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Sergio López-Soria, Miquel Nofrarías, Maria Calsamiglia, Anna Espinal, Oliver Valero, et al..
Post-weaning multisystemic wasting syndrome (PMWS) clinical expression under field conditions
is modulated by the pig genetic background. *Veterinary Microbiology*, 2011, 149 (3-4), pp.352.
10.1016/j.vetmic.2010.12.009 . hal-00683506

HAL Id: hal-00683506

<https://hal.science/hal-00683506>

Submitted on 29 Mar 2012

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Accepted Manuscript

Title: Post-weaning multisystemic wasting syndrome (PMWS) clinical expression under field conditions is modulated by the pig genetic background

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PII: S0378-1135(10)00582-1
DOI: doi:10.1016/j.vetmic.2010.12.009
Reference: VETMIC 5121

To appear in: *VETMIC*

Received date: 29-8-2010
Revised date: 23-11-2010
Accepted date: 7-12-2010

Please cite this article as: López-Soria, S., Nofrarías, M., Calsamiglia, M., Espinal, A., Valero, O., Ramírez-Mendoza, H., Mínguez, A., Serrano, J.M., Marín, Ó., Callén, A., Segalés, J., Post-weaning multisystemic wasting syndrome (PMWS) clinical expression under field conditions is modulated by the pig genetic background, *Veterinary Microbiology* (2010), doi:10.1016/j.vetmic.2010.12.009

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1 **Post-weaning multisystemic wasting syndrome (PMWS) clinical expression under**
2 **field conditions is modulated by the pig genetic background**

3
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26 **ABSTRACT**

27

28 Post-weaning multisystemic wasting syndrome (PMWS) is a worldwide
29 distributed disease of multifactorial origin and porcine circovirus type 2 (PCV2) has
30 been identified as its essential infectious aetiology. Pig genetic background has been
31 pointed to influence disease expression. In the present study, three different boar lines,
32 namely A (100% Pietrain), B (50% Large White x 50% Pietrain) and C (25% Large
33 White x 75% Duroc), were used to inseminate sows from the same genetic line (37.5%
34 Large White x 37.5% Duroc x 25% Landrace) located on two PMWS-affected farms
35 (farm-1 and farm-2). The PMWS clinical expression of their offspring was studied from
36 weaning to slaughter, evaluating three parameters: total post-weaning mortality (PWM),
37 PWM associated to PMWS (PMWS-PWM) and body weight (BW) evolution. The
38 effect of other variables potentially related with PMWS, including sow and piglet PCV2
39 exposure, sow parity, piglet gender and piglet BW at weaning, were also considered in
40 the study design. Overall, a total of 6.5% PWM and 4.3% PMWS-PWM occurred in the
41 monitored farms. Pigs from boar line C showed the highest PWM (16.3%) and PMWS-
42 PWM (12.4%), and the lowest BW; pigs from boar line A showed the lowest PWM
43 (1.8%) and the highest BW. Furthermore, PWM was also higher in piglets from farm-2
44 and from multiparous sows. In farm-2, PMWS-PWM was higher in piglets from
45 multiparous sows. Finally, BW was influenced by interactions between genetics and
46 both farm and pig age, and was lower in piglets from farm-2. This study represents a
47 consistent observation of the genetic background effect on PMWS clinical expression
48 under field conditions.

49

50 *Key Words:* Genetics, Pig, Porcine circovirus type 2, Post-weaning multisystemic
51 wasting syndrome.

52

53 **1. Introduction**

54

55 Porcine circovirus type 2 (PCV2) is found worldwide in pigs and has been
56 linked to several pathological conditions collectively named porcine circovirus diseases
57 (PCVD) (Segalés et al., 2005). The most economically important PCVD is post-
58 weaning multisystemic wasting syndrome (PMWS), which results in losses of €900
59 million per year in the European Union (Armstrong and Bishop, 2004).

60

61 Infection of pigs with PCV2 and other infectious/non-infectious triggers are
62 required for PMWS to occur (Segalés et al., 2005). Evaluation of the role of these other
63 triggers is essential in order to understand the pathogenesis of PMWS. Several studies
64 have linked PMWS expression to management measures, presence of concurrent viral
65 infections, stimulation of the immune system, PCV2 viraemia and low serological titres
66 to PCV2 of the sow at farrowing, nutrition, male castration and lower piglet weight at
67 weaning (Segalés et al., 2005).

68

69 Farmers and veterinarians in the field have suggested that different pig breeds or
70 genetic lines have different susceptibilities to PMWS. Similar effects have been
71 previously demonstrated for other diseases, including bacterial (Michaels et al., 1994;
72 Wigley, 2004), parasitic (Reiner et al., 2002a) and viral (Depner et al., 1997; Reiner et
73 al., 2002b; Vincent et al., 2006) diseases. Preliminary experimental studies have
74 suggested a higher susceptibility to PCV2-associated lesions and even on PMWS

75 development of Landrace pigs compared to Duroc, Large White and Pietrain pigs
76 (Opriessnig et al., 2006, 2009). Experiences in the field have reported a significantly
77 less often occurrence of clinical signs resembling PMWS in pure bred conventional
78 Hampshire boars than in pure bred conventional Yorkshire or Landrace boars (Wallgren
79 et al., 2009). However, the introduction of a terminal Pietrain boar onto affected farms
80 showed no effect on PMWS expression (Rose et al., 2005). Besides these preliminary
81 studies minimal scientific work has so far been focused on the relationship between
82 genetics and PMWS development. The objective of the present study was to compare
83 the effect of 3 different genetic boar lines on the expression of PMWS in their offspring.

84

85 **2. Materials and methods**

86

87 Animal care and use conformed to the European Union guidelines and Good
88 Clinical Practice.

89

90 The study was carried out in 2 almost identical 5000-sow farms (farm-1 and
91 farm-2) separated by 300 m. Farm-1 and farm-2 belonged to the same producer
92 company, which had a multi-site production system that used the same sow genetic line
93 (37.5% Large White x 37.5% Duroc x 25% Landrace) across all sites. Farms were
94 seronegative to porcine reproductive and respiratory syndrome (PRRSV) and
95 Aujeszky's disease virus (ADV), and no evidence of porcine parvovirus (PPV)
96 circulation was found in a subsample of 90 piglets from the studied batches (data not
97 shown). Post-weaning mortality in the year before study start ranged from 4 to 8% in
98 both farms and was mainly attributed to PMWS, according to previous diagnostic
99 analyses performed in the farms.

100

101 Boars from three genetic lines, A (100% Pietrain), B (50% Large White x 50%
102 Pietrain) and C (25% Large White x 75% Duroc), were used for artificial insemination.
103 Fifteen A, eight B, and four C boars were used. Sow insemination with each boar line
104 was assigned randomly. Each sow was not always inseminated with semen from the
105 same boar in repeated inseminations, but the boars were always from the same genetic
106 line. A total of 63 pregnant sows was obtained on farm-1 (24 pregnant from A boars, 20
107 from B boars and 19 from C boars) On farm-2 the figures were 67 pregnant sows (29 A,
108 23 B and 15 C). Sows were randomly placed in the farrowing facilities in both farms
109 taking into account that approximately one third of sows inseminated with each boar
110 line had to be present in each room (there were three rooms per farm). No cross-
111 fostering was allowed.

112

113 Semen (diluted for insemination and non-diluted from direct extraction) and
114 serum samples were collected from boars at the moment of the semen extraction. Serum
115 samples from sows were collected 1 week before farrowing.

116

117 A total of 1062 piglets (517 from farm-1 and 545 from farm-2) were obtained
118 and ear-tagged before entering the nursery period (3 weeks of age) and monitored until
119 the end of the fattening period (21 weeks of age). Piglet distribution by farm, genetic
120 background, gender and sow parity is shown in Table 1. Sow parity was categorized as
121 1 or >1 farrowings (Calsamiglia et al., 2007). Nursery pigs (3 to 10 weeks of age) from
122 farm-1 and farm-2 were placed in the same nursery building but in separate rooms (two
123 rooms per group). Fattening pigs (from 10 weeks of age to slaughter) from farm-1 were
124 placed in pens located in front of those of farm-2 from the same room and farm. All

125 pens in both the nursery and fattening units contained pigs from all three genetic
126 backgrounds.

127

128 Mortality was monitored during the post-weaning period, from 3 to 21 weeks of
129 age; all dead pigs during this period were necropsied and tissue samples (mesenteric
130 lymph node and lung) collected. A subpopulation of 207 piglets was randomly selected,
131 blocked by genetic background, farm, sow of origin and sex (33 to 36 pigs for each
132 genetic background and farm); these pigs were bled at 3 weeks of age and weighed at 3,
133 9, 15 and 21 weeks of age.

134

135 *2.1 Laboratory Analyses*

136

137 A standard polymerase chain reaction (PCR) method to detect PCV2 (Quintana
138 et al., 2002) was performed on serum samples from sows and piglets and serum, diluted
139 and non-diluted semen from boars. An immunoperoxidase monolayer assay (IPMA)
140 was used to detect PCV2 antibodies (Rodríguez-Arrijoja et al., 2000) in sera from boars,
141 sows and piglets. Antibody titres were classified as negative or low titre ($<1:320$) or
142 medium to high titre ($\geq 1:320$) (Rodríguez-Arrijoja et al., 2000). Mesenteric lymph node
143 and lung samples collected from necropsied pigs were fixed by immersion in 10%
144 buffered neutral formalin and routinely processed for histopathology. The presence of
145 PCV2 in these tissues was detected using an *in situ* hybridization technique (Rosell et
146 al., 1999). A pig was considered as suffering from PMWS when moderate to severe
147 lymphocyte depletion and histiocytic infiltration were found in lymphoid tissues
148 associated with moderate to high amount of PCV2 (Segalés, 2002).

149

150 *2.2 Statistical Analysis*

151

152 PMWS expression was evaluated using 3 parameters: body weight (BW) at 3, 9,
153 15 and 21 weeks of age, total post-weaning mortality (PWM), and PWM due to PMWS
154 (PMWS-PWM). Total PWM, which includes non-PMWS-related mortality, was
155 considered as a relevant production parameter because of the reported synergism
156 between PMWS and other causes of mortality (Segalés et al., 2005).

157

158 Two logistic regression models (Hosmer and Lemeshow, 2000) were established
159 to evaluate both PWM and PMWS-PWM, including the sow as a random effect. A
160 longitudinal linear mixed model with repeated measures (Verbeke and Molenberghs,
161 1997) was performed to analyze BW. Covariates included in all models were genetic
162 background, farm, sow presence of PCV2 viraemia and antibody titre at farrowing, sow
163 parity, piglet's sex and BW, PCV2 infectious status and PCV2 antibodies at 3 weeks of
164 age. Interactions with farm were also included. The sow was included as a random
165 effect.

166

167 All results were obtained using GLIMMIX and MIXED procedures of the SAS
168 System V.9.1 (SAS Institute Inc.). Significance level was fixed at 5%.

169

170 **3. Results**

171

172 PCV2 was not detected in any boar and sow serum sample, or any semen
173 sample. The proportion of sows with medium to high PCV2 antibody titres as well as
174 the proportion of piglets that came from them is shown in Table 1.

175

176 PMWS-PWM occurred on farm-1 from 10 to 15 weeks of age (except for one
177 pig at 20 weeks), and from 9 to 15 weeks of age on farm-2. Further information on
178 PWM and PMWS-PWM expression by farm and genetic background is shown in Table
179 1. The antibody titres and BW changes of the 207 monitored piglets are also shown in
180 Table 1.

181

182 Logistic regression models showed a significant effect of genetic background (P
183 <0.001), farm ($P = 0.001$) and parity ($P = 0.038$) on total PWM. Specifically, PWM was
184 more likely in piglets from C boars than both A (OR=11.95, CI_{OR} = 5.10 to 28.02) and
185 B (OR=4.42, CI_{OR} = 2.29 to 8.55). Also, PWM was more likely for B than for A
186 (OR=2.70, CI_{OR} = 1.08 to 6.77) backgrounds. In addition, PWM was more likely in
187 piglets from farm-2 than farm-1 (OR=2.88, CI_{OR} =1.56 to 5.33). Finally, PWM was
188 more likely in piglets from multiparous than primiparous sows (OR= 2.18, CI_{OR} = 1.04
189 to 4.54).

190

191 A significant effect of genetic background ($P <0.001$) and a farm and parity
192 interaction ($P = 0.048$) on PMWS-PWM was obtained. PMWS-PWM was more likely
193 for piglets from C boars than both A (OR=15.55, CI_{OR}= 4.92 to 43.06) and B (OR=8.26,
194 CI_{OR} = 3.19 to 21.39). An effect of sow parity was only observed on farm-2, where
195 PMWS-PWM was more likely in piglets from multiparous than primiparous sows
196 (OR=6.86, CI_{OR} = 1.35 to 34.94).

197

198 Significant covariates for BW in the longitudinal mixed models were genetic
199 background ($P <0.001$), farm ($P = 0.003$), age ($P <0.001$), genetics and farm interaction

200 ($P = 0.044$) and genetics and age interaction ($P = 0.004$). Piglets from farm-2 showed
201 lower weights than those from farm-1. Detailed results from the longitudinal mixed
202 model are shown in Table 2.

203

204 **4. Discussion**

205

206 Most evidence of the effect of genetic background on PMWS susceptibility has
207 come from the experimental side (Opriessnig et al., 2006, 2009). These studies included
208 a limited number of pigs and used pure-bred animals, which is unusual under field
209 conditions. Furthermore, few studies have been performed in the field in regards
210 genetics and PMWS occurrence, where no apparent relationship between boar genetic
211 background and disease expression was observed in the offspring (Rose et al., 2005) or
212 minimal information was available when genetic background susceptibility was
213 observed (Wallgren et al., 2009).

214 This study aimed to assess whether clinical expression of PMWS was influenced
215 by genetic background. Three different boar lines that swine producers had suggested as
216 having different PMWS outcome severity in their offspring were used. Using BW,
217 PMWS-PWM and total PWM as measures of PMWS expression, this study confirmed
218 those suggestions. It also confirmed that other factors, such as farm of origin, sow parity
219 and piglet age, were associated with the effects of PMWS.

220

221 Several measures to diminish potential biases that may occur under field
222 conditions were adopted for this study. Two sow farms which were located together,
223 with the same farm management and characteristics and sow genetic background were
224 used. Piglets were reared on the same nursery and fattening farms, so were kept under

225 the most similar environmental conditions. Furthermore, any potential biases due to
226 concurrent diseases are unlikely in this study as PPV, PRRSV and ADV, three viruses
227 reported to be related to clinical expression of PMWS (Ellis et al., 2004), did not
228 circulate in the studied batches. In addition, total PWM was mainly associated to
229 PMWS based on pathological findings. Finally, other factors, i.e. sow and pig PCV2
230 infectious status and antibody titre, sow parity, piglet gender and weaning BW, that
231 could influence PMWS expression were also studied.

232

233 PCV2 infectious status of sows, boars and weaned piglets was assessed as PCV2
234 status has a significant effect on litter mortality in PMWS-affected farms (Calsamiglia
235 et al., 2007), and the earlier the pig is infected with PCV2, the higher the risk of
236 suffering from PMWS (Rose et al., 2003; López-Soria et al., 2005). The fact that no
237 sample demonstrated PCV2 infection reinforces the role of the genetic background as a
238 risk factor for PMWS, and suggests that it was probably the most significant one on the
239 farms in this study.

240

241 Significant differences between genetic backgrounds were observed in the
242 present study. Piglets from C boars were the most affected, showing lower BW and
243 higher rates of PWM and PMWS-PWM than those from A and B boars. Piglets from A
244 boars had higher BW at slaughter age and lower PWM compared to those from the
245 other two studied boar lines. These findings are in agreement with the experimental
246 study by Opriessnig et al., (2009) who reported that Landrace piglets developed more
247 severe PMWS-like lesions than Pietrain. However they contradict a previous French
248 field study which did not find any difference when the usual terminal boar breed was
249 replaced by Pietrain (Rose et al., 2005). These results may seem contradictory; however,

250 differences in study design may be the cause of these inconsistencies. Moreover, such
251 differences could be attributed to the fact that different Pietrain genetic lines were used
252 in different studies, and it is possible that PMWS genetic susceptibility/resistance might
253 be related to particular genetic lines rather than breeds or potential allele variants within
254 lines.

255

256 The critical period for BW differences between lines was between 15 and 21
257 weeks of age, just after the PMWS outbreak. The significantly higher weights found in
258 piglets from A boars at 21 weeks of age was noteworthy because Duroc and Large
259 White breeds are expected to show better growth rates than Pietrain (Whittemore,
260 1998). This result thus supports the idea of a significant impact of PMWS on average
261 daily gain, and is consistent with the improvement of growth rate in pigs vaccinated
262 against PCV2 (Fachinger, et al., 2008; Horlen et al., 2008; Kixmüller et al., 2008).

263

264 The link reported here (farm-2) between sow parity and PMWS-associated
265 mortality, and also reported in another study (Armstrong and Bishop, 2004), seems to
266 be a controversial point since others did not find it (Madec et al., 2000; Calsamiglia et
267 al., 2007). In fact, piglets from multiparous sows showed higher total PWM on both
268 farms, but it was only higher for PMWS-PWM on farm-2. There are no apparent
269 consistent explanations for these discrepancies and they may be attributable to the
270 multifactorial nature of PMWS, in which unknown triggering factors may account for
271 specific farm differences.

272

273 Several studies have shown that humoral immunity plays a major role on PMWS
274 development. PCV2 maternally derived antibodies seem to protect against piglet

275 mortality based on field (Allan et al., 2002; Calsamiglia et al., 2007; Grau-Roma et al.,
276 2009) and experimental (Allan et al., 2002; McKeown et al., 2005; Ostanello et al.,
277 2005) data. However, no effect of sow IPMA antibody titre at farrowing or piglet titre at
278 3 weeks of age in PMWS-PWM were observed in the present study, probably because
279 of the very high percentage of piglets coming from sows with medium to high PCV2
280 antibody titres. Curiously, piglets from A boars experienced lower total PWM and
281 PMWS-PWM despite showing the lowest proportion of piglets with medium to high
282 PCV2 antibody titres in farm-1 and the highest in farm-2. Again, PCV2 antibody titres
283 in sows and piglets should be considered as elements that modulate PMWS expression
284 within the context of a multifactorial disease. Therefore, not all the risk factors so far
285 identified for PMWS have an equal on different farms with different production
286 scenarios.

287

288 PMWS-PWM records in the present study were very similar between females
289 and males, being 4.3 and 4.4%, respectively. Previous studies have found that castrated
290 males had higher PMWS-associated mortality than females (Corrégé et al., 2001;
291 Rodríguez-Arrijoja et al., 2002). In the present study males were not castrated,
292 suggesting that physiological and behavioural changes or surgical complications due to
293 male castration (Prunier et al., 2006) may be a risk factor for PMWS occurrence.

294

295 Susceptibility of lighter weanling pigs to clinically compatible PMWS has been
296 reported (Corrégé et al., 2001). This association between BW and PMWS has not been
297 observed in the present study, although disease has been measured with different
298 parameters in both studies.

299

300 **5. Conclusion**

301

302 This study represents a consistent observation of the genetic background effect
303 on PMWS clinical expression under field conditions. However, such study cannot be
304 used to determine if the observed effect was an effect of breed (such as a protective
305 effect for Pietrain or susceptibility in Duroc), particular boar lines or individuals (only 4
306 boars from genetic line C were used in the study, so the effect of each individual was
307 higher than in the other genetic lines). Furthermore, it cannot be concluded that this
308 effect would appear if a different sow genetic line was used. Further studies are needed
309 to elucidate the exact role by which porcine genetics affect susceptibility/resistance to
310 PMWS.

311

312 **Acknowledgements**

313

314 This work was partly funded by the Special Action AGL2002-10252-E from the
315 Spanish Government. The Spanish Government had no involvement in the study design,
316 in the collection, analysis or interpretation of data, in the writing of the manuscript, or in
317 the decision to submit the manuscript for publication. The authors are grateful to M.
318 Pérez and E. Huerta from CReSA for the technical assistance, and all the colleagues and
319 farmers who collaborated during the farm work.

320

321 **Conflict of interest statement**

322

323 None of the authors of this paper has a financial or personal relationship with
324 other people or organisations that could inappropriately influence or bias the content of
325 the paper.

326

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483 **Table 1.** Descriptive statistics on explanatory and response variables from piglets included in the study.

484

Variable	Farm-1			Farm-2		
	A	B	C	A	B	C
No. of boars	13	7	4	10	6	4
No. of sows	24	20	19	29	23	15
No. of piglets	196	169	152	243	203	99
Piglets' male : female ratio	50 : 50	54 : 46	55 : 45	51 : 49	46 : 54	63 : 37
Piglets from first parity sows, %	20	22	26	33	37	27
Sows with medium to high PCV2 IPMA antibody titres, %	79	85	89	100	100	100
Piglets from sows with medium to high PCV2 IPMA antibody titres, %	82	75	87	100	100	100
PWM, % (n)	1.5 (3)	4.7 (8)	9.9 (15)	2.1 (5)	5.9 (12)	26.3 (26)
PMWS-PWM, % (n)	1.5 (3)	2.4 (4)	6.6 (10)	0.8 (2)	3.0 (6)	21.2 (21)
PMWS-PWM in piglets from primiparous sows – multiparous sows, %	2.6 – 1.3	0 – 3.1	7.7 – 6.2	0 – 1.2	1.3 – 3.9	3.7 – 27.8
PMWS-PWM (Males – Females), %	1.0 – 2.0	3.3 – 1.3	7.2 – 5.8	0.8 – 0.8	2.1 – 3.7	18.0 – 26.3
Piglets with medium to high PCV2 IPMA antibody titres at 3 weeks of age, % ^a	9	70	26	47	37	23
BW at 3 weeks of age ($\mu \pm$ SD), Kg ^a	7.0 \pm 1.5	6.8 \pm 1.4	5.9 \pm 1.3	6.9 \pm 1.4	6.0 \pm 1.2	6.2 \pm 1.7
BW at 9 weeks of age ($\mu \pm$ SD), Kg ^a	24.7 \pm 3.7	22.8 \pm 3.3	21.7 \pm 3.2	22.6 \pm 4.0	20.6 \pm 2.9	21.9 \pm 3.6
BW at 15 weeks of age ($\mu \pm$ SD), Kg ^a	55.7 \pm 7.7	53.2 \pm 8.3	50.0 \pm 9.6	53.1 \pm 6.7	50.3 \pm 5.8	48.1 \pm 7.2
BW at 21 weeks of age ($\mu \pm$ SD), Kg ^a	88.2 \pm 10.4	82.9 \pm 12.8	78.4 \pm 15.2	85.2 \pm 10.5	80.2 \pm 10	80.2 \pm 5.6

485 PCV2: Porcine circovirus type 2; IPMA: immunoperoxidase monolayer assay; PWM: post-weaning mortality; PMWS-PWM: post-weaning
 486 mortality associated to post-weaning multisystemic wasting syndrome.

487 ^aStatistics were obtained using the subpopulation of 207 pigs.

488 **Table 2.** Longitudinal mixed model estimates for BW evolution.

489

Covariate/s	Estimate	Confidence Interval ^a		P ^a
		Lower	Upper	
<i>Genetic background</i>				
A vs B	2.300	0.893	3.708	< 0.001
A vs C	4.009	2.563	5.455	< 0.001
C vs B	-1.708	-3.159	-0.258	0.016
<i>Genetic background and farm interaction</i>				
Farm-1: A vs C	5.168	2.665	7.670	< 0.001
C vs B	-3.185	-5.685	-0.686	0.004
Farm-2: A vs B	2.618	0.257	4.979	0.020
A vs C	2.850	0.373	5.326	0.014
B farm-1 vs B farm-2	2.711	0.280	5.142	0.019
<i>Genetic background and age interaction</i>				
15 weeks of age ^b : A vs C	5.601	1.489	9.713	< 0.001
21 weeks of age ^c : A vs B	4.479	0.499	8.460	0.013
A vs C	7.493	3.271	11.715	< 0.001

490 ^aConfidence intervals and P-values adjusted with the Tukey correction.

491 ^bMean weight±standard deviation for piglets with A and C background were
492 54.6±7.2Kg and 49.1±8.6Kg, respectively.

493 ^cMean weight±standard deviation for piglets with A, B and C background were
494 86.6±10.5Kg, 81.5±11.4Kg and 79.1±12.1Kg, respectively.