during the three hour

observation period was also calculated. Individual bouts of suckle grunting were exported from The Observer for each gilt or sow, to calculate the frequency of bouts, the mean duration of each bout, and the mean inter-bout intervals. These behavioural variables were analysed using linear mixed models with the lmer function, including treatment (treated or control), parity group (gilt or sow) and additional treatment (yes or no) and their interactions as fixed factors, with batch in the random model.

Results

Feed intake

Total feed consumed did not differ by treatment × gilt/sow (t = -0.49, *P* = 0.62), treatment × additional treatment (t = 1.39, *P* = 0.17), or gilt/sow × additional treatment (t = 1.19, *P* = 0.23), by treatment (t = 0.33, *P* = 0.74), or between gilts and sows (t = 1.37, *P* = 0.17) (Fig.1). However, total feed consumed differed by day × additional treatment (t = -3.65, *P* = 0.0003), day × gilt/sow (t = 3.20, *P* = 0.002), and overall by additional treatment (t = -2.92, *P* = 0.004). Post hoc analysis revealed that sows consumed more feed compared with gilts on days 6 and 7 post-farrowing (Fig.1 b) and that although individuals requiring additional treatment consumed less feed throughout, the difference was not significant until day 2 post farrowing (Fig.1 c).

Immunoglobulin-G (IgG)

Colostrum IgG concentrations were available for 52 of the 56 gilts and sows. No significant interactions (treatment × gilt/sow: t = 0.40, *P* = 0.69; treatment × additional treatment: t = 0.85, *P* = 0.40; gilt/sow × additional treatment: t = -0.32, *P* = 0.75) were found, or differences for treatment (t = -0.81, *P* = 0.42), between gilts and sows (t = 0.73, *P* = 0.47), or with additional treatment (t = -0.14, *P* = 0.89) (Fig.2, A-C).

Of the 168 piglets that were blood sampled, serum IgG concentrations were available for 147 piglets. There were no differences by treatment × gilt/sow (t = -0.75, P = 0.46), treatment × additional treatment (t = 1.03, P = 0.31), or gilt/sow × additional treatment (t = -0.78, P = 0.44). Piglets from sows had greater IgG concentrations than those from gilts (t = 2.10, P = 0.04), but piglet serum IgG, did not differ by treatment (t = -0.15, P = 0.88), or additional treatment (t = -0.22, P = 0.82) (Fig.2, D-F).

Production data

Table 1 presents production information, including litter, gilt/sow- and piglet-based measures, by treatment, for gilts and sows, and by additional treatment. Table 2 presents the total frequencies and causes of death, and frequencies of piglets fostered on and off treated and control gilts and sows, to illustrate the total numbers of piglet deaths by treatment for gilts and sows, and the imbalance in piglet fostering between treatments. Figure 3 is a dot plot showing the number of live-born deaths for individual treated and control gilts and sows, which shows the individual variation in piglet pre-weaning deaths. There were no significant treatment × gilt/sow, treatment × additional treatment, or gilt/sow × additional treatment interactions for any of the results presented in Table 1 ($P > 0.05$). As shown, none of the results presented differed by treatment, or additional treatment ($P > 0.05$). However, pre-farrow and post-wean weight differed between gilts and sows, as did the piglet weight and crown-rump measurements for piglets from gilts and sows (see Table 1). In addition, gilt or sow weight (t = -12.25, $P < 0.001$), back-fat (t = -10.66, $P < 0.001$), and body-condition (t = -5.12, $P < 0.001$) were greater overall pre-farrowing, compared with post-weaning.

Of the 705 piglets born alive, any row with missing values for any of the variables was excluded, leaving 659 rows of data for analysis. The best logistic regression model included the variables piglets born alive, additional treatment, piglet gender, sow back-fat, and piglet 6

hour post-injection weight, which were significant predictors of death before weaning. For every increase in piglet born alive in the litter, the log odds of dying before weaning increased (log-odds = 0.11, $P = 0.03$). Requiring additional treatment (log-odds = 0.87, $P = 0.006$), as well as being male (log-odds = 0.97, $P = 0.0005$) increased the log odds of dying before weaning. For every mm increase in gilt or sow back-fat, the log-odds of piglet death increased (log-odds = 0.16, $P < 0.0001$). Every kg increase in piglet 6 hour post-injection bodyweight, decreased the log-odds of dying before weaning, (log-odds = -4.18, $P < 0.0001$).

Behaviour

Behaviour was observed for 53 of the 56 individuals and results are shown in Table 2. There were no significant interactions for treatment × gilt/sow, treatment × additional treatment, or gilt/sow × additional treatment, for any of the behaviours shown in Table 3 ($P > 0.05$). For nursing behaviour, ketoprofen treated dams suckle grunted less (t = -2.02, $P = 0.05$) than the controls, but there were no other differences between treatment groups, gilts and sows and those requiring additional treatment or not ($P > 0.05$). For the postures observed, sitting and kneeling behaviour differed between gilts and sows (t = 2.08, $P = 0.04$ and t = 2.49, $P = 0.02$ respectively), with greater values for sows compared with gilts. Lying lateral also differed (t = -2.38, $P = 0.02$) with greater values for gilts than sows. There were no differences in drinking behaviour between treatment groups, gilts and sows or those requiring additional treatment or not ($P > 0.05$).

Discussion

This study investigated effects of the provision of the NSAID ketoprofen to gilts and sows following farrowing. Few effects of the treatment were seen, with production parameters being more affected by whether individuals were treated for disease, or between gilts and sows.

Feed intake

In contrast to a previous study (Viitasaari et al., 2013), there was no difference in feed consumption by gilts or sows given ketoprofen compared with controls. The previous study administered ketoprofen for three consecutive days following farrowing, which could have had a greater effect on sows, and overall feed refusal rather than consumption was measured (Viitasaari et al., 2013). In another study where the NSAID meloxicam was administered for three days post-farrowing, feed intake was not affected by drug treatment, but a difference between primiparous and multiparous sows was found, as multiparous sows had consumed a greater number of meals within an hour of feeding on days one, two and three post-farrowing (Mainau et al., 2012). In the current study, sows consumed more feed than gilts on days six and seven post-farrowing, as sows increased their feed intake at a greater rate than gilts. The feed that was not consumed was only measured at the next feeding time in this study, whereas the previous study scored feed as being completely consumed or not, one hour after it was given (Mainau et al., 2012). From day two after farrowing, and overall, there was a difference in the amount of feed consumed by individuals that required additional treatment compared to those that did not. This is not surprising as reduced feed intake is a good indicator of illness. In future studies, it would be interesting to measure the latency to feed and the time taken to fully consume the meal, as this could be an early indicator of subclinical PPDS and prompt treatment could produce a better outcome for the sow and litter.

Immune transfer

Piglets obtain passive immunity through the ingestion of immunoglobulin from sow colostrum (Rooke and Bland, 2002), and those with low concentrations of immunoglobulin are less likely to survive (Cabrera et al., 2012). Therefore, this is an important measure in identifying the benefits of administering post-farrowing NSAIDs. No differences in colostrum

or piglet serum IgG concentrations were detected in this study with drug treatment or whether additional treatment was required. A previous study found greater colostrum concentrations of piglets on day one and two post-farrowing from sows given oral meloxicam at farrowing (Mainau et al., 2016). As piglets were numerically heavier at six hours post-injection in this study, which could indicate greater colostrum intake, a difference may have been found if piglets were sampled at later time points.

Some studies have shown a link between colostrum intake and piglet birth weight (Devillers et al., 2007; Fraser and Rushen, 1992; Nguyen et al., 2013; Quesnel, 2011), although the link between colostrum consumed and piglet plasma IgG concentration plateau over a certain value, i.e. the link is stronger at lower concentrations (Devillers et al., 2011). No association between piglet weight and IgG at the point of sampling was found in this study, which was similar to a previous study (Cabrera et al., 2012), however, this could be explained by excessively small and/or weak piglets not being selected for blood sampling in the current and previous study (Cabrera et al., 2012). In addition, Fraser and Rushen, (1992) suggest that the failure to find a link between birth weight and IgG could be because of differences in blood volume (affecting the concentration) between large and small piglets.

Sow colostrum had a numerically greater IgG concentration than gilt colostrum, and piglet serum IgG was greater for piglets from sows compared with gilts. No link between piglet plasma IgG concentration and parity was detected at birth in one study (Quesnel, 2011), and another study showed a similar result, although it was not mentioned whether primiparous sows were included (Nguyen et al., 2013). Other studies measuring sow colostrum have found differences by parity, including lower concentrations measured 24 hours after birth in lower parity sows (Quesnel, 2011) and lower colostrum IgG concentrations in primiparous compared with multiparous sows 48-72 hours after birth (Cabrera et al., 2012).

Production data

There were no overall significant differences in pre-weaning piglet deaths, weight or size by treatment, or between those requiring additional treatment or not. However, it is worth discussing that numerically fewer piglets died in the ketoprofen compared with the saline-treated group, especially for gilts. High individual variation in piglet mortality was seen in this study, which possibly resulted in this difference not reaching significance. As piglet weight six hours after the injection was also numerically greater in ketoprofen-treated gilts and sows, it is also possible that piglet birth weight was greater for treated gilts and sows, resulting in the mortality difference. It is also possible that ketoprofen treatment increased piglet weight at six hours through increased colostrum intake, however, based on previous studies measuring early piglet weight gain, this may not have accounted for all of this weight difference (e.g. de Passillé and Rushen, 1989; Fraser and Rushen, 1992; Quesnel, 2011). This cannot be confirmed, since piglets were not weighed before the injection was given, and in a previous study, where 16 sows were randomly allocated to be given butorphanol tartrate or a saline placebo post-farrowing, Haussmann et al., (1999) found a significant difference in birth weight of the piglets, with those from control sows being significantly heavier. So this may be an accidental outcome in this study and an important consideration for the piglet mortality difference between treatment groups.

A reduction in piglet mortality with the use of ketoprofen post-farrowing has been demonstrated previously in a study of 15 commercial farms (Homedes et al., 2014) and on a farm with a high incidence of PPDS (Sabaté et al., 2012), but another study reported no difference in mortality with the use of ketoprofen (Viitasaari et al., 2013). The individuals responsible for the care of the animals in the current study were blind to the treatments, and cross-fostering was performed to even litter size, resulting in more piglets being fostered off

439 the ketoprofen-treated gilts and more piglets being fostered onto the control gilts. This meant,
440 despite a difference in mortality, no difference in the numbers of piglets weaned was detected
441 between treatment groups for gilts, which is a result found in previously, where fostering was
442 only conducted within treatment groups (Homedes et al., 2014; Sabaté et al., 2012). If
443 ketoprofen does have an influence on piglet mortality, given the individual variation in the
444 number of deaths, early identification to enable targeted use of drugs to those that could benefit
445 the most would be the best use of drugs. No difference in mortality between treatment groups
446 was detected the post-farrowing administration of the NSAID meloxicam (Mainau et al., 2012;
447 Tenbergen et al., 2014) or with the opioid butorphanol tartrate (Haussmann et al., 1999).
448 However, average daily weight gain of low birth weight piglets (<1180g) was increased
449 (Mainau et al., 2012), growth rate of medium sized litters (11 to 13 piglets) tended to be greater
450 (Tenbergen et al., 2014), and average daily gain and weaning weight was greater (Mainau et
451 al., 2016) for multiparous sows treated with meloxicam compared with a placebo.

452 Piglet mortality in this study was most influenced by previously demonstrated risk
453 factors, including piglet weight, sow back-fat, piglet gender, sow post-farrowing illness and
454 the number of piglets born alive (for a review see Baxter and Edwards, 2015). It is widely
455 agreed that birth weight is the most important factor in neonatal piglet survival and lower
456 average piglet weight at six hours post-injection in this study was most strongly associated with
457 pre-weaning death. Larger litter sizes come at the expense of reduced piglet viability, as well
458 as increased competition for colostrum and milk (Baxter and Edwards, 2015). Interestingly,
459 greater sow back-fat was associated with an increase in the odds of a piglet dying before
460 weaning. A previous study using a high number of sows found a quadratic effect of sow back-
461 fat at farrowing on the number of piglets weaned, with low and high back-fat being associated
462 with fewer piglets weaned (Kim et al., 2015). Male-biased pre-weaning mortality has been
463 found elsewhere, where piglets born were male-biased, and males were heavier at birth (Baxter

et al., 2012). This demonstrates a life-history strategy in domestic pig populations, with greater pre-natal maternal investment and an over-supply of more vulnerable males, in expectation of greater mortality (Baxter et al., 2012). Litter from sows developing PPDS suffer greater mortality (Klopfenstein et al., 2006), and treatment with NSAIDs in addition to antibiotics, can aid in the treatment of infectious causes of PPDS (Sabaté et al., 2012; Tummaruk and Sang-Gassanee, 2013).

Behaviour

Posture was observed during nursing behaviour observations, with no differences by treatment. Previous studies investigating the administration of ketoprofen (Viitasaari et al., 2014) and meloxicam (Mainau et al., 2012) for three consecutive days post-farrowing showed differences in the level of activity between individuals given the NSAID or a saline placebo only on the third day post farrowing. This included a decrease in the time spent lying by meloxicam treated gilts and sows (Mainau et al., 2012) and an increased activity in younger (parity 2 -3) sows treated with ketoprofen, compared with their placebo treated counterparts, although older sows did not differ (Viitasaari et al., 2014). Greater activity suggests an improvement in the speed of recovery following parturition with the use of NSAIDs. By contrast, another study, using the opioid analgesic butorphanol tartrate post-farrowing showed a reduced number of posture changes 48 hours post farrowing (Haussmann et al., 1999).

Sows showed more sitting and kneeling behaviour compared with gilts, which could be related to the difference in size, weight and fitness between these two groups and the ease of changing body position. The gilts in this study spent more time lying lateral, in contrast to a previous study that showed younger sows to be more active (Viitasaari et al., 2014). This could be due to genetic improvements, as the gilts in this study were acquired directly from a breeding company, whereas the sows were home bred from an older genetic line of the same breed.

Modern breeding programs have focused on maternal traits to improve productivity, which could be reflected in greater lateral lying, allowing piglets access to the udder. Although there were no significant differences in posture between individuals that required additional treatment for PPDS, numerical differences for postures and the frequency of posture changes indicate PPDS individuals appear less active and, as with a reduction in feed intake, could be used as an early indication of PPDS to provide prompt treatment.

For the nursing behaviours observed, there was greater suckle grunting in control, compared with ketoprofen-treated dams. These data could indicate that ketoprofen dams had settled into a pattern of milk let-down sooner, providing support for the fact that the weight difference between ketoprofen and control-treatment dams could be due to greater colostrum intake. No previous studies have recorded nursing behaviour in relation to the use of post-farrowing NSAIDs.

Conclusion

This study did not demonstrate production benefits to the immediate post-farrowing administration of ketoprofen. However, in this study, as with others, high individual sow variation in piglet mortality was seen, with some performing well and the majority of piglet mortality often coming from a low number of sows (Baxter et al., 2015; Hales et al., 2013). Investigating whether pain is a component of decreased performance in these sows, could enable the targeted use of drugs. Additionally, identifying sows that could benefit from pain relief using measures of farrowing ease (e.g. Mainau et al., 2010), feed intake, activity and other behaviour measures, could assist with targeted drug treatment.

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611

612 Fig.1. Mean ± SEM of the total feed consumed (kg) per day by a) treatment (treated or
613 control); b) gilts and sows and; c) additional treatment (yes or no). Bars with a * indicate a
614 significant difference ($P < 0.05$).

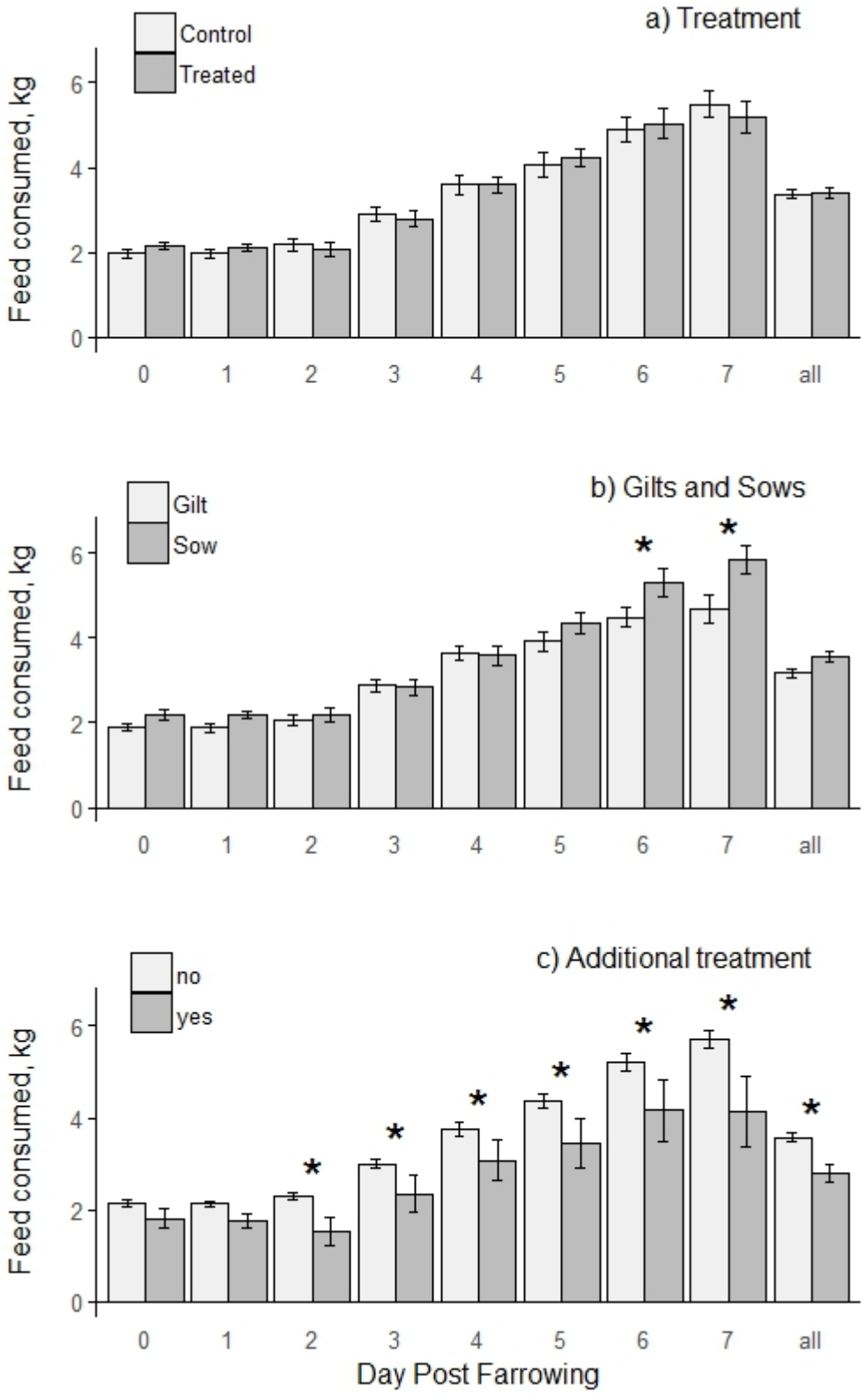

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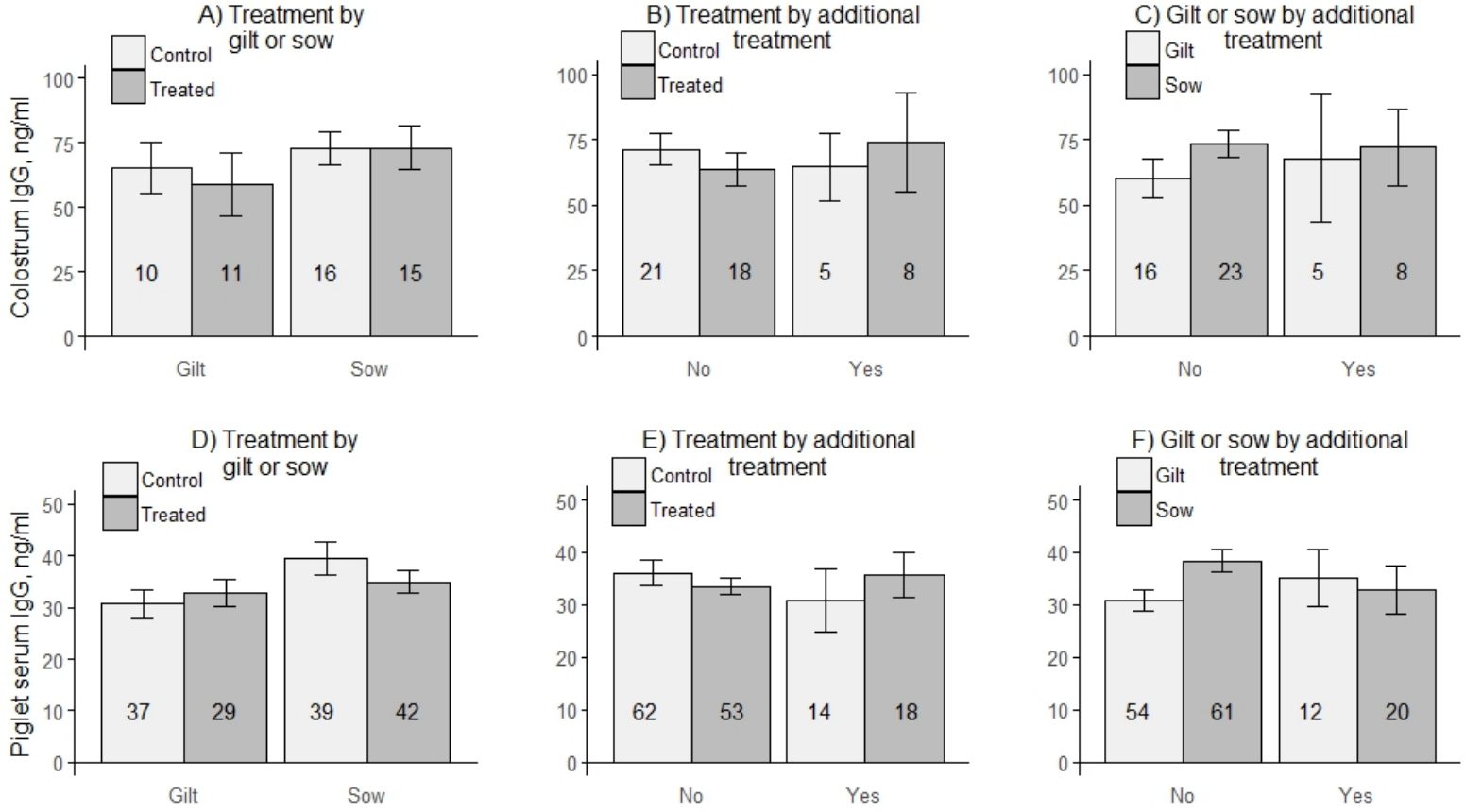
Fig.2. Mean ± SEM for colostrum immunoglobulin-G concentrations (mg/ml) for A) gilts and sows × treatment; B) additional treatment (yes or no) × drug treatment and; C) additional treatment (yes or no) × gilts and sows. Mean ± SEM for piglet serum immunoglobulin-G concentrations (mg/ml) for D) gilts and sows × treatment; E) additional treatment (yes or no) × drug treatment and; F) additional treatment (yes or no) × gilts and sows. Labels on the bars indicate the number of samples represente



621 Fig.3. Dot plot of individual gilt or sow live-born piglet deaths by treatment.

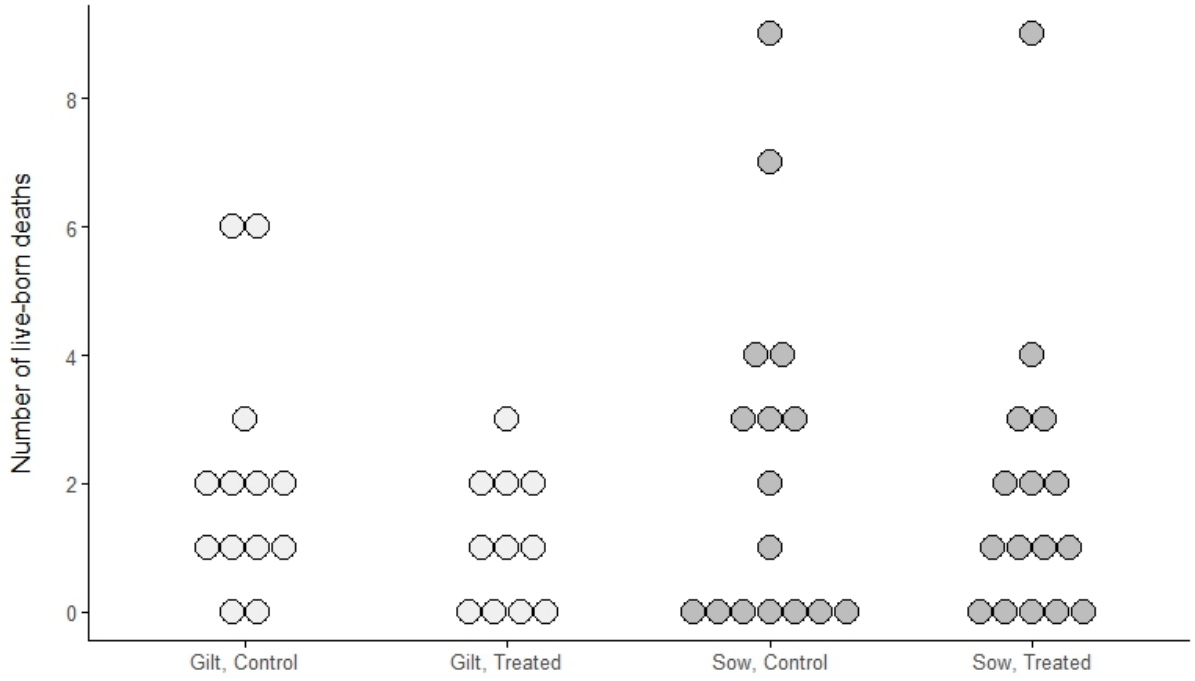


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Table 1. Production information presented by treatment, gilts and sows, and additional treatment, including litter-based measures, gilts/sow based measures taken before moving in and at weaning, and piglet-based measures. Body condition was scored from 1 to 5 (1 = very thin, 5 = very fat) Gilt/sow data with different letters, represents an overall difference pre-farrowing, compared with post-weaning ($P < 0.001$). *One sow weaning weight is missing.

Production data	Treatment			Gilt or sow			Additional treatment		
	Treated	Control	*P*	Gilt	Sow	*P*	Yes	No	*P*
Litter data									
Born alive, frequency	12.6±0.7	13.0±0.7	0.92	12.3±0.8	13.2±0.6	0.65	13.5±0.9	12.6±0.5	0.65
Still born, frequency	0.4±0.2	0.5±0.2	0.66	0.2±0.1	0.7±0.2	0.16	0.3±0.2	0.5±0.1	0.99
Number weaned, frequency	10.7±0.4	10.9±0.3	0.91	10.8±0.4	10.9±0.3	0.62	10.5±0.4	10.9±0.3	0.72
Live-born deaths, frequency	2.4±0.3	3.0±0.4	0.37	2.5±0.3	2.9±0.4	0.83	3.4±0.6	2.5±0.3	0.23
Gilt/sow data									
[a] Pre farrow weight, kg	260.2±7.7	261.5±7.7	0.87	223.4±5.8	289.0±3.5	0.00003	266.5±10.9	259.2±6.3	0.89
[b] Post wean weight, kg	228.5±7.9	231.7±7.9	0.96	199.2±5.96	254.2±5.1*	0.01	228.2±12.5	230.8±5.9	0.52
[a] Pre farrow back-fat, mm	19.0±0.8	18.8±0.9	0.44	17.4±0.9	20.0±0.8	0.33	19.1±1.4	18.8±0.7	0.48
[b] Post wean back-fat, mm	14.0±0.8	14.2±0.7	0.93	13.3±0.9	14.7±0.6	0.85	13.5±0.9	14.3±0.6	0.79
[a] Pre farrow body condition score	3.1±0.1	3.2±0.1	0.69	3.3±0.1	3.1±0.1	0.34	3.2±0.1	3.2±0.04	0.54
[b] Post wean body condition score	2.6±0.1	2.7±0.1	0.18	2.7±0.1	2.7±0.1	0.35	2.7±0.1	2.7±0.1	0.87
Piglet data									
Piglet 6 hour weight, kg	1.5±0.02	1.4±0.02	0.19	1.3±0.02	1.51±0.02	0.002	1.5±0.03	1.4±0.02	0.87
Piglet 6 hour crown-rump, cm	27.1±0.1	26.4±0.1	0.34	25.8±0.1	27.37±0.12	0.002	26.9±0.2	26.7±0.1	0.74
Piglet day 3 weight, kg	1.8±0.02	1.7±0.02	0.25	1.7±0.02	1.86±0.02	0.009	1.8±0.03	1.8±0.02	0.57
Piglet wean weight, kg	8.00±0.1	7.6±0.1	0.24	7.2±0.1	8.16±0.09	0.008	7.6±0.2	7.8±0.1	0.75
Piglet wean crown-rump, cm	50.3±0.3	49.5±0.2	0.62	48.7±0.3	50.72±0.25	0.06	49.2±0.4	50.1±0.2	0.74

628 **Table 2.** Frequencies of pre-weaning deaths, including totals and separated by suspected cause
629 of death, and the frequencies of piglets that were fostered on and off the litter for the 11 treated
630 and 13 control gilts and 16 treated and 16 control sows.

	GILT		SOW		**Totals**
	Treated (n = 11)	Control (n = 13)	Treated (n = 16)	Control (n = 16)	
Crushed	4	12	7	10	**33**
Low viability	2	8	8	8	**26**
Starve	1	1	6	7	**15**
Savage	0	1	4	1	**6**
Greasy pig	2	2	2	10	**16**
Other	0	3	1	2	**6**
Total deaths	**9**	**27**	**28**	**38**	**102**
Fostered on	4	13	5	7	**29**
Fostered off	14	5	11	12	**42**

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Table 3. Behaviour results (mean ± SEM) by treatment, gilts or sows and additional treatment, for three hour observations between 15 and 18 hours after the last piglet was born. Results are displayed as a percentage of time in the three hour observation (% of time), frequency of events in the observation, duration in seconds or minutes. Columns with a different letter indicate a difference ($P < 0.05$).

Behaviour	Treatment		Gilts vs. Sow		Additional treatment	
	Treated	Control	Gilt	Sow	Yes	No
Sow behaviour						
Stand, % of time	8.4±1.5	9.2±1.9	7.6±1.6	9.8±1.8	6.1±1.6	9.4±1.4
Sit, % of time	1.1±0.3	2.2±0.5	1.1±0.2[a]	2.2±0.5[b]	1.8±1.1	1.6±0.3
Kneel, % of time	0.1±0.04	0.1±0.03	0.1±0.01[a]	0.2±0.04[b]	0.1±0.04	0.1±0.03
Lie lateral, % of time	79.7±3.3	77.2±3.6	83.3±2.9[a]	74.4±3.7[b]	86.1±3.5	76.6±2.8
Lie ventral, % of time	10.7±2.9	11.3±2.9	8.0±1.9	13.5±3.3	5.9±2.4	12.2±2.4
Posture changes, frequency	12.8±1.8	13.3±2.1	11.1±1.7	14.7±2.1	9.6±2.7	13.9±1.6
Drinking, seconds	121.2±25.0	122.1±26.6	124.5±31.0	119.3±21.4	142.0±38.4	116.9±20.6
Nursing behaviour						
> 50 % of piglets active at udder, % of time	16.9±1.3	18.7±1.2	17.8±1.2	17.8±1.3	16.9±1.8	18.1±1.0
Suckle grunt duration, % of time	11.9±0.9[a]	14.5±1.0[b]	13.8±1.1	12.8±0.9	11.2±0.9	13.7±0.8
Suckle grunt bouts, frequency	5.2±0.4	5.9±0.4	5.4±0.4	5.7±0.5	5.0±0.5	5.7±0.4
Mean suckle grunt bout duration, seconds	254.9±8.9	276.7±10.5	280.8±11.6	253.7±8.0	245.6±15.7	270.7±7.8
Inter bout interval, minutes	34.0±2.3	30.6±1.9	32.3±2.3	32.2±2.0	33.3±2.2	32.0±1.8