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1 **The effect of post-farrowing ketoprofen on sow feed intake, nursing behaviour and**
2 **piglet performance**

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14 **Abstract**

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

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

45

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

47 **Introduction**

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

57 Post-partum dysgalactia syndrome (PPDS) describes any condition that affects milk
58 production in the sow, including infections of the uterine tract (metritis) and udder (mastitis),
59 but milk production can also decline with no obvious signs of infection (Klopfenstein et al.,
60 2006). A number of non-infectious causes of PPDS have been discussed (Klopfenstein et al.,
61 2006) and pain experienced by the sow could contribute to a decreased interest in the piglets

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

66 A previous study, involving 15 commercial farms, investigated the production
67 benefits of providing the NSAID ketoprofen post-farrowing to all sows, and demonstrated a
68 reduction in piglet mortality and a greater number of piglets weaned (Homedes et al., 2014).
69 Another study found no piglet performance benefits of administering ketoprofen, but did
70 identify other sow health and welfare benefits including a reduced loss in back-fat, body
71 condition and constipation, less severe shoulder sores, and a delay in feed refusal (Viitasaari
72 et al., 2013). Two studies in which meloxicam was administered after farrowing found no
73 mortality differences but did show an increased average daily weight gain of low birth weight
74 piglets (Mainau et al., 2012) and a tendency for increased piglet weight gain of litters of 11 to
75 13 piglets (Tenbergen et al., 2014). Another study using oral meloxicam, demonstrated
76 improvements in piglet weaning weight, average daily gain, and plasma IgG concentrations
77 measured on day 1 and 2 post-farrowing (Mainau et al., 2016). The administration of
78 NSAIDs in addition to antibiotics has also been shown to aid in treatment of infectious causes
79 of PPDS (e.g. Hirsch et al., 2003; Tummaruk and Sang-Gassanee, 2013) and on a farm with a
80 high incidence of PPDS, piglet mortality was reduced and the number of piglets weaned
81 increased in sows given ketoprofen and antibiotics (Sabaté et al., 2012).

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

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

94 **Materials and Methods**

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

98 Animal housing and husbandry

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

110 farrowing. Lights were switched on immediately before the morning feed, turned off at 1630
111 and an additional night-light was provided in the centre of each room of crates.

112 During the experiment and only after the six hour post-injection data collection, cross-
113 fostering was conducted where necessary to even up litter sizes to maximise piglet survival as
114 per normal farm practice. Cross fostering was conducted regardless of experimental
115 treatments. When litter sizes were uneven, the largest piglet(s) were removed and placed on a
116 gilt or sow with a smaller litter. Beyond the time of cross-fostering, data for individual foster
117 piglets was then recorded against the foster sow. Piglets received an intramuscular injection
118 of iron on day 3 post-farrowing, and on the fourth week after farrowing (mean age $26.39 \pm$
119 0.20), weaning took place. At weaning, piglets were ear tagged and vaccinated (CircoFLEX)
120 as per farm practice.

121 Blinding and treatments

122 This study was a randomised, blinded, placebo controlled trial, with gilts and sows
123 allocated to receive a single intra-muscular (IM) injection of ketoprofen (Ketofen; Merial
124 Animal Health Limited, Harlow, Essex, UK) or the equivalent volume of saline, 90 minutes
125 following the birth of the last piglet. Gilts and sows in each batch were randomly allocated to
126 receive either ketoprofen (**treated**; 3 mg per kg bodyweight or 1 ml per 33 kg pre-farrowing
127 bodyweight rounded down to the nearest 0.5 ml) or the equivalent volume of saline as a
128 placebo control (**control**). The 56 individuals were balanced as much as possible across
129 batches and for parity over the two treatment groups, however, an error in the treatment
130 allocation, resulted in unbalanced groups for gilts (gilts: treated, n = 11, control, n = 13;
131 sows: parity 2 to 4; treated, n = 9, control, n = 8; parity 5 to 7; treated, n = 5, control, n = 6;
132 parity 8+; treated, n = 2, control, n = 2). One experimenter allocated individuals to the two
133 treatment groups and a second added the ketoprofen or saline to individual brown medicine

134 bottles, sealed with rubber stoppers (Adelphi Healthcare Packaging, Haywards Heath, West
135 Sussex, UK), which were labelled only with the individual gilt or sow ear tag for
136 identification. Ketofen contains the active ingredient ketoprofen at 100 mg/ml contained in a
137 solution of l arginine, benzyl alcohol (10 mg/ml), citric acid monohydrate and water. It is a
138 clear colourless solution, with low viscosity, making it indistinguishable from the saline
139 placebo to the third experimenter administering the injection, who was unaware of the
140 treatment.

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

150 Piglet measurements

151 Six hours after the treatment administration, the litters were processed and three
152 piglets per litter were blood sampled. All piglets were collected and shut into the heated creep
153 area during processing. Each piglet was weighed, crown-rump length measured (from the tail
154 base to the top of the crown, in between the ears) and were labelled numerically on the back
155 with a permanent marker. Three piglets per litter were selected to be blood sampled for
156 immunoglobulin-G (IgG), based on weight: one less than 1.3 kg, one between 1.31 and 1.63
157 kg and one greater than 1.64 kg, balanced across litters for sex. If piglets at all weight ranges

158 were not available, alternatives were selected as close as possible, and very weak piglets were
159 avoided.

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

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

180 Gilt and sow measurements

181 On moving in before farrowing and out at weaning, all gilts and sows were weighed,
182 body condition scored (1 = very thin, 2 = thin, 3 = not too thin, not too fat, 4 = fat, 5 = very
183 fat) and had their back-fat depth measured at the P2 position (Piglog 105; Carometec Food
184 Technology, Smørum, Denmark).

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

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

201 Behaviour

202 Closed-circuit television (CCTV) cameras (LL20, infra-red cameras, FR concepts,
203 Ireland) were mounted above each farrowing crate and were connected to a computer to
204 record behaviour using GeoVision Digital Surveillance System software (ezCCTV Ltd, Herts,

205 UK). This surveillance system was also set up to enable remote monitoring of individuals.
206 Digital video footage was collected and stored to be observed later using The Observer XT
207 11.0 (Noldus Information Technology, Wageningen, The Netherlands). Three hour
208 observations were made for suckling behaviour between 15 and 18 hours after the last piglet
209 was born, to coincide with a regular pattern of milk let down and udder massage by the
210 piglets, (Castren et al., 1989) which enabled obvious nursing bouts to be recognised on video.
211 The frequencies and duration of suckle grunting (rapid flank movements indicating suckle
212 grunting), whether more than 50% of piglets were active at the udder (performing udder
213 massage/rapid suckling movements), as well as gilt and sow posture (stand, sit, kneel, lie
214 lateral, lie ventral) and drinking behaviour (snout in the drinking trough with head
215 movements indicating drinking behaviour) were recorded.

216 Analysis of Immunoglobulin G (IgG) concentrations

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

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

227 Quality control (QCs) samples were created using pooled colostrum samples to run
228 across and between plates to measure drift within and between plates. To avoid drift in the

229 time taken to add the samples to the coated plate, 130 µl of standards, blanks, samples and
230 QCs were added to an uncoated 96-well plate according to the plate layout, before using a
231 multi-channel pipette to transfer into the coated plate. The plate was read using a
232 Multiskan™ FC Microplate Photometer plate reader and results calculated using a 5 point
233 logistic regression curve using Thermo Scientific SkanIt™ for Multiskan™ FC software
234 (version 2.5.1) (Thermo Fisher Scientific Inc, Waltham, Massachusetts, USA). Samples were
235 spread across nine assay runs, balanced as much as possible for treatment, sample type
236 (colostrum or serum), for gilts and sows and between farrowing batches. Duplicate samples
237 with a coefficient of variation (CV) above 10% were repeated and those that failed to reach a
238 CV% of less than 10% were left as missing values. The assay range was 1.37 – 1000 ng/ml.

239 The lower and upper detectable limits of the samples analysed were 4.76 and 77.37
240 ng/ml respectively. The average intra-assay CV was 6.66% (7.79, 6.91, 4.51, 6.69, 9.35, 6.17,
241 6.58, 9.07 and 2.82 for assay runs 1 to 9 respectively) and the inter-assay CV was 8.69%.

242 Data analysis

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

252 were conducted using the `spearman.test` function. Results were considered statistically
253 significant at $P < 0.05$.

254 *Feed intake*

255 Feed consumed was analysed with linear mixed models, using the `lmer` function, with
256 dam identity and batch in the random model. Initially, total feed consumed was analysed with
257 treatment (treated or control), parity group (gilt or sow) and additional treatment (yes or no)
258 and their interactions as fixed factors. Then each of the factor interactions with day was tested
259 (0, 1, 2, 3, 4, 5, 6, and 7), including: $\text{day} \times \text{treatment}$, $\text{day} \times \text{gilt/sow}$ and $\text{day} \times \text{additional}$
260 treatment. Post hoc analyses were conducted using the `lsmeans` function.

261 *Immunoglobulin-G (IgG)*

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

272 *Production data*

273 The frequency of piglets born alive, still born, and number weaned, as well as live-
274 born pre-weaning deaths were analysed at the litter level with a generalized linear mixed

275 model, using the glmer function, using a Poisson distribution and log link function. Sow
276 weights, bat-fat thickness, and piglet weights and crown rump distances were analysed using
277 linear mixed models with the lmer function. The number of piglets born alive was included as
278 a random variable in the piglet mortality model. Gilt/sow identity and batch were included in
279 the random model for the piglet measures, and batch for the sow measures. Treatment,
280 additional treatment, gilt or sow and the interactions as fixed factors in all models. No piglets
281 were fostered before the 6 hour post-injection sampling, therefore fostered piglets were
282 analysed with their birth dam for the 6 hour post-injection measures, and with their foster
283 dam for the other piglet measures. Sow weight and back-fat thickness was then analysed with
284 moving in or post-weaning as a fixed factor, also with batch and ID in the random model.
285 Body condition scores were analysed with ordinal logistic regression models using the polr
286 function, with treatment, additional treatment, gilt or sow and the interactions, and batch as
287 fixed factors, and with moving-in or post-weaning, and batch as fixed factors.

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

297 *Behaviour*

298 Postures (stand, sit, kneel, lie lateral, lie ventral), suckle grunting and the duration
299 when there were more than 50 % of piglets active at the udder, were converted to percentages
300 of the three hour observation duration. The frequency of posture changes during the three
301 hour observation period was also calculated. Individual bouts of suckle grunting were
302 exported from The Observer for each gilt or sow, to calculate the frequency of bouts, the
303 mean duration of each bout, and the mean inter-bout intervals. These behavioural variables
304 were analysed using linear mixed models with the lmer function, including treatment (treated
305 or control), parity group (gilt or sow) and additional treatment (yes or no) and their
306 interactions as fixed factors, with batch in the random model.

307 **Results**

308 Feed intake

309 Total feed consumed did not differ by treatment \times gilt/sow ($t = -0.49$, $P = 0.62$),
310 treatment \times additional treatment ($t = 1.39$, $P = 0.17$), or gilt/sow \times additional treatment ($t =$
311 1.19 , $P = 0.23$), by treatment ($t = 0.33$, $P = 0.74$), or between gilts and sows ($t = 1.37$, $P =$
312 0.17) (Fig.1). However, total feed consumed differed by day \times additional treatment ($t = -3.65$,
313 $P = 0.0003$), day \times gilt/sow ($t = 3.20$, $P = 0.002$), and overall by additional treatment ($t = -$
314 2.92 , $P = 0.004$). Post hoc analysis revealed that sows consumed more feed compared with
315 gilts on days 6 and 7 post-farrowing (Fig.1 b) and that although individuals requiring
316 additional treatment consumed less feed throughout, the difference was not significant until
317 day 2 post farrowing (Fig.1 c).

318 Immunoglobulin-G (IgG)

319 Colostrum IgG concentrations were available for 52 of the 56 gilts and sows. No
320 significant interactions (treatment \times gilt/sow: $t = 0.40$, $P = 0.69$; treatment \times additional

321 treatment: $t = 0.85$, $P = 0.40$; gilt/sow \times additional treatment: $t = -0.32$, $P = 0.75$) were found,
322 or differences for treatment ($t = -0.81$, $P = 0.42$), between gilts and sows ($t = 0.73$, $P = 0.47$),
323 or with additional treatment ($t = -0.14$, $P = 0.89$) (Fig.2, A-C).

324 Of the 168 piglets that were blood sampled, serum IgG concentrations were available
325 for 147 piglets. There were no differences by treatment \times gilt/sow ($t = -0.75$, $P = 0.46$),
326 treatment \times additional treatment ($t = 1.03$, $P = 0.31$), or gilt/sow \times additional treatment ($t = -$
327 0.78 , $P = 0.44$). Piglets from sows had greater IgG concentrations than those from gilts ($t =$
328 2.10 , $P = 0.04$), but piglet serum IgG, did not differ by treatment ($t = -0.15$, $P = 0.88$), or
329 additional treatment ($t = -0.22$, $P = 0.82$) (Fig.2, D-F).

330 Production data

331 Table 1 presents production information, including litter, gilt/sow- and piglet-based
332 measures, by treatment, for gilts and sows, and by additional treatment. Table 2 presents the
333 total frequencies and causes of death, and frequencies of piglets fostered on and off treated
334 and control gilts and sows, to illustrate the total numbers of piglet deaths by treatment for
335 gilts and sows, and the imbalance in piglet fostering between treatments. Figure 3 is a dot plot
336 showing the number of live-born deaths for individual treated and control gilts and sows,
337 which shows the individual variation in piglet pre-weaning deaths. There were no significant
338 treatment \times gilt/sow, treatment \times additional treatment, or gilt/sow \times additional treatment
339 interactions for any of the results presented in Table 1 ($P > 0.05$). As shown, none of the
340 results presented differed by treatment, or additional treatment ($P > 0.05$). However, pre-
341 farrow and post-wean weight differed between gilts and sows, as did the piglet weight and
342 crown-rump measurements for piglets from gilts and sows (see Table 1). In addition, gilt or
343 sow weight ($t = -12.25$, $P < 0.001$), back-fat ($t = -10.66$, $P < 0.001$), and body-condition ($t = -$
344 5.12 , $P < 0.001$) were greater overall pre-farrowing, compared with post-weaning.

345 Of the 705 piglets born alive, any row with missing values for any of the variables
346 was excluded, leaving 659 rows of data for analysis. The best logistic regression model
347 included the variables piglets born alive, additional treatment, piglet gender, sow back-fat,
348 and piglet 6 hour post-injection weight, which were significant predictors of death before
349 weaning. For every increase in piglet born alive in the litter, the log odds of dying before
350 weaning increased (log-odds = 0.11, $P = 0.03$). Requiring additional treatment (log-odds =
351 0.87, $P = 0.006$), as well as being male (log-odds = 0.97, $P = 0.0005$) increased the log odds
352 of dying before weaning. For every mm increase in gilt or sow back-fat, the log-odds of
353 piglet death increased (log-odds = 0.16, $P < 0.0001$). Every kg increase in piglet 6 hour post-
354 injection bodyweight, decreased the log-odds of dying before weaning, (log-odds = -4.18, $P <$
355 0.0001).

356 Behaviour

357 Behaviour was observed for 53 of the 56 individuals and results are shown in Table 2.
358 There were no significant interactions for treatment \times gilt/sow, treatment \times additional
359 treatment, or gilt/sow \times additional treatment, for any of the behaviours shown in Table 3 ($P >$
360 0.05). For nursing behaviour, ketoprofen treated dams suckle grunted less ($t = -2.02$, $P =$
361 0.05) than the controls, but there were no other differences between treatment groups, gilts
362 and sows and those requiring additional treatment or not ($P > 0.05$). For the postures
363 observed, sitting and kneeling behaviour differed between gilts and sows ($t = 2.08$, $P = 0.04$
364 and $t = 2.49$, $P = 0.02$ respectively), with greater values for sows compared with gilts. Lying
365 lateral also differed ($t = -2.38$, $P = 0.02$) with greater values for gilts than sows. There were
366 no differences in drinking behaviour between treatment groups, gilts and sows or those
367 requiring additional treatment or not ($P > 0.05$).

368 **Discussion**

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

373 Feed intake

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

392 Immune transfer

393 Piglets obtain passive immunity through the ingestion of immunoglobulin from sow
394 colostrum (Rooke and Bland, 2002), and those with low concentrations of immunoglobulin
395 are less likely to survive (Cabrera et al., 2012). Therefore, this is an important measure in
396 identifying the benefits of administering post-farrowing NSAIDs. No differences in
397 colostrum or piglet serum IgG concentrations were detected in this study with drug treatment
398 or whether additional treatment was required. A previous study found greater colostrum
399 concentrations of piglets on day one and two post-farrowing from sows given oral meloxicam
400 at farrowing (Mainau et al., 2016). As piglets were numerically heavier at six hours post-
401 injection in this study, which could indicate greater colostrum intake, a difference may have
402 been found if piglets were sampled at later time points.

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

413 Sow colostrum had a numerically greater IgG concentration than gilt colostrum, and
414 piglet serum IgG was greater for piglets from sows compared with gilts. No link between
415 piglet plasma IgG concentration and parity was detected at birth in one study (Quesnel,

416 2011), and another study showed a similar result, although it was not mentioned whether
417 primiparous sows were included (Nguyen et al., 2013). Other studies measuring sow
418 colostrum have found differences by parity, including lower concentrations measured 24
419 hours after birth in lower parity sows (Quesnel, 2011) and lower colostrum IgG
420 concentrations in primiparous compared with multiparous sows 48-72 hours after birth
421 (Cabrera et al., 2012).

422 Production data

423 There were no overall significant differences in pre-weaning piglet deaths, weight or
424 size by treatment, or between those requiring additional treatment or not. However, it is
425 worth discussing that numerically fewer piglets died in the ketoprofen compared with the
426 saline-treated group, especially for gilts. High individual variation in piglet mortality was
427 seen in this study, which possibly resulted in this difference not reaching significance. As
428 piglet weight six hours after the injection was also numerically greater in ketoprofen-treated
429 gilts and sows, it is also possible that piglet birth weight was greater for treated gilts and
430 sows, resulting in the mortality difference. It is also possible that ketoprofen treatment
431 increased piglet weight at six hours through increased colostrum intake, however, based on
432 previous studies measuring early piglet weight gain, this may not have accounted for all of
433 this weight difference (e.g. de Passillé and Rushen, 1989; Fraser and Rushen, 1992; Quesnel,
434 2011). This cannot be confirmed, since piglets were not weighed before the injection was
435 given, and in a previous study, where 16 sows were randomly allocated to be given
436 butorphanol tartrate or a saline placebo post-farrowing, Hausmann et al., (1999) found a
437 significant difference in birth weight of the piglets, with those from control sows being
438 significantly heavier. So this may be an accidental outcome in this study and an important
439 consideration for the piglet mortality difference between treatment groups.

440 A reduction in piglet mortality with the use of ketoprofen post-farrowing has been
441 demonstrated previously in a study of 15 commercial farms (Homedes et al., 2014) and on a
442 farm with a high incidence of PPDS (Sabaté et al., 2012), but another study reported no
443 difference in mortality with the use of ketoprofen (Viitasaari et al., 2013). The individuals
444 responsible for the care of the animals in the current study were blind to the treatments, and
445 cross-fostering was performed to even litter size, resulting in more piglets being fostered off
446 the ketoprofen-treated gilts and more piglets being fostered onto the control gilts. This meant,
447 despite a difference in mortality, no difference in the numbers of piglets weaned was detected
448 between treatment groups for gilts, which is a result found in previously, where fostering was
449 only conducted within treatment groups (Homedes et al., 2014; Sabaté et al., 2012). If
450 ketoprofen does have an influence on piglet mortality, given the individual variation in the
451 number of deaths, early identification to enable targeted use of drugs to those that could
452 benefit the most would be the best use of drugs. No difference in mortality between treatment
453 groups was detected the post-farrowing administration of the NSAID meloxicam (Mainau et
454 al., 2012; Tenbergen et al., 2014) or with the opioid butorphanol tartrate (Hausmann et al.,
455 1999). However, average daily weight gain of low birth weight piglets (<1180g) was
456 increased (Mainau et al., 2012), growth rate of medium sized litters (11 to 13 piglets) tended
457 to be greater (Tenbergen et al., 2014), and average daily gain and weaning weight was greater
458 (Mainau et al., 2016) for multiparous sows treated with meloxicam compared with a placebo.

459 Piglet mortality in this study was most influenced by previously demonstrated risk
460 factors, including piglet weight, sow back-fat, piglet gender, sow post-farrowing illness and
461 the number of piglets born alive (for a review see Baxter and Edwards, 2015). It is widely
462 agreed that birth weight is the most important factor in neonatal piglet survival and lower
463 average piglet weight at six hours post-injection in this study was most strongly associated
464 with pre-weaning death. Larger litter sizes come at the expense of reduced piglet viability, as

465 well as increased competition for colostrum and milk (Baxter and Edwards, 2015).
466 Interestingly, greater sow back-fat was associated with an increase in the odds of a piglet
467 dying before weaning. A previous study using a high number of sows found a quadratic effect
468 of sow back-fat at farrowing on the number of piglets weaned, with low and high back-fat
469 being associated with fewer piglets weaned (Kim et al., 2015). Male-biased pre-weaning
470 mortality has been found elsewhere, where piglets born were male-biased, and males were
471 heavier at birth (Baxter et al., 2012). This demonstrates a life-history strategy in domestic pig
472 populations, with greater pre-natal maternal investment and an over-supply of more
473 vulnerable males, in expectation of greater mortality (Baxter et al., 2012). Litter from sows
474 developing PPDS suffer greater mortality (Klopfenstein et al., 2006), and treatment with
475 NSAIDs in addition to antibiotics, can aid in the treatment of infectious causes of PPDS
476 (Sabaté et al., 2012; Tummaruk and Sang-Gassanee, 2013).

477 Behaviour

478 Posture was observed during nursing behaviour observations, with no differences by
479 treatment. Previous studies investigating the administration of ketoprofen (Viitasaari et al.,
480 2014) and meloxicam (Mainau et al., 2012) for three consecutive days post-farrowing showed
481 differences in the level of activity between individuals given the NSAID or a saline placebo
482 only on the third day post farrowing. This included a decrease in the time spent lying by
483 meloxicam treated gilts and sows (Mainau et al., 2012) and an increased activity in younger
484 (parity 2 -3) sows treated with ketoprofen, compared with their placebo treated counterparts,
485 although older sows did not differ (Viitasaari et al., 2014). Greater activity suggests an
486 improvement in the speed of recovery following parturition with the use of NSAIDs. By
487 contrast, another study, using the opioid analgesic butorphanol tartrate post-farrowing

488 showed a reduced number of posture changes 48 hours post farrowing (Hausmann et al.,
489 1999).

490 Sows showed more sitting and kneeling behaviour compared with gilts, which could
491 be related to the difference in size, weight and fitness between these two groups and the ease
492 of changing body position. The gilts in this study spent more time lying lateral, in contrast to
493 a previous study that showed younger sows to be more active (Viitasaari et al., 2014). This
494 could be due to genetic improvements, as the gilts in this study were acquired directly from a
495 breeding company, whereas the sows were home bred from an older genetic line of the same
496 breed. Modern breeding programs have focused on maternal traits to improve productivity,
497 which could be reflected in greater lateral lying, allowing piglets access to the udder.
498 Although there were no significant differences in posture between individuals that required
499 additional treatment for PPDS, numerical differences for postures and the frequency of
500 posture changes indicate PPDS individuals appear less active and, as with a reduction in feed
501 intake, could be used as an early indication of PPDS to provide prompt treatment.

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

508 **Conclusion**

509 This study did not demonstrate production benefits to the immediate post-farrowing
510 administration of ketoprofen. However, in this study, as with others, high individual sow
511 variation in piglet mortality was seen, with some performing well and the majority of piglet

512 mortality often coming from a low number of sows (Baxter et al., 2015; Hales et al., 2013).
513 Investigating whether pain is a component of decreased performance in these sows, could
514 enable the targeted use of drugs. Additionally, identifying sows that could benefit from pain
515 relief using measures of farrowing ease (e.g. Mainau et al., 2010), feed intake, activity and
516 other behaviour measures, could assist with targeted drug treatment.

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- 619

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

623 Fig.2. Mean \pm SEM for colostrum immunoglobulin-G concentrations (mg/ml) for A) gilts and
624 sows \times treatment; B) additional treatment (yes or no) \times drug treatment and; C) additional
625 treatment (yes or no) \times gilts and sows. Mean \pm SEM for piglet serum immunoglobulin-G
626 concentrations (mg/ml) for D) gilts and sows \times treatment; E) additional treatment (yes or no)
627 \times drug treatment and; F) additional treatment (yes or no) \times gilts and sows. Labels on the bars
628 indicate the number of samples represented.

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