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Genetic analyses of piglet survival and postnatal growth

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“I’ve learned that I still have a lot to learn.”

Maya Angelou

Für Felix, meine Familie und meine Freunde

Abstract

Piglet survival determines the success of piglet production. Decreased piglet survivability raises animal welfare concerns and increasing litter sizes intensified this situation. In the recent work, the prospects to select for improved piglet survival were analysed. Therefore, the complex determinants of survivability were evaluated with respect to the immune system. In addition, traits representing piglet survival were analysed genetically in Landrace and Large White.

The complex relationships between piglet survival and the immune system were reviewed in the chapter 3. The aim was to discuss potential selection strategies and especially the missing conditions that have to be created in order to include survival traits and immune parameters into reasonable breeding programs for improved survivability and immunocompetence.

In chapter 4, the piglet traits stillbirth (SB), pre-weaning loss (PWL) and birth weight (BW) as well as litter traits were investigated using univariate and bivariate generalized linear mixed models. For this purpose, comprehensive data sets including 168,823 piglets and 4,642 sows of a German breeding organization were available. The analysis focused especially on the binary character of SB and PWL applying threshold models and a logit link function. Due to the large data sets available and accurate records of cross-fostering (CF) the maternal genetic effect of the CF dam was investigated.

In conclusion, the consideration of piglet survival and the immune system in selection indexes is complex and should be designed population specific. Immune traits revealed profound genetic variability. However, it remains unclear how they should be included into a breeding program. Piglet survival and BW traits show low heritabilities, except for the mean BW within litter, and unfavourable genetic correlations (r_g) to LS. In addition, the r_g estimated for SB, PWL and BW revealed distinct relationships between the traits indicating that uniform individual BW are required to reduce the odds for a piglet to be stillborn and to ensure the vitality needed to survive until weaning. Breeding for piglet survival is possible and can be even more efficient if genotypic information is included in the analyses via genome-wide association studies (GWAS) and genomic selection (GS).

Kurzfassung

Die Überlebensfähigkeit (ÜFK) von Ferkeln ist ausschlaggebend für den Erfolg der Ferkelproduktion. Verminderte ÜFK ist vor allem unter Tierwohlaspekten kritisch zu betrachten. Gesteigerte Wurfgrößen (WG) verstärkten diese Situation noch zusätzlich. Das Ziel dieser Arbeit war es, die Möglichkeiten einer Selektion auf eine verbesserte ÜFK zu untersuchen. In diesem Rahmen wurden die komplexen Einflussfaktoren auf die ÜFK auch unter Einbeziehung des Immunsystems (IS) evaluiert. Zusätzlich wurden Merkmale der ÜFK in Landrasse und Edelschwein genetisch untersucht.

Die komplexen Zusammenhänge zwischen der ÜFK von Ferkeln und dem IS wurden in Kapitel 3 untersucht. Das Ziel war es, mögliche Selektionsstrategien zu diskutieren, aber besonders die fehlenden Voraussetzungen zu benennen, die geschaffen werden müssen, um die Merkmale der ÜFK sowie die Immunparameter in ein umsetzbares Zuchtziel für verbesserte Überlebensraten und Immunkompetenz zu übersetzen.

In Kapitel 4 wurden die ferkelindividuellen Merkmale Totgeburt (TG), Saugferkelverlust (SFV) und das Geburtsgewicht (GG) sowie Wurfmerkmale mittels uni- und bivariaten gemischten Modellen untersucht. Dafür standen umfangreiche Datensätze eines deutschen Schweinezuchtunternehmens für 168,823 Ferkel und 4,642 Sauen zur Verfügung. Der Fokus lag hier besonders auf der Berücksichtigung des binären Charakters der Merkmale TG und SFV durch den Einsatz von Schwellenwert-Modellen und Logit-Link-Funktionen. Die umfangreiche Datengrundlage sowie die Erfassung des Wurfausgleiches ermöglichte zusätzlich die Untersuchung des maternal genetischen Effektes der Amme.

Generell ist die Einbeziehung der ÜFK und des IS in einen Selektionsindex komplex und sollte für jede Population spezifisch konzipiert werden. Immunmerkmale weisen eine ausgeprägte genetische Variabilität auf. Allerdings bleibt unklar, wie diese in einem Zuchtprogramm berücksichtigt werden sollten. Die Merkmale der ÜFK und des GG zeigten, bis auf das mittlere GG im Wurf, niedrige Heritabilitäten und unvorteilhafte genetische Korrelationen (r_g) zur WG. Zusätzlich wiesen die r_g zwischen TG, SFV und GG unterschiedliche Beziehungen zueinander auf. Diese Ergebnisse zeigen, dass uniforme GG die Voraussetzung sind, um die Chancen eines Ferkels, tot geboren zu werden, zu verringern und gleichzeitig die Vitalität für das Überleben der Saugferkelphase sicher zu stellen. Eine Zucht auf eine verbesserte ÜFK ist möglich und kann durch genomweite Assoziationsstudien (GWAS) und genomische Selektion (GS) noch effizienter umgesetzt werden.

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List of abbreviations

B	Biological dam/litter
BLUP	Best linear unbiased prediction
BMI	Body mass index
BW	Birth weight
c^2	Common environment effect
CD163	Cluster of differentiation 163
CF	Cross-foster dam/litter
CM	Complete model
EBV	Estimated breeding values
ER	Erhulian
G×E	Genotype by environment interaction
GLMM	Generalized linear mixed model
GG	Geburtsgewicht
GS	Genomic selection
GWAS	Genome-wide association study
h^2	Heritability
hrs	Hours
HYS	Herd-year-season-effect
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IS	Immunsystem
IUGR	Intrauterine growth retardation
LogL	Log-likelihood
LR	Landrace
LRT	Likelihood-ratio-test
LS	Litter size
LS5	Litter size at day 5 after farrowing

LW	Large White
m^2	Maternal genetic effect
MBW	Mean birth weight within litter
MCMC	Marcov chain monte carlo
MEV	Marginal economic value
min	Minutes
MS	Meishan
NBA	Number of piglets born alive
NBD	Number of piglets born dead
NBT	Number of piglets born total
n.e.	Not estimable
NWP	Number of piglets weaned
OCD	Osteochondrosis
P	Probability value
pe^2	Permanent environment effect
PI	Ponderal index
Pi	Piétrain
PQL	Penalized quasi-likelihood
PRRS	Porcine respiratory reproductive syndrome
PWL	Pre-weaning loss
PWM	Pre-weaning mortality
QTL	Quantitative trait loci
r_{AM}	Additive genetic maternal genetic correlation
r_g	Genetic correlation
r_p	Phenotypic correlation
RMA	Respiration, meconium staining and activity

SB	Stillborn
SE	Standard error
SEM	Standard error of the mean
SFV	Saugferkelverlust
SNP	Single nucleotide polymorphism
TG	Totgeburt
ÜFK	Überlebensfähigkeit
VBW	Variance of birth weights within litter
WG	Wurfgröße

Chapter 1. General introduction

1.1. Relevance of piglet mortality

The intensification of agricultural production caused an increase in pig productivity in the last decades. In 2016, 1.917 million breeding sows were kept and 59.391 million pigs were slaughtered in Germany (AHDB Pork, 2017). However, the monetary value of each animal decreased (Winter *et al.*, 1998). Therefore, to realize an increase in the number of marketable animals per sow, the number of piglets weaned per year is the main determinant for the economic success of piglet producers (Spoetter and Distl, 2006; Rutherford *et al.*, 2013; Edwards and Baxter, 2015). As a consequence, breeding organizations have focused successfully on the genetic improvement of reproduction traits by introducing hyperprolific dam lines that caused a substantial increase of litter size (LS) and the number born alive (NBA) in the last decades (Beaulieu *et al.*, 2010). According to Rutherford *et al.* (2013), LS is defined as the sum of piglets born dead and alive excluding mummies, malformed piglets and piglets that died before expulsion. Improvement of management strategies including nutrition, housing (e.g. farrowing crates) and health monitoring resulted in an European average of 13.9 piglets born per litter in 2016 (Beaulieu *et al.*, 2010; Prunier *et al.*, 2010; AHDB Pork, 2017). One reason for this success is the low phenotyping effort in breeding herds of NBA. According to Prunier *et al.* (2010), French data bases showed an increase in LS of 25 % between 1986 and 2006. Van Engen *et al.* (2010) reported a progress of one additional piglet per litter within three years.

However, Prunier *et al.* (2010) specified that the number of weaned piglets has only increased by 15 % because of higher numbers of piglet losses between farrowing and weaning. In 2016, the mean share of pre-weaning losses was 13.4 % in the EU (AHDB Pork, 2017) and in Germany the latest piglet pre-weaning mortality rate was 14.87 % (erzeugerring.info, 2018). Considering the development of overall reproduction performance, the proportion of pre-weaning losses did not change whereas the NBA still keeps increasing (Welp, 2014; erzeugerring.info, 2018). The results of Rocadembosch *et al.* (2016) confirmed this observation. The authors revealed that even though sow prolificacy increased, the pre-weaning mortality stabilized between 2010 and 2014.

Although pigs naturally overproduce offspring (Edwards and Baxter, 2015), it was observed that increasing LS decreased individual birth weights and raised piglet mortality rates (Roehe and Kalm, 2000; Milligan *et al.*, 2002a; Damgaard *et al.*, 2003; Rutherford *et al.*, 2013). According to the definition of Rutherford *et al.* (2013), piglet mortality is usually recorded by counting the piglets in a litter that are stillborn and those died until weaning excluding any losses occurred before the start of the farrowing process. Piglet losses during and after farrowing are caused by an unfavourable interaction between the piglet, the sow and the environment (Alonso-Spilsbury *et al.*, 2007). According to Pandolfi *et al.* (2017), total piglet mortality in French pig farms makes an average share of 19.9 % whereas of these 21.4 % died because of missing viability due to underweight. Furthermore, Rootwelt *et al.* (2013) and Fix *et al.* (2010) described that breeding for important production traits has resulted in piglets with reduced physiological maturity at birth as well as poor vigour. Knol (2001), who reported moderate positive genetic correlations between survivability and finishing traits, confirmed this unfavourable relationship.

Kirkden *et al.* (2013) stated that the amount of piglet losses pre- and post-weaning depend, apart from the genotype and the dam, on housing conditions, management and nutrition. For the piglet producer an increased amount of management tasks and difficulties (e.g. colostrum supply, cross-fostering and delayed slaughter age) result from less viable piglets. These are labour and cost intensive (Crooks, 1993; Fix *et al.*, 2010). However, to prevent piglet losses during farrowing and pre-weaning, these preliminaries are the key to realize the number of weaned piglets required (Rootwelt *et al.*, 2013).

Apart from the economic detriments, piglet mortality and increased LS were described and discussed to influence animal welfare in pigs negatively (e.g. Mellor and Stafford, 2004; Rutherford et al., 2013). Societal concerns towards animal welfare in pig production have increased in recent years (Kanis *et al.*, 2003). According to Harper and Henson (2001), some consumers even use animal welfare as an indicator for food quality and safety. Media reports and protests by animal welfare organisations have intensified this situation (Franz *et al.*, 2012).

Due to an on-going unfavourable production and market logic, farmers have to deliver high quality meat at low production costs (Bourlakis *et al.*, 2007). This implies that pigs should possess a low management effort and a low susceptibility for diseases to realize a low need for medication (e.g. antibiotics) and meeting consumer protection simultaneously (Kanis *et al.*, 2004; Merks *et al.*, 2012). As a consequence, this complex set of demands and challenges calls for breeding strategies producing vital, robust, unelaborate animals originating from large and uniform litters (Knol, 2001; Knap, 2005; Merks *et al.*, 2012).

In this context, this thesis aims to investigate the possibilities to select for improved piglet survivability based on quantitative genetic and genomic selection measures.

1.2. Aim of this thesis

The aim of this thesis is to analyse and discuss the prospects to select for improved piglet survivability. This evaluation is based on quantitative genetic methods. In addition, the biological relationships and potential selection traits are incorporated to assess adequate selection strategies for improved piglet survival.

To achieve this, **chapter 2** introduces the determinants of piglet survival at sow and piglet level between conception and weaning. The complex interactions between piglet, sow and environment are elucidated to understand the biological background and appropriately choose for possible selection traits.

Chapter 3 aims to discuss piglet survival and its relationship to the immune system. Furthermore, the objective is to determine the gap of knowledge to characterize this relationship. Especially the potential selection of immune parameters and the most favourable direction of an immune response are discussed in this context.

In **chapter 4**, the quantitative genetic background of stillbirth (SB), pre-weaning losses (PWL) and the individual birth weight (BW) is investigated at piglet and sow level to characterize the possibilities of breeding for improved piglet survival. Furthermore, the genetic relationships of the piglet traits and the reproduction traits of the sows are estimated, respectively. We hypothesize that especially piglets with low birth weights underlie a higher probability to die at farrowing and before weaning. Furthermore, we investigate if cross-fostering does influence the adequacy of the model for the estimation of variance components for PWL.

The general discussion included in **chapter 5** aims to debate how and to what extend the traits of interest can be improved by selection and how these can be implemented into realizable breeding programs. In addition, the appropriateness of the genetic models applied as well as the relationship between survival and robustness are examined

Chapter 2. Literature review

2.1. Causes for piglet mortality

Genetic effects

In general, piglet survivability is chronologically defined as the period between conception and weaning (figure 1). Roehe *et al.* (2009) described direct genetic effects for survivability as the genetic potential of the piglet to survive including e.g. vitality, growth and resistance. Moreover, maternal genetic effects being the genetic potential of the sow to prevent piglet losses including mothering abilities during and after farrowing, uterus quality (blood flow, nutrients, efficiency), and colostrum production (amount and composition) (Knol *et al.*, 2002a; Roehe *et al.*, 2009; Edwards and Baxter, 2015). Already Edwards (2002) stressed to understand the "multifaceted nature of piglet mortality" to decrease piglet losses by coordination of genetic, nutritional, management and stockpersons intervention. Genetically, the complex relationship between direct or additive genetic, maternal genetic (m^2) and common litter (c^2) effects determine individual piglet survival (figure 1) (Knol, 2001; Roehe *et al.*, 2010).

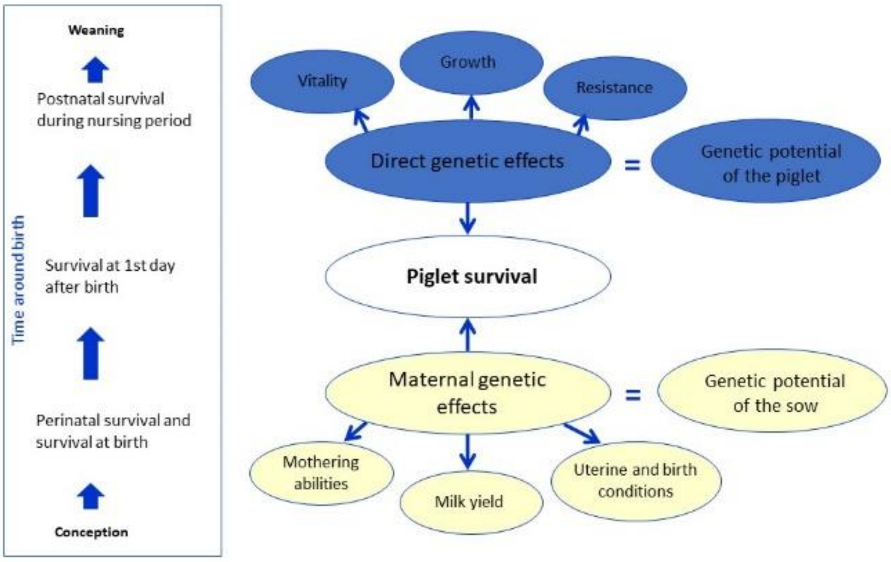

Figure 1: *Complex interactions between the genetic effects determining piglet survival. Modified according to Roehe et al. (2009)*

Common litter effects incorporate the impact of LS, the sows' constitution, management stressors and health condition which can influence the development of piglets between conception and weaning (Roehe *et al.*, 2009; Edwards and Baxter, 2015).

Cross-fostering is a prevailing strategy in piglet production to either standardize litters according to number of piglets nursed and to their individual BW. However, when it comes to genetic analyses of survival traits the separation of dam and nurse sow effects may be complicated and only possible if enough piglets are cross-fostered (Knol *et al.*, 2002a). In order to define traits that are suitable to breed for improved piglet survival and to understand reduced survivability the causes for piglet mortality are described in the following sections.

Causes for piglet mortality

The various causes for piglet mortality including their respective frequencies are described in figure 2. Prenatal mortality mainly occurs around the implantation of the embryo and less in late gestation (Prunier *et al.*, 2010). The highest proportion of *post-partum* piglet losses occurs within the first three to five days of the neonatal period (Su *et al.*, 2007). Dyck and Swiersta (1987) found three main causes for piglet mortality, (1) stillbirth, (2) crushing by the sow and (3) starvation that are still consistently found in literature (Dyck and Swiersta, 1987; Edwards and Baxter, 2015). However, Pandolfi *et al.* (2017) recently described stillbirth (23.0 %), missing viability of the piglets (21.4 %) and early sepsis (17.6 %) as the three main causes for piglet losses. Early sepsis occurs within the first three days after farrowing caused by a maternal transfer of invasive microorganisms (Nguyen *et al.*, 2016). In humans, it is a typical infection of premature infants that are underweight, miss colostrum intake and show an underdeveloped immune system (Simonsen *et al.*, 2014). Mummification (11.0 %) was followed by starvation (5.58 %) and crushing by the sow (7.83 %). The authors discussed, however, that crushing and starvation are most likely a result of low vitality and therefore part of a cascade initiated by poor vigour as described by Edwards and Baxter (2015) (figure 2).

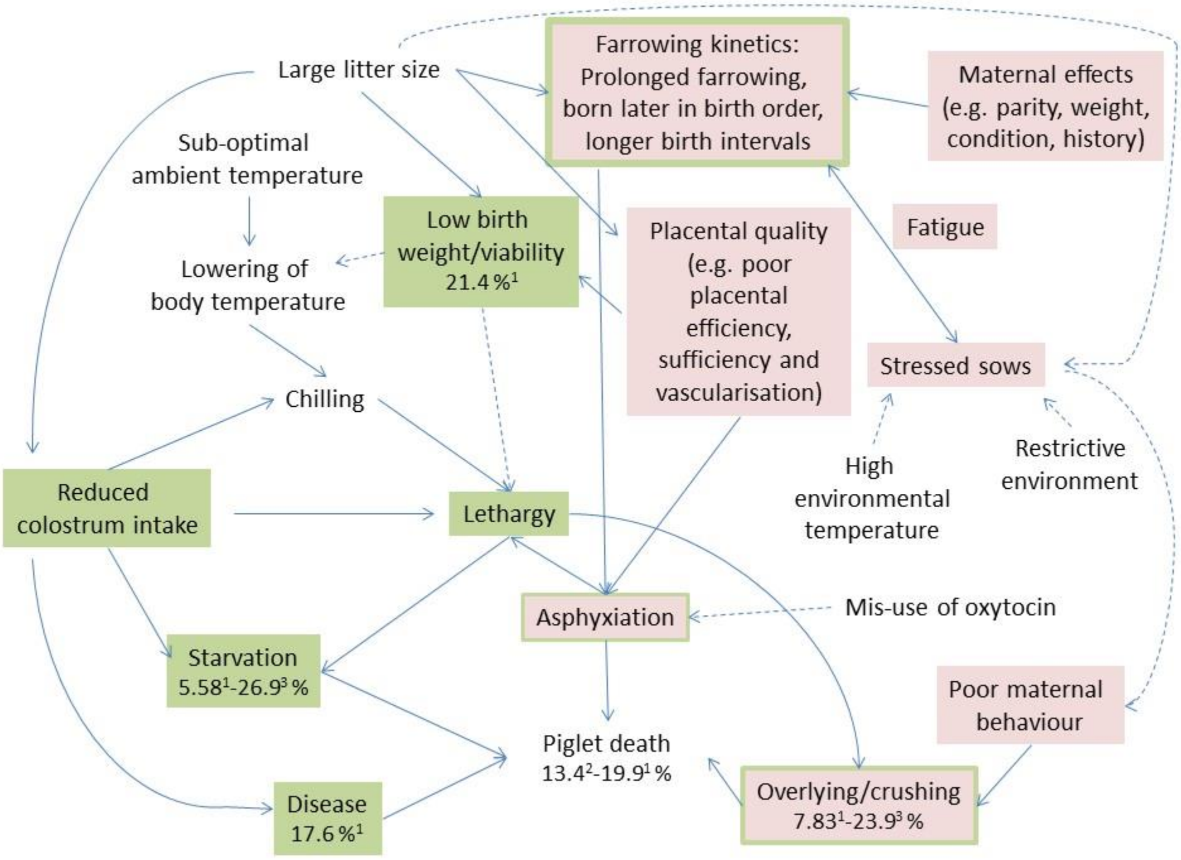

Figure 2: *Complex interactions between the factors causing piglet mortality. Individual piglet factors in green and maternal factors in red. Modified according to Edwards and Baxter (2015), [1] Pandolfi et al. (2017), [2]ADHB Pork (2017), [3] Dyck and Swiersta (1987)*

A detailed explanation of potential factors influencing piglet survival, which are described in figure 2, is given in the following subsections.

2.2. Sow level

Uterine effects and litter size

After successful conception, uterine effects have an eminent effect on piglet survival. According to the review of Edwards and Baxter (2015), the main intrauterine effects essential for foetal survival are the blood flow to uterus, the supply of maternal nutrients and the effectiveness of placental transfer. The placental development is limited if the number of foetuses implanted exceeds the uterine capacity (Rutherford *et al.*, 2013). Père and Etienne (2000) described that even though the blood flow to the uterus increases with LS, the blood flow per foetus declines. Subsequently, nutrient transfer and viability at birth and pre-weaning decrease. Therefore, large litters can cause intrauterine crowding influencing the placental development and piglet development negatively resulting in decreased individual piglet vitality and IUGR (**I**ntra**u**terine **G**rowth **R**estriction and **R**etardation) (Prunier *et al.*, 2010; Matheson *et al.*, 2018). Moreover, Foxcroft *et al.* (2006) described that losses in utero during the embryo elongation phase can increase post-implantation losses under crowded uterine conditions. Vallet *et al.* (2011) found that the placental area is limited by the uterine size, especially in commercial pig breeds. However, there are only few and contradictory results about the relationship between placental area and pre-weaning mortality (Baxter *et al.*, 2009; Rootwelt *et al.*, 2013). Due to the disproportionate allocation of resources for the litter, an intense rivalry exists during and after gestation (Edwards, 2002; Geisert and Schmitt, 2002; Rutherford *et al.*, 2013). This unfavourable situation continues, especially if the number of piglets born exceeds the number of functional teats. The resulting competition between littermates can be fatal for weak piglets (Rootwelt *et al.*, 2013).

Constitution and nutrition

The constitution and weight of the sow can affect pre- and post-farrowing losses. Prunier *et al.* (2010) discussed an increased risk for nutritional deficiency, and subsequent mobilization of fat and protein body reserves with increased LS (e.g. Noblet and Etienne, 1986; Eissen *et al.*, 2000). This may have negative consequences on the following fertility rate. For instance, insemination post-weaning may be delayed if a sow undergoes a catabolic status during lactation. Milk production is demanding in minerals and vitamins and this demand increases with LS (Prunier *et al.*, 2010). However, Leenhouwers *et al.* (2001) reported that the farrowing ability can be aggravated in obese sows. In addition, overfeeding can cause big piglets increasing the inter-birth interval, umbilical cord occlusion and SB. Additionally, a rapid live weight increase during pregnancy caused by an increased feed level can result in leg weakness and osteochondrosis (OCD) with severe impact on reproductive performance and replacement of the breeding animals. Hence, the energy intake has to be balanced to reduce excessive weight gain on the one hand but hunger as well as behavioral disorders on the other hand (Prunier *et al.*, 2010). Cross-fostering may reduce the demand for milk and therefore balance the catabolic status of the sow.

Parity

Several studies showed that the parity of the sow has a significant effect on the amount of stillborn piglets and pre-weaning losses. Li et al. (2012), Koketsu et al. (2006) and Muns *et al.* (2015) found negative relationships between parity and pre-weaning mortality rates and therefore reduced pre-weaning mortality in multiparous sows. Carney-Hinkle et al. (2013) reported reduced body weights and serum concentrations of immunoglobulins in gilts compared to sows in higher parities. Hoshino and Koketsu (2009) showed that sows with higher number of mummified and stillborn piglets had also low milk yields. Devillers *et al.* (2007) found highest colostrum yields in second and third parity sows. Furthermore, Eissen et al. (2000) revealed that milk production decreases after the fourth parity and Ferrari *et al.* (2014) described that piglets show better development if reared by multiparous sows. Moreover, lower experience and increased stress levels in gilts affected piglet survival negatively (Marchant et al., 2000; Ruediger and Schulze, 2012). In contrast, Knol *et al.* (2002a) found, however, no effect of parity on the amount of piglet losses.

Colostrum production and quality

Colostrum and sows milk is composed by nutritional (e.g. lactose, proteins, lipids) and non-nutritional (e.g. immunoglobulin A (IgA), immunoglobulin G (IgG), macrophages, lactoferrin, lysozyme) components (Tizard, 2013). The non-nutritional products regulate intestinal physiology and health in piglets, especially when it comes to the protection of the digestive tract against pathogens (Prunier *et al.*, 2010). However, the composition of the sows milk changes strongly until weaning, especially regarding the concentration of immunoglobulins (Tizard, 2013).

Le Dividich *et al.* (2005) reviewed that the amount of colostrum ingested does not only depend on the piglets' ability to suckle, but also on the amount of colostrum the sow produces. Theil et al. (2006) reported that regular suckling is crucial to maintain colostrum and milk production. Prolific sows do have an increased milk yield (Etienne *et al.*, 2000) even though the increase is not proportional, resulting in a lower intake per piglet in larger litters (Prunier *et al.*, 2010). Colostrum production on the other hand declines with every additional piglets (Prunier *et al.*, 2010) and as a result "piglets from larger litters have less colostrum available on an individual basis" (Devillers *et al.*, 2007). With every additional piglet in the litter colostrum intake decreases by 20g (Prunier *et al.*, 2010). Le Dividich *et al.* (2005) named especially diseases, feed restriction during gestation, reproductive hormone cascades and possible genetic components responsible for the individual colostrum yield. Furthermore, Quesnel (2011) estimated a negative correlation between colostrum yield and the number of stillborn piglets, indicating that the hormone status in late gestation might have an unfavourable effect on farrowing and lactogenesis.

Stress

Stress is a biological response of an animal to an event disturbing its homeostasis (Moberg, 1997). The close relationship between the cascades of stress reactions, hormone production, immune response and the nervous system, do have an impact on the reproduction performance of sows (Segerstrom and Miller, 2004). High temperatures, weaning, relocation, group size and aggression within a group can cause stressful situations in sows. Stress reduces reproduction performance in the form of hampered implantation, embryo development, puberty, weaning to first service interval and oestrus activity (Veru *et al.*, 2014).

Asphyxia is one risk factor for stillbirth caused by difficult farrowing conditions resulting in fatigue or stress of the sow, particularly in larger litters (Edwards and Baxter, 2015). Hence, as recommended by English and Edwards (1996), the supervision of farrowing and decrease of intra-birth intervals are the keys to reduce the amount of stillbirths. Tuchscherer *et al.* (2002) analysed the effect of stress on pregnant sows and on the reactivity immune system of their offspring. Maternal stress in late gestation does impair the humoral and the cellular immune function of piglets pre-weaning with negative consequences for disease susceptibility and immune responsiveness in the offspring. Otten *et al.* (2001) found lower litter weights, increased morbidity and mortality rates due to lowered piglet vitality after their dams experienced gestational stress. Therefore, Segerstrom and Miller (2004) and Veru *et al.* (2014) conclude that the reduction of stress during gestation in livestock will decrease the susceptibility to subsequent diseases post-farrowing.

Maternal and farrowing behaviour

The trait complex of maternal behaviour is complicate to characterize because of non-standardized tests, high environmental impacts and elaborate phenotyping (Appel, 2016). Appel (2016) summarized good maternal behaviour as the combination of good farrowing and rearing behaviour. This means no complications, low extra work per sow and post-parturient disorders (Appel, 2016). Duration of farrowing and the behavior of the sow during birth are determined by LS, individual conditions of the sow, management and inter-birth intervals (Van Dijk et al., 2005). According to Grandison et al. (2003), maternal behavior is characterized by bonding, nursing, responsiveness, attentiveness as well as protectiveness. To access the udder safe and easy the sow must lie laterally and be reasonably passive.

If a sow is restless or aggressive, the risk for crushing is increased and the chances for early colostrum intake are decreased (Edwards and Baxter, 2015). The highest proportion of piglet losses is caused by the sow due to crushing or not preventing starvation (Weary *et al.*, 1998; Hellbrügge *et al.*, 2008; Appel *et al.*, 2016). In the first three days *post-partum* especially weak and non-vital piglets are vulnerable to crushing (Hellbrügge *et al.*, 2008). As mentioned before, crushing was named by Edwards and Baxter (2015) the “ultimate cause of the majority of neonatal deaths" and a part of the "hypothermia-starvation-crushing-complex". Crushing is characterized firstly by a lack of attentive pre-lying behavior and subsequently by a missing response of rising in case a piglet is trapped (Andersen et al., 2005; Thodberg et al., 2002; Edwards and Baxter 2015). According to Grandinson *et al.* (2002), individual differences exist when it comes to the reaction to a screaming piglet or other stimuli. Muns *et al.* (2013) reported that not the screaming of the piglet prevented crushing, but the sow's response did. The responsiveness is therefore a trait of the sow and matches the trait complex of maternal behaviour. Other reasons for crushing are body condition, parity and housing conditions (Edwards and Baxter, 2015). Moreover, fearfulness may limit productivity due to increased piglet losses via crushing (Lensik et al. 2009).

2.3. Piglet level

Vitality

Vitality is an eclectic trait complex in pig production based on miscellaneous physiological and visual phenotypes. Muns *et al.* (2016) described piglet vitality as "physical strength or vigour". In contrast, Merks *et al.* (2012) defined piglet vitality as "survival until slaughter", which is rather focused on viability.

Pigs develop an epitheliochorial placenta, which prevents the transfer of immunoglobulins to the foetus. Subsequently, newborn piglets are immunologically underdeveloped at farrowing because they lack an exposure to antigens (Rooke and Bland, 2002). This exposure to the new environment is crucial for the development of the immune system and antigens. Therefore, the piglet depends on the transfer of passive immunity via the colostrum within the first hours (hrs) after birth (Tizard, 2013). A comprehensive review on piglet immunity as well as its relationship to piglet survival and vitality is given in chapter 3 (page 26 ff). This situation is intensified, because colostrum is only provided within the first 12 to 24 hrs after farrowing in most sows (Quesnel *et al.*, 2012). In addition, the period between farrowing and gut closure is the only possibility during which intact immunoglobulins can be absorbed (Rooke and Bland, 2002). Yet, according to Rooke and Bland (2002) the mechanism of gut closure are still not clear. Speer *et al.* (1959) already observed the decline of antibody absorption after 24 hrs after farrowing. Alexopoulos *et al.* (2018) recommend in their review to maintain the piglets at least 12 hrs with the birth sow, because Tuboly *et al.* (1988) found improved immune cell absorption through the intestinal barrier from birth sow colostrum. Furthermore, Bandrick *et al.* (2011) observed cell mediated immune parameters only if they were kept with their birth sow for a minimum of 12 hrs.

Apart from immunoglobulins, colostrum is rich in protein as well as fat. Piglets are born with low energy reserves and a high demand of their metabolism *post-partum*. Therefore, colostrum is crucial for the provision of energy for activity, growth and thermoregulation in newborn piglets (Le Dividich *et al.*, 2005). Quesnel *et al.* (2012) concluded in their review: "From these findings, we estimate that 200 g of colostrum per piglet during the first 24 hrs after birth is the minimum consumption to significantly reduce the risk of mortality before weaning, provide passive immunity and allow a slight weight gain. A consumption of 250 g could be recommended to achieve good health and pre- and post-weaning growth."

As a consequence, Trujillo-Ortega *et al.* (2007) summarized that piglet vitality determines the ability of a newborn piglet to find a teat, compete for it and to suckle as soon after farrowing as possible. As described before, the causes of increasing piglet mortality are diverse and often interact with each other. Missing piglet vitality can be caused by e.g. IUGR, low or variable BW (see section *The individual birth weight* (page 16 ff.)), or difficulties/delays during farrowing (see section *Birth order and farrowing length* (page 17 ff.)). Increased susceptibility to diseases, starvation, reduced mobility and hypothermia are the main reasons why the lack of vigour often ultimately causes in piglet mortality (Edwards, 2002).

The individual birth weight

Roehe and Kalm (2000) found that the BW is the main predisposing factor decreasing the piglets vitality and survivability. Consecutively, various studies have shown that piglets with a low BW have a lower chance to survive and have discussed if BW would be a reasonable substitution trait to breed for improved survival (Milligan *et al.*, 2002a; Arango *et al.*, 2006; Fix *et al.*, 2010; Roehe *et al.*, 2010). Lightweight piglets are less vital, show decreased colostrum intake and missing thermoregulatory abilities (Theil *et al.*, 2014). Especially piglets with low BW have to consume more colostrum per kg birth weight compared to their heavier littermates (Curtis, 1970). Curtis (1970) described that the increased surface area per unit body weight in low birth weight piglets needs more energy to maintain the homeothermic balance. In addition, decreased litter uniformity was observed to increase piglet mortality (Milligan *et al.*, 2002b). This holds especially in litters with low mean BW (Milligan *et al.*, 2002a). Therefore, delayed colostrum intake does intensify their disadvantage in competing with heavier littermates at the udder (Quesnel *et al.*, 2008; Baxter *et al.*, 2009). The resilience of lightweight piglets to diseases, their development and future weight gain is decreased whilst the impact of postnatal environmental factors cannot be compensated adequately (Edwards, 2002; Le Dividich *et al.*, 2005; Fix, 2010). Rootwelt *et al.* (2013) showed that a BW-threshold of 1 kg for *post-partum* survival has to be crossed. Furthermore, van der Lende and de Jager (1991) reported that piglets below this threshold have an increased risk to die before weaning, independently of the within-litter variability. Pre-weaning mortality rates were 25 % of piglets weighting less than 1 kg and for piglets weighting more than 1.6 kg mortality rates decreased to 5 % (Roehe and Kalm, 2000; Quiniou *et al.*, 2002; Prunier *et al.*, 2010). Hence, management strategies for low BW piglets include colostrum supplementation and cross-fostering for live-born piglets based on their respective BW (Muns et al. 2003).

Muns et al. (2013) and Milligan (2001) found that the variation of BW within litters was consistent until recording the weaning weight. Furthermore, piglets with a low BW and viability at birth show a slower growth until and after weaning as well as a compromised carcass quality (Knol, 2001; Gondret *et al.*, 2006; Beaulieu *et al.*, 2010; Fix *et al.*, 2010). Even though a low BW is associated with a reduced potential for future growth the relationship between BW and future weight is not linear per se (Fix, 2010). The author has shown that a decrease in BW below the mean cause a higher decrease of the future weight. As a result, light BW result in lighter pigs at harvest or a longer fattening period (Fix, 2010).

Birth order and farrowing length

According to Randall (1972), birth order has a huge impact on the number of stillborn piglets. Baxter *et al.* (2009) found that an increased number in the birth order has an unfavourable association with piglet mortality. This situation was confirmed by Rootwelt *et al.* (2012) and by Le Dividich *et al.* (2017) who observed that 43 % of the stillbirths of their study were born in the last quarter of the relative birth order. According to Rootwelt *et al.* (2013) and Stanton and Carroll (1974), the piglets born later have a cranial location in the uterus and are heavier. Trujillo-Ortega *et al.* (2007) stated that heavy piglets prolong the farrowing process resulting in an increased risk of asphyxia and subsequent stillbirth for themselves as well as the following littermates. However, on the association between BW and birth order also contradictory results exist (Motsi *et al.*, 2006; Beaulieu *et al.*, 2010).

Herpin *et al.* (1996) explained that hypoxia at farrowing mainly occurs in late-born piglets with the consequence that these piglets are weaker and less competitive for colostrum which is essential for the piglet to gain passive immunity. The umbilical cord is primarily responsible for oxygen and nutrient delivery in the fetus, which can influence especially the survivability at birth. A ruptured umbilical cord therefore increases the susceptibility to die before weaning (Rootwelt *et al.*, 2013). Alonso-Spilsbury *et al.* (2005) reported that if the umbilical cord is ruptured, irreversible brain damage can occur due to hypoxia and compromised blood-flow between dam and foetus (Curtis, 1974; Mota-Rojas *et al.*, 2012). In utero hypoxia can also result in meconium staining, which is characterized by a yellow discoloration. It is the result of the relaxed anal sphincter tone and the expulsion of meconium into the amniotic fluid after hypoxia (Mota-Rojas *et al.*, 2012). In the study of Rootwelt *et al.* (2013), the time between the expulsion of the first piglet and subsequent births was associated unfavourably with a decreased **R**espiration, **M**econium **S**taining and **A**ctivity (RMA) score. These piglets showed a lowered vitality. For RMA the lowest value describes no respiration or activity and gross meconium staining whereas the highest value stands for normal respiration and activity and no meconium staining (Rootwelt *et al.*, 2013). However, pre-weaning losses were found independent of the birth order in other studies (Cabrera *et al.*, 2012; Le Dividich *et al.*, 2017).

Intrauterine growth retardation

The studies of Baxter *et al.* (2009) and Rootwelt *et al.* (2012) showed that piglet survival and vitality during gestation, farrowing and *post-partum* are linked to IUGR. IUGR can not only result in an increased number of stillborn piglets, but as well in subsequent constrained vigour and postnatal survival due to an insufficient physiological development (Bauer *et al.*, 1998). Pardo *et al.* (2013) investigated differences in uterine space of sows had either crowded or not crowded uterine conditions. The authors found IUGR phenotypes (reduction of BW, organ and muscle weights, brain sparing effects, delayed myofibril maturity) in litters under crowded uterus conditions caused by placental insufficiency. Hales *et al.* (2013) and Amdi *et al.* (2013) have investigated visual scores of piglets head morphology and found that especially dolphin-like head shapes indicate IUGR. These piglets had an insufficient colostrum intake, lower glucose levels at 24 hrs *post-partum* and unfavourable organ ratios (Amdi *et al.*, 2013).

Other traits

Further traits to investigate piglet vitality post farrowing are, apart from the BW (Hales et al. 2013, Baxter et al. 2008): (1) body temperature and (2) behavioural characteristics like e.g. mobility, (3) udder stimulation and (4) screaming (Muns *et al.*, 2013). Muns et al. (2013)

found that udder stimulation and the piglet's mobility within a given enclosure are suitable traits for the on-farm application to identify the piglets' individual vitality. Rootwelt *et al.* (2013) stated that the analysis of the Body Mass Index (BMI), described as the BW divided by the squared length of the piglet, showed that not only smaller but also thinner piglets are more prone to die before weaning. Therefore, as reported by Leenhouwers *et al.* (1999) and Rootwelt *et al.* (2012), small (lightweight) does not equal less vital. Baxter *et al.* (2009) found stillborn neonates were disproportionately long and thin compared to their live born littermates. The authors concluded that not only the BMI, but also the Ponderal Index (PI) would be a reasonable indicator of piglet loss. This index additionally includes the cubed crown-to-rump length of the piglet. Furthermore, Baxter *et al.* (2012) observed that the gender of the piglet has an influence on piglet survival. Even though male piglets were heavier than their female littermates their thermoregulatory capacities after birth were impaired, resulting in higher piglet losses in male piglets.

2.4. Breeding for piglet survival

Livestock breeding made vast progress after the implementation of best linear unbiased prediction (BLUP) based on phenotypic records (Boichard *et al.*, 2016; Meuwissen *et al.*, 2016). This method allows for the estimation of breeding values (EBV) and variance components by estimating the random effects in a mixed model (Piepho *et al.*, 2008). Thereby, the genetic merit of an animal is estimated using the pedigree-based relationship between the individuals and correcting the phenotypic records for environmental effects, simultaneously. Selection decisions are based on the EBVs that are usually combined into a selection index (SI) with weighting factors. These weighting factors are made according to the marginal economic value (MEV) of each trait (Schneeberger *et al.*, 1992; Knap, 2014). Furthermore, mature progeny is needed to provide the phenotypes for the basis of the next selection decision (Hill). The application of single nucleotide polymorphisms (SNP) for the statistical investigation of the genetic background of a trait using quantitative trait loci (QTL) indicated possible genotype-phenotype associations (Meuwissen *et al.*, 2001). Based on these structures genome-wide association studies (GWAS) were implemented to gain in-depth knowledge about potential candidate genes and therewith the genetic background of production traits as well as low heritable phenotypes of interest (Visscher *et al.*, 2017). To improve selection decisions SNP were used firstly in marker assisted selection (MAS) and subsequently in genomic BLUP (GBLUP) methods (Meuwissen *et al.*, 2016). GBLUP methods are favourable because the show higher accuracies in the prediction of the breeding values and therewith allow a selection before the individual is born or tested (Hayes *et al.*, 2009; Meuwissen *et al.*, 2016). Traits influencing piglet survival at piglet and sow level can be considered in breeding and were already implemented in breeding goals (Knol, 2001; Rydhmer, 2005; Nielsen *et al.*, 2013; Knap, 2014).

The investigation of the genetic background of a trait is crucial to evaluate the potential for a breeding-based improvement of a population. Thereby, the distinct genetic variability of a trait is a critical prerequisite to be heritable (Hill; Ibanez-Escriche *et al.*, 2009). Furthermore, the relationships to important production traits have to be investigated to evaluate potential side effects if the trait of interest is included into the breeding scheme. For example Rydhmer (2000) stressed that the breeding goal has to be balanced if the focus lies on increased LS and therefore not only maternal and piglet performance traits, but traits of maternal behaviour have to be included. The traits that are associated with piglet survival were analysed as traits of the litter and at individual piglet level (Su *et al.*, 2007; Ibanez-Escriche *et al.*, 2009).

2.5. Genetic background of piglet survival

Litter and sow traits

Breeding for increased LS was very successful although this trait shows a low heritability 0.11-0.16 (Kapell et al., 2011). However, as mentioned before, LS has influenced piglet survival negatively (Rutherford et al., 2013). Therefore, alternative litter-based traits were investigated in various studies to potentially improve piglet survival and result in large, uniform litters at the same time (Damgaard *et al.*, 2003; Täubert and Henne, 2003; e.g. Hellbrügge *et al.*, 2008; Wittenburg *et al.*, 2011). Most piglet losses occur within the first five days after farrowing. As an example, LS at day five (LS5) was introduced into the breeding goal in Denmark (Su *et al.*, 2007; Nielsen *et al.*, 2013). An in-depth review of the results of these studies is given in chapters 3 and 4. Typical traits that are recorded at litter level to improve survivability are NBA, the number of stillborn piglets, the number of pre-weaning losses, the average birth weight within litter or the variance of birth weights within litter.

Besides, records of maternal behaviour traits, colostrum production, teat number and IUGR proportions, represent mothering abilities and uterine capacity. For example, the necessity of birth assistance was investigated by Pedersen and Jensen (2008), Holm *et al.* (2004) and Canario *et al.* (2006) who reported low h^2 between 0.03-0.05. Hellbrügge *et al.* (2008) estimated h^2 of 0.09 for the trait responsiveness towards separating the piglet 24 hrs after birth and Grandinson *et al.* (2003) found h^2 of 0.08 for fear measured as avoidance of stockpersons. Matheson *et al.* (2018) studied the potential of selection against IUGR at maternal level. The authors concluded that the within-litter proportion of IUGR piglets should be included additionally to increase piglet survival and remain current LS. Moreover, colostrum production can be improved with the help of genetic selection, however, the difficulties in phenotyping limit the amount of research available in this area (Farmer and Quesnel, 2009). Recently, Rohrer and Nonneman (2017) reported that the number of teats shows a h^2 of 0.49 and found genetic markers for this trait. Moreover, various studies investigated the genetic background of litter traits associated with piglet survival (see also chapter 3) using linkage studies, GWAS and genomic selection (GS) approaches (Schneider *et al.*, 2015; Sell-Kubiak *et al.*, 2015b; e.g. Guo *et al.*, 2016; Verardo *et al.*, 2016). The results show potential QTL especially for survival traits. Birth weight related traits usually appear to be under increased polygenic influence.

Individual piglet survival and birth weight

Individual piglet survival pre- and post-farrowing is classically a binary coded trait (Knol *et al.*, 2002a). It is recorded at farrowing (SB) or pre-weaning (PWL) and can be even further divided into survival between birth and day five and survival between day six and weaning (Roehe and Kalm, 2000; Su *et al.*, 2008; Roehe *et al.*, 2010). Su *et al.* (2008) reported that SB and PWL are different traits because they show low genetic correlations (r_g). Early analyses of these binary traits assumed linear models ignoring the categorical nature of these traits (Ibanez-Escriche *et al.*, 2009). These evaluations usually underestimated the variance components, and therefore, the h^2 of these traits (Roehe *et al.*, 2010). The use of threshold models is elaborate and complex, especially if maternal genetic and litter effects are included in the respective models (Gianola, 1982; Knol *et al.*, 2002a; Su *et al.*, 2008). Furthermore, an extensive and precisely recorded data basis is needed with a vast number of piglet losses (Gianola, 1982; Knol *et al.*, 2002a; Su *et al.*, 2008). Roehe et al. (2010) reported that if a common litter effect (c^2) is modelled, this accounts for the effect of LS, which does not have to be incorporated into the model as fixed effect. The individual BW was analysed as continuous trait (Arango *et al.*, 2006; Roehe *et al.*, 2010). The h^2 for traits associated with the individual piglet survival and the individual BW were low in pure-bred pig populations and variance components showed that maternal genetic (m^2) and c^2 have a major impact on these traits (Arango *et al.*, 2006; Su *et al.*, 2008; Ibanez-Escriche *et al.*, 2009; Roehe *et al.*, 2010). However, if cross-fostering was included in the statistical model it was only considered as a fixed effect (Roehe *et al.*, 2009). An in-depth review on the results of these studies is given in chapters 3 and 4. The genomic analysis and selection of individual piglet survival and the individual BW were not realized up to now. Case-control studies would be the adequate model for the analysis of categorical individual piglet survival traits.

2.6. Breed differences in piglet survivability

Differences in the breeding goals can be found between dam (reproduction) and sire (production) lines, which resulted in differences in reproduction performance (e.g. Ibanez-Escriche *et al.*, 2009; Kapell *et al.*, 2011). Within dam lines the differences in variance components for piglet survival and the individual BW were only marginally different (Täubert and Henne, 2003; Su *et al.*, 2008; Nielsen *et al.*, 2013). Ibanez-Escriche *et al.* (2009) reported very similar h^2 and m^2 for farrowing mortality for Landrace (LR), Large White (LW) and Piétrain (Pi). However, direct and m^2 effects are negatively correlated in LR and PI, but positively in LW. Therefore, the authors concluded that direct and m^2 effects have to be modelled in LR and Pi. In LW, however, farrowing mortality should be considered as trait of the sow. Kapell *et al.* (2011) investigated three dam and two sire lines for individual piglet survival and traits associated with the individual BW. All lines showed considerable genetic variation; however, the authors recommended that breeding strategies should be designed line specific because the relationships between the traits differed in direction and magnitude.

Breed specific (occidental versus oriental) differences in reproduction traits were reported by Canario *et al.* (2006). Especially, the Chinese Meishan (MS) breed is a positive example for high prolificacy and survival rates. Canario *et al.* (2006) compared MS, LW and other occidental cross-bred sows and found that MS produce larger litters with an increased number of viable piglets and significantly decreased number of stillborn. The reason is the enhanced placental efficiency MS dams possess as described by Biensen *et al.* (1998). Canario *et al.* (2007) found that LW sows produced larger heterogenous litters and heavier, faster growing piglets. Herpin *et al.* (1993) described that MS piglets are physiologically more mature, even though they are smaller, show higher percentage of carcass fat and larger adipose tissue adipocytes compared to piglets from occidental breeds. Recently, Ma *et al.* (2018) reported genomic regions affecting LS and candidate genes for uterine horn length in Chinese Erhulian

(ER) pigs that are also known to be high prolific that could also be favourable for larger litters in European pig breeds.

Survivability in crossbred piglets was analysed by Roehe et al. (2010; 2009) and Dufrasne *et al.* (2013). Dufrasne *et al.* (2013) found low h^2 for pre-weaning mortality and the individual BW in crossbred pigs. Roehe et al. (2010; 2009) reported higher h^2 for survival traits and the individual BW. The authors created a population of crossbred piglets from three lines selecting for piglet survival that was reared under outdoor conditions. Heritabilities estimated the second generation were already doubled for individual piglet survival and the individual BW even though an additional m^2 effect was modelled.

Chapter 3. Invited Review: Piglet Survival – Benefits of the immunocompetence

Short title: Piglet Survival – Benefits of the immunocompetence

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Abstract

Piglet mortality has a negative impact on animal welfare and public acceptance. Moreover, the number of weaned piglets per sow mainly determines the profitability of piglet production. Increased litter sizes are associated with lower birth weights and piglet survival. Decreased survival rates and performance of piglets make the control of diseases and infections within pig production even more crucial. Consequently, selection for immunocompetence becomes an important key aspect within modern breeding programs. However, the phenotypic recording of immune traits is difficult and expensive to realize within farm routines. Even though immune traits show genetic variability, only few examples exist on their respective suitability within a breeding program and their relationships to economically important production traits. The analysis of immune traits for an evaluation of immunocompetence to gain a generally improved immune response is promising. Generally, in-depth knowledge of the genetic background of the immune system is needed to gain helpful insights about its possible incorporation into breeding programs. Possible physiological drawbacks for enhanced immunocompetence must be considered with regards to the allocation theory and possible trade-offs between the immune system and performance. This review aims to discuss the relationships between the immunocompetence of the pig, piglet survival as well as the potential of these traits to be included into a breeding strategy for improved robustness.

Implications

Piglet mortality fuels critical discussions regarding animal welfare concerns. Furthermore, the number of weaned piglets per sow determines the economic success of piglet production. Robustness and a well-performing immune system are a prerequisite for piglet survivability, which is determined by the complex relationships between direct and maternal genetic effects,

common litter and management driven environmental effects. This review aims to summarize mechanisms and relationships between immunity, robustness and piglet vitality.

Keywords

Pig immunity, robustness, piglet survivability, piglet vitality, animal welfare

3.1. Introduction

General implications

The number of weaned piglets per sow is the main determiner of the profitability of piglet production. Therefore, breeding organizations have focused on the genetic improvement of litter size, leading to a substantial increase of the number of piglets born alive (NBA). It is well known that increasing NBA leads to lower birth weights and increased piglet mortality (e.g. Knol, 2001). Piglet mortality has a negative impact on animal welfare, public acceptance and decreases the subsequent viability of pig performance (Rutherford *et al.*, 2013). However, the causes of piglet mortality are diverse and often interact with each other. Besides birth weight, the immune system also has a strong impact on pig performance, but parameters of immune response and general health have seldom been considered on a large scale in modern breeding programs so far (Clapperton *et al.*, 2008b). However, animals should have low medication needs, whilst meeting consumer protection requirements. This situation was intensified by an extensive use of antimicrobials in livestock production causing resistances and consequences for human health (Merks *et al.*, 2012). The customer expects farm animals to be kept under ethologically optimized animal welfare standards, requiring robust livestock needing little management effort and resistant to disease (Kanis *et al.*, 2004; Merks *et al.*, 2012).

The basic relationships of the immune system, robustness and resilience, survival and vitality of piglets were recently studied as well as reviewed in a comprehensive manner (e.g. Edwards and Baxter, 2015; Colditz and Hine, 2016). Until now, a common consideration of these three complexes has not been performed. Therefore, we aim to focus on the relationship between pig immunity and robustness as well as the possibilities of implementing these traits in breeding programs to improve piglet survivability.

3.2. Immune system

The immune system is a highly interactive system composed of integrated, genetically and environmentally regulated sets of cells and molecules. Classically, immunity itself is separated in two pillars, innate and adaptive host defence mechanisms (Tizard, 2013).

The innate immune response is the first line of defence and provides an effective protection. This system is involved in first detection, recognition, killing and delivery of antigens to the next lymphoid tissue and enables the pig to respond rapidly to an infectious agent (Chase and Lunney, 2012). It consists of physical barriers, phagocytic cells and the production of various mediators with the task to protect, recruit cells through an inflammatory process and activate the adaptive immune system (Tizard, 2013). However, these defence mechanisms are not antigen-specific (Chase and Lunney, 2012).

The adaptive immune system is antigen-specific. It consists of an immunological memory and takes about two to three weeks to operate properly after birth and antigen exposure. Mounting an immune response takes longer at first antigen exposure compared to the following encounters with the same antigen. This can result in protection (e.g. vaccination) even if there is no prevailing burden by antigens (Chase and Lunney, 2012).

Influences on the immune system

Blood performs a wide variety of tasks in the body, including the transport of nutrients, hormones and neurotransmitters, as well as protection against infections (Watson, 2015). The easiest way to get a first insight into the state of the immune system is to analyse the differential blood count (Zhang *et al.*, 2014a). However, the evaluation of blood values should always be considered in connection to the respective environment, because the variation in host response to pathogens and diseases are influenced through genotype by environmental (G×E) interactions (Mallard and Wilkie, 2007; Rashidi *et al.*, 2014). This means that animals with advantageous immune phenotypes according to their blood values, should express those in a broad range of environments and not only in the environment they are selected in

(Mallard and Wilkie, 2007). In this context, it is important to understand the immune response during various life conditions and phases including stress, infection pressure, changing environmental effects, parturition, post-partum, growth and development (Henryon *et al.*, 2006). For example, Schalm *et al.* (1975) and Seutter (1995) established relevant blood values for various pig production cycles, but an actualization for modern pig populations and environments is needed. The crucial factors influencing the differential blood count are psychological and physical stress, even during blood collection, as well as sex. Furthermore, species differences in the composition of blood have been known for a while (Schalm *et al.*, 1975), but breed-specific differences have only been considered recently (e.g. Seutter, 1995; Henryon *et al.*, 2006). Going forward, this should be studied intensively with current breeds, crossbreds as well as with current and changing housing conditions.

In recent years, various authors (Clapperton *et al.*, 2009; Flori *et al.*, 2011a) have reported on the porcine immune system, giving us a deeper understanding of the reticulation of the immune system. The question “What is a good immune system?” is not answered completely. To answer this question and achieve breeding progress, detailed insights into the immune system of pigs during their developmental stages are necessary.

3.3. Immunocompetence

The immunocompetence of a host is determined by the sum of tolerance and resistance (Rauw, 2012). In livestock, tolerance is described as the ability of an individual to limit the impact of a given pathogen burden on performance (Mulder and Rashidi, 2017). Resistance, however, is characterized by the ability of an individual to reduce the probability of infection or growth of the pathogen by limiting the pathogen burden within itself (Hermesch, 2014). Based on the definition by Knap (2005), robustness was defined by Colditz and Hine (2016), as the consistency of the phenotype of an animal independent of the persistent characteristics of the environment it is kept in. Resilience, however, was defined as the “capacity of the animal to return rapidly to its pre-challenge state following short-term exposure to a challenging situation" (Colditz and Hine, 2016).

Tolerance and resistance can be abstracted mathematically using reaction norm models (e.g. Raberg *et al.*, 2009) describing the dynamics of these traits regarding host health and infection intensity (Rauw, 2012). The gap between promising genotypes and their effective performance due to an insufficient provision of resources can be described as unfavourable G×E interactions (Knap, 2005). Thereby, reaction norm models quantify G×E interactions by ranking the sensitivity of an individual towards its environment. Tolerance is defined by Simms (2000) as the regression of the relationship between fitness and infection intensity or by Raberg *et al.* (2009) as “the rate of change in fitness as parasite burden increases”. Resistance is typically defined as the amount of pathogens in a host or as the inverse of infection intensity (Raberg *et al.*, 2009).

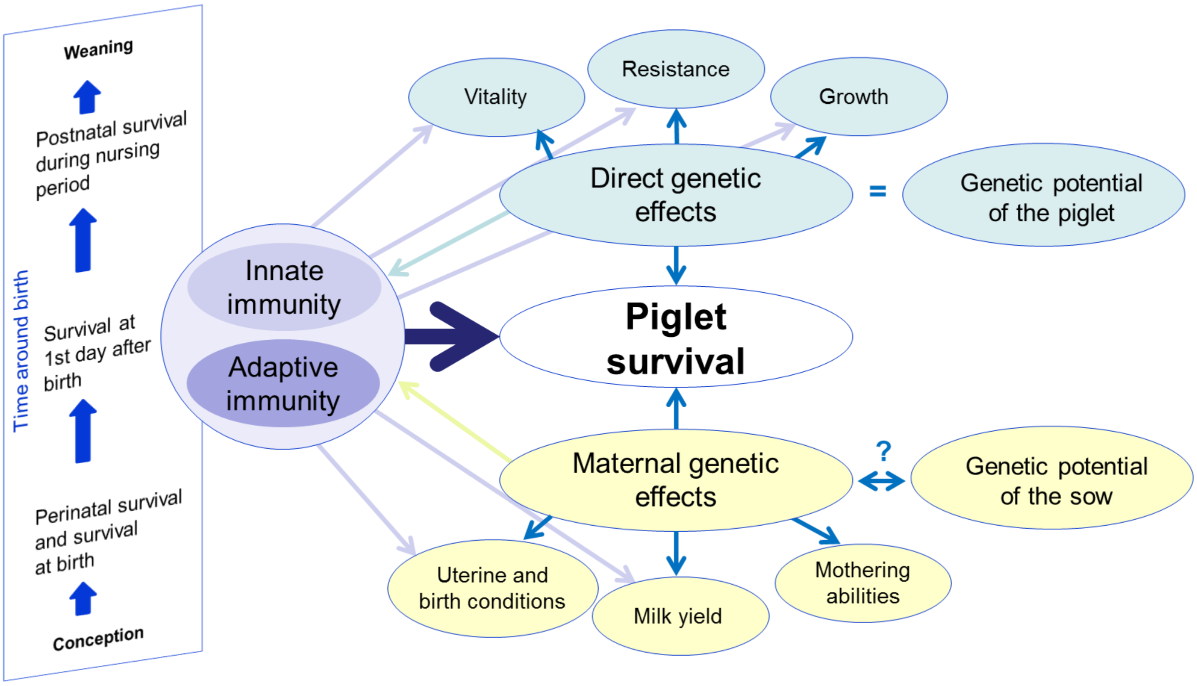
Generally, tolerance, resistance and resilience are characterized by the need for (re)allocation of resources (Rauw, 2012). According to the allocation theory, an individual possesses a set of resources which are limited and have to be invested amongst the systemic functional areas (Friggens *et al.*, 2017). These include growth, metabolism, reproduction, maintenance, retention of energy and nutrition for future use. In this zero-sum system, each unit of resource is only directed to one function, resulting in trade-offs between these systemic functions (Rauw, 2012; Friggens *et al.*, 2017). If an immune response is activated, the transformation rate of energy and nutrients is expected to be considerably increased. These resources are then needed and allocated to the immune system; conversely, these mechanisms also work vice versa (Guy *et al.*, 2012; Rauw, 2012). If an individual passes through life conditions and phases (e.g. extensive growth, reproduction), nutrients and energy are allocated to those somatic functions and immune responses are decreased due to limited physiological resources (Rauw, 2012). It cannot be totally dismissed, that in the situation of a specific immune reaction, deficiencies in, for example, growth and reproduction performance appear. These ‘costs’ for the organism are determined by the environment, the availability of needed resources, and the host’s genotype; however, they cannot be assessed completely (Colditz, 2009).

3.4. Evaluation of tolerance, resistance and resilience

Guy *et al.* (2012) indicated the importance of analysing the immune response critically before attempting to measure tolerance and resistance. Thus, tolerance has to be measured under different environments to detect the fitness of an individual facing various stressors (Friggens *et al.*, 2017), which makes phenotyping very difficult and detailed (Wilkie and Mallard, 1999; Doeschl-Wilson *et al.*, 2012). The same effort has to be applied to characterize resistance, because it requires quantifying the pathogen load in the individual under a given pathogen challenge (Kause, 2011). However, Mulder and Rashidi (2017) reported that selecting for resilience via performance measures only is an efficient way to improve disease resistance and tolerance sparing the need to evaluate the pathogen burden. But the authors found the selection responses to be higher if the pathogen challenge is recorded (Mulder and Rashidi, 2017).

3.5. Piglet vitality and survival

Piglet vitality is the “ability of a piglet to survive based on its survival at birth and till weaning” (Merks *et al.*, 2012). Vitality and survival traits are influenced by additive genetic (e.g. behaviour, vigour, immunity), maternal genetic (e.g. behaviour, milk quality and quantity, uterus quality) (figure 1), common litter (e.g. litter size) and various environmental effects (e.g. temperature, stress and difficulties during farrowing, help with colostrum intake) which are difficult to disentangle mathematically (Knol, 2001; Roehe *et al.*, 2010).



The connection between piglet survival and immunity

Figure 3: *This figure captures the questions and knowledge gaps behind the relationships of the immunocompetence and piglet survival described in this review. Piglet survival is considered within the timeframe between conception and weaning. Thereby, direct genetic and maternal genetic effects influence survivability. The relationship between piglet survivability and immunity and their genetic factors are rarely investigated. However, it is clear that a functioning immune system is a necessary prerequisite for the newborn to survive. (Modified according to Roehe et al., 2009).*

In Germany, the current piglet pre-weaning mortality rate is 14.87 % (erzeugerring.info, 2018). The proportion of pre-weaning losses, however, remained stable whereas the number of piglets born alive kept increasing (erzeugerring.info, 2018). This development confirms that breeding for important production traits and larger litters resulted in higher amounts of piglet losses caused by an increased risk for less developed piglets and low individual birth weights (e.g. Edwards, 2002; Grandinson *et al.*, 2002; Alonso-Spilsbury *et al.*, 2007; Hellbrügge *et al.*, 2008; Fix, 2010; Baxter *et al.*, 2013; Rutherford *et al.*, 2013). The rivalry in large litters starts in utero, resulting in within-litter variation of birth weights (Rutherford *et* *al.*, 2013) and continues post-farrowing if the number of piglets born exceeds the number of functional teats on the sow (Rootwelt *et al.*, 2013).

The main causes for piglet losses are stillbirth, crushing by the sow and starvation and can still be consistently found in literature (Dyck and Swiersta, 1987; Edwards, 2002; Edwards and Baxter, 2015). However, these causes were discussed to be effectively the result of low vitality and therefore part of a cascade initiated by poor vigour on the one hand (Edwards and Baxter, 2015) and missing mothering abilities on the other (Grandinson *et al.*, 2002). Dyck and Swiersta (1987) concluded that the main cause for a piglet loss is inadequate colostrum and milk intake in the first days of life. The complex interactions between genetic prerequisites and the environment make it difficult to determine a single reason or rather the real cause for a loss between conception and weaning (Edwards, 2002; Grandinson *et al.*, 2002).

Birth weight was described to be the main factor influencing piglet survival (Roehe and Kalm, 2000) and to be a suitable substitute trait to breed for increased piglet survivability due to its higher heritability (Grandinson *et al.*, 2002; Roehe *et al.*, 2010). The increase in litter size did not only enhance the risk of lower individual birth weight, but also for a decreased uniformity of birth weights within litters (e.g. Knol, 2001). Piglets with a low birth weight and viability at birth show a slower growth and compromised carcass quality (Knol, 2001; Fix, 2010). However, breeding for higher birth weights does not solve the problem single-handedly (Knol, 2001). Heavy piglets prolong the farrowing process for themselves as well as for the following littermates resulting in an increased risk of asphyxia (Grandinson *et al.*, 2002; Trujillo-Ortega *et al.*, 2007). This non-linear relationship between birth weight and stillbirth was also described by, for example, Roehe and Kalm (2000).

Baxter *et al.* (2008) found stillborn piglets were disproportionately long and thin compared to their live born littermates. The authors concluded that not only the Body Mass Index (BMI) but also the Ponderal Index (PI) would be reasonable indicators of piglet loss. Fay *et al.*

(1991) studied human infants and found that the PI is a more reliable indicator for intrauterine growth problems than the birth weight. The PI additionally includes the cubed crown-to-rump length of the piglet (Baxter *et al.*, 2008) and reflects the change in relative weight for length during gestation (Gluckman and Hanson, 2005). van der Lende and de Jager (1991) and Rootwelt *et al.* (2013) showed that a threshold of 1 kg for postpartum survival is needed. Piglets with a birth weight lower than 1 kg have an increased mortality risk, independent of their status in the within-litter variation in birth weight (van der Lende and de Jager, 1991). Low birth weight piglets are less vital, with decreased colostrum intake, a lack of immunoglobulins, and a higher risk of pre-weaning mortality due to missing energy reserves, causing hypothermia, crushing and starvation related deaths (Edwards, 2002). Their resilience to disease, development and future weight gain is decreased whilst the impact of postnatal environmental factors is increased (Edwards, 2002; Le Dividich *et al.*, 2005; Fix, 2010).

3.6. Relationship between immunity and piglet survival

The primary immune response of the piglet needs seven to ten days to develop (Chase and Lunney, 2012). It is well known that piglet survivability and performance of the immune system are associated via colostrum intake. Newborn piglets are characterized by a lack of immunoglobulins, due to the missing antibody supply from the placenta (Chase and Lunney, 2012) and missing energy reserves (Theil *et al.*, 2014). Piglets are immediately exposed to microorganisms and pathogens, resulting in a complex microbial flora on its surfaces and in its gastrointestinal tract within hours *post-partum*. The intestinal microflora is crucial for the development of the immune system. Antibodies are concentrated in the colostrum in the last days of gestation and transferred intact via the gut of the piglet. The intestinal absorption of immunoglobulins from colostrum decreases after one to four days *post-partum*. Generally, the concentration of colostrum components changes substantially and rapidly after birth (Theil *et al.*, 2014). The provision of colostrum is crucial for the piglet's survival, its thermoregulation and growth after birth (Le Dividich *et al.*, 2005). Reasons for reduced colostrum intake lie e.g. in the vitality of the piglet, the competition at the udder, and the quantity of colostrum produced by the sow (Tizard, 2013). Le Dividich *et al.* (2017) showed that the level of passive immunity acquired through colostrum determines the level of systemic immunity at weaning. Further, they found that piglets with a lower birth weight who survived, needed more colostrum than their heavier littermates. The colostrum production of the sow was independent of litter size and weight. Generally, the birth order was not associated with colostrum intake but with lower immunoglobulin G (IgG) concentrations in piglets that were born later (Le Dividich *et al.*, 2017).

3.7. Genetic aspects of piglet survival and immunity

Immunity

Phenotypes representing the immune system usually include subtypes of leukocytes, as well as T/B lymphocytes (Mangino *et al.*, 2017). To select pigs for improved health, suitable traits have to be heritable and preferably associated with enhanced performance (Clapperton *et al.*, 2008b). The homeostatic control of the various cell types within the immune system are under genetic and environmental control to a varying extent (Mangino *et al.*, 2017). Mangino *et al.* (2017) estimated variance components and heritabilities (h^2) in human twins and found that adaptive immune traits are more influenced by genetics, whereas innate immune traits underlie a higher environmental influence.

Table 1 shows a reasonable genetic foundation for most immune parameters from quantitative genetic studies in pigs. Estimations of h^2 are highly variable between the studies. These different results could be caused by the number of animals (~200 to 4000), breed and line analysed (Clapperton *et al.*, 2005) as well as the age or life phase of the animals phenotyped. The fact that challenge studies were conducted (on-farm health status, vaccination reactions, targeted infection) could cause differences in h^2. Furthermore, the statistical models used as well as the fixed effects considered (e.g. weight, age, farm, breed) influence h^2 estimations. These characteristics make it difficult to compare the findings due to diverse study approaches. For a meaningful estimation of h^2 and genetic correlations (r_g), large numbers of phenotyped animals are needed. However, this prerequisite is difficult to realize because taking blood samples is time consuming and the analysis relatively expensive. Furthermore, the impact of the immune system of the sow on the colostrum supply for the piglets and the development of the respective piglets remains uncertain.

The relationships between the innate and adaptive immune response were estimated by Flori et al. (2011a) and demonstrated the complementarity of innate and adaptive immunity. However, the analyses did not provide any clusters of immune parameters or significant correlations between cell subsets (Flori et al., 2011a). The relationships between innate and adaptive immunity were described by Seutter (1995) with the help of the haematological traits neutrophil and lymphocyte concentration. Neutrophil concentrations are expected to have an antagonistic relationship to lymphocyte concentrations, because of the activation of the adaptive immune response (Tizard, 2013). However, this relationship can also be determined by the challenges or the state of development the pig is experiencing. Seutter (1995) described that sows show a neutrophil dominated blood count after farrowing due to the physical strain of birth. In contrast, piglets express a blood count dominated by lymphocytes indicating that their immune system is responding to their new environment

Table 1: *Heritabilities (h^2 ± SEM) in blood parameters of the porcine immune system (Full table in Appendix (table S3))*

Parameters	Henryon *et al.* (2006)	Clapperton *et al.* (2008b)	Clapperton *et al.* (2009)	Flori *et al.* (2011a)	Mpetile *et al.* (2015)	Ponsuksili *et al.* (2016)
Breed	Duroc, Landrace, Yorkshire	Large White	Large White, Landrace	Large White	Yorkshire	Landrace
n	4 204	500	606	443	518	591
Leukocytes	0.25 (0.05)	0.24 (0.15)	0.28 (0.11)	0.73 (0.20)	0.23 (0.19)	0.23
Neutrophiles	0.22 (0.04)			0.61 (0.20)	0.31 (0.21)	
Lymphocytes	0.24 (0.05)			0.72 (0.21)	0.15 (0.19)	0.49
Monocytes	0.22 (0.04)	0.52 (0.17)	0.26 (0.13)	0.38 (0.20)	0.36 (0.20)	
Eosinophils	0.30 (0.05)			0.80 (0.21)	0.58 (0.12)	
Basophils					0.12 (0.19)	
Thrombocytes				0.56 (0.19)	0.11 (0.23)	0.39
Erythrocytes				0.43 (0.20)	0.62 (0.25)	0.41
Haemoglobin					0.56 (0.13)	0.40
Hematocrit				0.57 (0.03)	0.06 (0.14)	0.34

To our knowledge, only Clapperton *et al.* (2008b, 2009) investigated the relationships between immune parameters and growth performance. The authors found negative correlations between some of the investigated leukocyte blood cells and daily gain and also estimated negative genetic correlations between CD11R1+ cells and average daily gain under lower health status. Against this background, we can postulate that a major knowledge gap exists about the genetic impact of the porcine immune system, especially with regards to performance traits and piglet survivability. Furthermore, no studies were conducted to investigate the complex interactions between the dam and her litter or maternal genetic effects (figure 1). The immune system of the dam could affect phenotypes expressing maternal genetic effects like colostrum quality and quantity as well as uterus and birth conditions. This, however, would influence the ability of the piglet to survive pre and post-farrowing. The maternal effects are possibly decreasing with time whilst the challenges for the direct genetic effects are increasing until weaning. Besides, the immune system of the piglet affects phenotypes such as vitality, robustness as well as growth and therefore the overall survivability of the piglet. In summary, there is a lack of knowledge about how the various parts of the immune system influence the genetic potential of the piglet to survive and the ability of the sow to rear her litter.

Piglet survival

Piglet survival can be recorded as survival at farrowing as well as pre-weaning survival at the piglet or sow level (Roehe and Kalm, 2000; Hellbrügge *et al.*, 2008). The individual birth weight or weight traits at the litter level were discussed to be suitable substitution traits. At the piglet level, direct genetic effects can be described as the genetic potential of piglet survival (Roehe *et al.*, 2009). As mentioned above, the genetic capability of the dam to rear piglets is included in the maternal genetic effects (Knol *et al.*, 2002b; Roehe *et al.*, 2009).

Quantitative genetic studies of piglet survival traits (table 2) at the sow or piglet level showed mostly low h^2 and considerable environmental influence (e.g. farm management).

Heritabilities for the individual birth weight are usually marginally higher at the piglet level. Maternal genetic effects are of a similar magnitude as h^2 for piglet survival traits and higher for individual birth weight. Traits like mean birth weight per litter showed moderate h^2.

Genetic correlations between individual survival traits and individual birth weights showed contradictory results. Various studies found negative correlations, indicating that low birth weight is associated with higher numbers of stillborn piglets (e.g. Arango *et al.*, 2006; Roehe *et al.*, 2010). However, Grandinson *et al.* (2002) found a positive r_g. Canario *et al.* (2006) as well as Mulder *et al.* (2015) confirmed the hypothesis that these traits exhibit a quadratic relationship. This indicates that an ideal birth weight exists (Mulder *et al.*, 2015). However, the correlation between pre-weaning survival and individual birth weight was distinctly negative whenever studied (e.g. Arango *et al.*, 2006; Roehe *et al.*, 2010). Therefore, piglets with higher individual birth weights have a higher probability of survival until weaning.

At the sow level, larger litters show higher mortality rates before weaning (Damgaard *et al.*, 2003; Hellbrügge *et al.*, 2008). Unfavourable correlations between the mean within-litter birth weight and litter size were found by Kapell *et al.* (2011). Damgaard *et al.* (2003) and Sell-Kubiak *et al.* (2015b) reported that the within-litter variation of birth weights is under genetic control. However, Sell-Kubiak *et al.* (2015b) stress that this trait should be included into a selection index to limit the decreasing impact on the individual birth weight when the selection focuses on reduced within-litter variance. In rabbits and mice, Blasco *et al.* (2017) and Gutiérrez *et al.* (2006), concluded that although the within-litter trait variation showed low h^2, a genetic foundation exists and consequently selection for a reduced phenotypic variability is possible.

Table 2: *Heritabilities (h^2 ± SEM) for survival traits in pigs (dam lines and crossbreds) (full table in appendix (table S4))*

Parameter	h_t^2	h_d^2	h_m^2	Breed
Number of piglets born alive	0.12 (0.04)[1] 0.08 (0.02)[3] 0.10 (0.03)[4]			Yorkshire[1] Large White[3] Landrace[4]
Number of stillborn piglets	0.19 (0.02)[3] 0.05 (0.03)[4]			Large White[3] Landrace[4]
Proportion of stillborn piglets	0.13 (0.04)[1]			Yorkshire[1]
Stillbirth		0.04[2a]	0.10[2a]	Large White[2]
Individual survival at birth	0.01-0.04[6]	0.00-0.02[6] 0.21[5]	0.04-0.12[6] 0.15[5]	Dam lines[6] Crossbreds[5]
Total pre-weaning mortality		0.03[2b]	0.09[2b]	Large White[2]
Pre-weaning survival		0.24[5]	0.14[5]	Crossbreds[5]
Individual birth weight		0.04[2b] 0.36[5]	0.15[2b] 0.28[5]	Large White[2b] Crossbreds[5]
Mean birth weight	0.39 (0.05)[1]			Yorkshire[1]

h_t^2=total heritability; h_d^2=direct heritability; h_m^2=maternal heritability; [1]Damgaard *et al.* (2003); [2]Arango *et al.* (2006) ([2a]Model 3, [2b]Model 1); [3]Canario *et al.* (2006), [4]Hellbrügge *et al.* (2008); [5]Roehe *et al.* (2010); [6]Kapell *et al.* (2011)

The estimation of direct and maternal genetic effects is difficult, because the quantity and quality of recorded phenotypes is limited. Modelling the litter effect (modelled as the id of the dam and parity) often hampers convergence because there is a considerable drop in observations after first parity caused by selection. Generally, the litter effect represents the same influences for the piglets in a litter (e.g. litter size, uniformity). However, imbalances in parity classes bias the estimations of these effects. The application of cross-fostering complicates the genetic evaluation further, due to the uncertainty whether or not the biological dam or the foster dam actually determines breeding values (Jonas and Rydhmer, 2018).

3.8. Quantitative trait loci, linkage studies and candidate genes

The application of single nucleotide polymorphism (SNP) information in genome-wide association studies (GWAS) give important information on quantitative trait loci (QTL), elucidating the genetic background of the traits of interest (Knol *et al.*, 2016). PigQTLdb (Hu *et al.*, 2016) shows the current state of research of identified QTL. GWAS for domestic animals largely focused on economically important growth and production factors such as fertility, meat quality and susceptibility to specific infections (e.g. Boddicker *et al.*, 2012; Onteru *et al.*, 2012). A search of the recent publications in this field shows that the amount of genomic analyses of immune and robustness traits increased in the last decade (Appendix Table S1).

Immunity

Few publications focusing on immunity deal with haematological traits to unravel the genetic mechanism and architecture of immune traits in swine (e.g. Lu *et al.*, 2011; Ponsuksili *et al.*, 2016) (appendix table S1). Lu *et al.* (2011) found promising QTL regions and candidate genes for T lymphocyte subpopulations, parts of innate immunity and interleukins. Ponsuksili *et al.* (2016) reported 24 overlapping QTL regions resulting from a single-marker and a Bayesian multi-marker approach applied to 12 haematological traits. The authors found potential candidate genes that influence the physiology of cells and the hemopoietic system. Interestingly, Rohrer *et al.* (2014) measured the colostrum intake of 5 312 piglets via the amount of immunocrit in serum and detected 7 QTL for the ability of the piglet to ingest and absorb γ-immunoglobulins. The study revealed promising candidate genes that control appetite and growth. However, no QTL were found associated with the passive transfer of immunity.

The study designs show clear differences in breed and number of animals as well as specific immune challenges limiting the comparability and applicability of the results. Targeted immune stimulation is not always feasible and necessary in order to get a comprehensive overview of the immune system (Hermesch and Luxford, 2018). It is a challenge to determine the genetic architecture of immunocompetence because haematological traits are complex and influenced by multiple genes. This was confirmed by Lu *et al.* (2011) who indicated that the genes controlling traits related to immunity in pigs act in tight linkage and tend to cluster in the same chromosomal regions or the same genes having pleiotropic effects.

Piglet survival

Traits associated with piglet survivability as well as birth weight have rarely been investigated using GWAS approaches, as mainly litter traits were analysed. This may be due to the high effort associated with extensive genotyping as well as the phenotyping of hard to measure traits like stillbirth and birth weight on individual piglet level (Knap, 2014; Knol *et al.*, 2016). GWAS on traits related to piglet survival (appendix table S2) were conducted for e.g. the number of stillborn piglets (e.g. Onteru *et al.*, 2012; Schneider *et al.*, 2012), the number of mummies (Onteru *et al.*, 2012; Schneider *et al.*, 2012), and litter size at day 5 (LS5) (Guo *et al.*, 2016). Schneider *et al.* (2012), and Wang *et al.* (2018) conducted GWAS for the average birth weight, whereas Wang *et al.* (2017) analysed piglet uniformity or birth weight variability. Furthermore, Sell-Kubiak *et al.* (2015a) reported novel QTLs for litter size and its variability in Large White. The results of the mentioned studies above ranged from one to 65 associations comprising breed specific QTLs and revealed overlapping QTLs or SNPs between traits that are associated with candidate genes known to be responsible for reproductive performance (e.g. placental quality) or physical development (e.g. embryonic development). Jonas and Rydhmer (2018) recently published a candidate gene analysis on e.g. the number of stillborn piglets and the average birth weight to analyse whether genes for maternal ability are potential markers to select for increased piglet survival.

The various results for purebred lines (e.g. Jonas and Rydhmer, 2018; Wang *et al.*, 2018) under investigation showed that birth weight on a litter basis seems to be under polygenetic control, whereas various peaks were observed by survival traits. However, Schneider *et al.* (2012) found no QTL for the number of stillborn and the number of mummified, but most putative QTL regions were found for the average birth weights in crossbred pigs. Investigations in dam lines revealed partly overlapping QTL (Guo *et al.*, 2016). Furthermore, results for genetic associations apparently depend on the parity number, indicating temporal gene effects in different parities (Onteru *et al.*, 2012; Wang *et al.*, 2017; Jonas and Rydhmer, 2018). To achieve sufficient statistical power for such poorly heritable traits, large numbers of animals have to be recorded, especially for stillbirth and pre-weaning loss which show low incident rates (Knol *et al.*, 2016).

3.9. Breeding strategies

Pig breeding programs classically apply selection indexes based on estimated breeding values (EBVs) and the marginal economic value of each trait using multivariate BLUP (best linear unbiased prediction) models (Knap, 2014). The use of genotypic information in the form of SNP and applying various statistical methods revolutionized the potential of breeding value information concerning improved reliabilities as well as reduced generation intervals (Knol *et al.*, 2016). The superiority of applying genotypic information into pig breeding programs (genomic BLUP) has also been reported (e.g. Guo *et al.*, 2015).

Selection of robust individuals is important because animal welfare concerns can be reduced, whereas the profitability of pig production is increased. The potential implementation of immune and piglet survival traits in a breeding goal for improved robustness is of particular interest and performance tests for selection candidates have to be conceptualized, accordingly. However, various authors (e.g. Onteru *et al.*, 2012; Schneider *et al.*, 2012; Guo *et al.*, 2016) stress the importance of substantial reference populations to estimate genomic breeding values and the importance of clean phenotyping of the traits of interest.

Breeding for piglet survival was applied in several breeding programs using different approaches in northern Europe. However, most breeding strategies focused on the inclusion of litter traits and not individual piglet survival. In Denmark, for example, the trait LS5 was introduced (Nielsen *et al.*, 2013). Norwegian and Swedish pig breeders included the NBA and the litter weight at week three (Rydhmer, 2005). In the Netherlands, however, it was discussed to tackle this trait complex by including individual piglet survival into the selection index even though it has a low h^2 (Knol *et al.*, 2002b). The advantages of selecting for higher birth weights were regarded critically (Knol *et al.*, 2002b). Roehe *et al.;* Roehe *et al.* (2009; 2010) investigated genetic parameters for survival traits in a crossbreeding experiment under outdoor conditions. Sires were selected according to their direct and maternal genetic effects on postnatal piglet survival and a considerable potential to improve individual piglet survival was found. Sell-Kubiak *et al.* (2015b) reported promising results for selecting for reduced within-litter variation of birth weights using pedigree and genomic information. Although, phenotypes for piglet survival are labour intensive to record, it has to be recognized that these traits have a high value, especially for breeding organizations (Knap, 2014).

Piglets require a well performing innate immune response directly after birth and sufficient colostrum supply is crucial, especially for weak and small piglets directly after birth. The piglet has no energy resources or adaptive immunity after farrowing. Hence, the quality of the dam’s immune system and its influence on the immunity of the respective offspring are of particular interest (Collins, 2014). Especially, the crucial immune reactions for survivability and robustness have to be studied and specified, preferably under different environments. Furthermore, the question if the colostrum quality and production of the sow or the vitality of the piglet is primarily responsible for an increased colostrum intake must be answered. Important traits of the sow like teat number, farrowing behaviour and mothering abilities should be considered in a selection index as well, especially if the focus in the breeding goal lies on litter size (Rydhmer, 2000).

Immunocompetence, characterized by specific immune parameters, has not been included in any selection index or breeding value yet. Selection for health traits is mainly concentrated on conformation scores and/or specific disease resistances (e.g. *Escherichia coli*) (Rydhmer, 2005). As described above, limited studies exist on determining the genetic variability of immune traits and the genomic background of the key players in immunity. It is difficult to determine one or two immune parameters to be reasonable traits for incorporation into a breeding program for improved robustness and survivability.

Challenge studies helped to improve pre-weaning survival in the offspring of boars, which were selected for higher cell-mediated immune response post vaccination (Harper *et al.*, 2018). Mallard *et al.* (1992) selected pigs with high and low immune response to study the performance and immune response of the animals post challenge (e.g. Magnusson *et al.*, 1998; Wilkie and Mallard, 1999). Stear *et al.* (2001) concluded that breeding for a specific immune response does result in higher susceptibility for other diseases.

Promising genetic resistance against the porcine reproductive and respiratory syndrome (PRRS) was reviewed by Reiner (2016) and Dekkers *et al.* (2017). However, Dekkers *et al.* (2017) stress that due to the variability of PRRS a resistance is not feasible, but a reduced susceptibility is. Furthermore, the need for a closer inspection of the complete function of potential candidate genes (e.g. receptors) was emphasized by Reiner (2016). This was confirmed by Popescu *et al.* (2017) who reported that genetically edited pigs lacking the virus receptor CD163 for African swine fever died post virus infection.

In order to characterize and breed for immunocompetence, specific immune responses towards challenges are not suitable as a basis for selection decisions. Otherwise, selection for a specific immune response cannot be calibrated without challenging the pigs immune system (Hermesch, 2014). Hence, what is crucially missing is the identification of traits or trait complexes to breed for improved immunity.

Breeding goals for immunocompetence and health traits changed in their specificity (tolerance, resistance, robustness, and resilience), definitions, context and requirements over the last two decades (Kanis *et al.*, 2004; Hermesch, 2014). Robust pigs should achieve high performance under all possible and even in non-optimised housing conditions and challenge situations (Knap, 2005). Accordingly, Knap (2009) defined sustainable breeding and increasing robustness as selection for animals combining a high production potential with resilience to external stressors (psychological, physical, or microbial). Studies on resilience focused on immunity, performance (Wilkie and Mallard, 1999; Mulder and Rashidi, 2017), animal behaviour (Kanis *et al.*, 2004), and stress reactions on endocrinological levels (e.g. Mormede and Terenina, 2012). In this context, the increased uniformity of livestock as well as G×E interactions (Mulder, 2016) are often discussed with the help of conceptual frameworks (e.g. the thermoregulation model in Kanis *et al.* (2004)) to discuss if the traits of interests can be translated into an applicable breeding goal (Hermesch, 2014).

Nevertheless, breeding for disease resistance can be seen critically. If resistance towards specific pathogens and viruses is established, the question arises whether or not this leads to breeding animals less flexible to different environmental conditions. Guy *et al.* (2012) and Flori *et al.* (2011a) discussed that selection for response to a specific pathogens may result in unpredictable responses to other pathogens. Therefore, Guy *et al.* (2012) recommend a careful evaluation of selection traits and criteria with regards to their consequences, before their incorporation into a breeding program. Mulder *et al.* (2015) described trade-offs between the flexibility of an animal to react to various environmental challenges on the one hand, and a lowered plasticity, resulting in high performance, on the other. This was already shown by a higher prevalence of reproductive and health related problems in livestock under non-optimized production premises (Knap and Su, 2008). Therefore, breeding for tolerance would be more beneficial to increasing robustness if it increases the genetic variability of pigs to react to environmental challenges without harming the limited variability of pig performance accepted by the following actors of the value chain.

Concerning the improvement of piglet survivability, the role of immunocompetence needs to be further investigated. Whether the immune reaction must be high or low to be vital and resilient is not defined yet. It is not clear if an optimized immune response is a substitute for piglet survival or could be included into a selection index for improved survivability. Moreover, the economic value of immunocompetence is intricate to evaluate.

3.10. Conclusion

The use of hyperprolific dam lines successfully increased the NBA in the last decades. However, piglet mortality rates remain constant, decreasing the profitability of piglet production. Furthermore, the growing critical attitude of the consumer resulted in increasing animal welfare concerns. The intensification of animal production included increased hygiene standards and application of antibiotics for disease prevention. Moreover, selection for enhanced productivity resulted in potential trade-offs in robustness especially in challenging environments according to the allocation theory. Consequently, breeding for improved immunocompetence and robustness is a major priority in pig breeding.

The immune system of pigs, survivability and robustness of piglets are intricate trait complexes of increasing priority for successful pig production. Moreover, all three trait complexes are involved with each other. The analysis of immune traits for an evaluation of a generally enhanced immune response is promising to gain improved survivability and robustness. This stresses the need to investigate the relationship between survivability, robustness and immune parameters extensively.

In addition, appropriate immune parameters or networks that favour an improved immunocompetence are neither identified nor evaluated considering their mode and direction of effectiveness. Even current reference values for the characterization of the pig populations are missing. Furthermore, the determination of these trait complexes is expensive and elaborate. Hence, on-farm phenotyping is difficult to realize as a routine. Available quantitative genetic and genomic studies on general immunocompetence in pigs are difficult to compare due to massive differences between study designs. Especially for the selection for genotypes with improved immunocompetence G×E interactions must be considered, because offspring from animals selected in high hygiene environments might not perform as expected in challenging environments. Therefore, fundamental research and characterization of the relationships between the immune parameters, networks causing immunocompetence, robustness, survivability and performance is needed.

Chapter 4. Genetic analyses of piglet survivability and litter traits in Landrace and Large White pigs

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Abstract

Piglet mortality at birth and before weaning has a negative impact on animal welfare and decreases the profitability of piglet production. The aim of this study was to investigate the quantitative genetic parameters of piglet survival and their relationship to birth weight in Landrace (LR) and Large White (LW) pigs. Therefore, individual piglet information (74’543 (LR), 94’280 (LW)) and reproduction performance of sows (2’200 (LR) and 2’442 (LW)) were collected. Variance components were estimated for the binary distributed traits stillbirth (SB), pre-weaning loss (PWL) and the individual birth weight (BW) of piglets using ASReml 4.0. A best model fit was tested for each trait using different appropriate approaches in a series of single-trait and subsequently multi-trait analyses. In addition, heritabilities (h^2) for reproduction performance of dams were investigated for traits which were the number of piglets born alive, number of piglets born dead, pre-weaning mortality, average birth weight within litter and the variance of birth weights per litter. SB and PWL were analysed with a threshold using a generalized linear mixed model (GLMM) and a logit link function in a bivariate animal model with BW, respectively. The h^2 estimated univariately for SB and PWL ranged in the LR breed between 0.014 and 0.019 (SB) and 0.016 and 0.022 (PWL). Corresponding parameters within the LW breed were slightly lower between 0.000 and 0.009 (SB) and 0.009 and 0.013 (PWL). For BW estimates from single-trait analyses were 0.037 (±0.009) and 0.057 (±0.009) for LR and LW, respectively. Maternal genetic correlations (m^2) and litter effects (c^2) were found and comprised a major part of the genetic variation in SB, PWL, and BW of both populations. SB and BW exhibited positive genetic (r_g) (0.221 (±0.300) (LR), 0.000 (±0.000) (LW)) and negative phenotypic (r_p) (-0.204 for LR and -0.215 for LW) correlations. The results for PWL and BW showed a r_g of -0.497 (±0.156) for LR and -0.700 (±0.120) for LW, as well as an r_p of -0.381 (LR) and -0.356 (LW). The positive genetic association between SB and BW shows that heavier piglets have a higher probability to be stillborn in LR. However, low BW piglets show a higher probability to die before weaning. At the litter level an increased number of born piglets was associated with higher numbers of stillbirths and pre-weaning mortality. An increased average birth weight within smaller litters led to lower rates of number born dead in LR and pre-weaning mortality in both populations.

Keywords: piglet mortality, reproduction, mixed models, binary traits

4.1. Introduction

The profitability of piglet production is mainly determined by the number of weaned piglets per sow (Täubert and Henne, 2003; Rutherford *et al.*, 2013). As a consequence, most commercial breeding organizations have focused on the genetic improvement of litter size which led to a substantial increase of the number of piglets born in total (Webb, 1998; Spoetter and Distl, 2006; Rutherford *et al.*, 2013). This trait is defined as the sum of piglets born dead and alive excluding mummies, malformed piglets and piglets that died before expulsion (Rutherford *et al.*, 2013). However, it has been shown in many studies (Rutherford *et al.*, 2013; Edwards and Baxter, 2015) that increasing litter sizes result in lower and more variable birth weights**,** which are directly linked to decreased piglet survival rates (Roehe and Kalm, 2000; Edwards, 2002; Damgaard *et al.*, 2003). Besides direct economic disadvantages for piglet producers**,** increased piglet mortality has a negative impact on animal welfare and public acceptance of pig production (Fix *et al.*, 2010; Prunier *et al.*, 2010).

In most breeding herds, specific causes for piglet losses between birth and weaning are mostly unknown and only rarely registered (Edwards and Baxter, 2015). Moreover, recording of the individual birth weight, which is the most important risk factor for piglet losses (Roehe and Kalm, 2000; e.g. Baxter *et al.*, 2009), is very labor-intensive and rarely implemented in farms.

Piglet mortality is highly influenced by environmental factors. The most important risk factors for neonates are poor placenta quality and difficulties during birth, increasing the number of stillborn piglets. Causes of mortality during the suckling period are mainly crushing and hypothermia. However, weakness or poor piglet vitality pre and post farrowing remain the main reasons for piglet losses (Leenhouwers *et al.*, 1999; Edwards, 2002; Knol *et al.*, 2002b).

From a genetic point of view, piglet mortality at birth and before weaning is influenced by direct as well as maternal genetic effects (Roehe *et al.*, 2010), such as the piglet’s potential to survive (e.g. vitality and resilience) and as the sow’s mothering abilities (e.g. milk yield). The genetic and environmental effects thereby interact in a complex manner (Arango *et al.*, 2006; Su *et al.*, 2008; Roehe *et al.*, 2010; Baxter *et al.*, 2013). As stillbirth (SB), most direct and indirect (individual birth weight (BW)) indicators for piglet mortality traits exhibit low h^2 in a range of 0.02-0.21 and 0.03-0.36, respectively (Arango *et al.*, 2006; Ibanez-Escriche *et al.*, 2009; Roehe *et al.*, 2010; Kapell *et al.*, 2011). However, as postulated by Kapell *et al.* (2011) and Knol *et al.* (2002a), the impact of the low h^2 can be compensated by the large amount of individual piglet information, so that selection for individual piglet survival is promising.

Because of the binary distribution of SB and pre-weaning loss (PWL), variance components of these traits cannot be efficiently estimated by standard linear models with an underlying normal distribution of the traits (Gianola, 1982; Knol *et al.*, 2002a). As a consequence, (e.g. Roehe *et al.*, 2010) suggested to use logistic regression and liability threshold models to analyze these traits. However, these methods are computationally demanding, particularly in bivariate analyses of binary and continuously distributed traits with a distinct number of relevant fixed and random effects.

In light of this, the present study aims to estimate (co)variance components for piglet survival traits, including individual BW in German Landrace (LR) and Large White (LW) pigs. Distinct statistical models were fitted and analysed to cover the best distribution characteristics of all traits and relevant direct (piglet) and indirect (dam) genetic effects best. In addition, the importance of the biological dam (B) and the cross-foster dam (CF) for PWL was analysed and discussed.

4.2. Material and Methods

Data

Data sets were provided by the German breeding organization BHZP GmbH (Bundeshybridzuchtprogramm GmbH). Records of their LR and LW nucleus populations from January 2010 until December 2017 were provided by four nucleus farms. In total, the data of 74,543 LR and 94,280 LW piglets were available and originated from 2,200 LR and 2,442 LW sows. Details on the number of investigated animals are reported in table 3.

The sows were artificially inseminated. Directly after birth, the piglets were registered as stillborn or alive. Stillborn piglets were defined as fully developed but missing any vital signs and without any possibility of revitalization. Based on this definition, the litter traits number of piglets born alive (NBA), number of stillborn piglets (NBD) and number of born piglets (NBT = NBA + NBD) were recorded.

In all herds, each piglet born alive was weighted individually. Additionally, stillborn piglets were weighted consistently in only one farm of each line (farms A and D in table 1). To record the individual BW most accurately for live born and stillborn piglets, the BHZP GmbH developed an automated weighting scale system. Weight information of all piglets born alive was aggregated into the litter based variance of birth weights (VBW) and the mean birth weight (MBW). Piglet survival during the weaning period (PWL) was individually recorded as a binary trait. For each litter pre-weaning mortality (PWM) was recorded as the number of piglets died before weaning.

Immediately after birth, piglets were cross-fostered and corresponding information of the B and CF dam was registered. However, the piglets that were cross-fostered to foster dams of another line were excluded from the analysis.

Animal care within all herds followed the general guidelines outlined in the European animal welfare regulations. All datasets were analysed with R$^{©}$ (R Core Team, 2016) and ASReml 4.0 (Gilmour *et al.*, 2015). The LR and LW datasets were analysed separately and the pedigrees were traced back up to 17 generations.

Table 3: *Structure of datasets analysed*

Trait	**Landrace**		**Large White**	
	$\mathbf{N_{Farm\ A}}$	$\mathbf{N_{Farm\ B}}$	$\mathbf{N_{Farm\ C}}$	$\mathbf{N_{Farm\ D}}$
NBA	60,792	9,581	51,739	39,822
SB with BW	5,207	-	(853) *	2,718
PWL	7,987	903	5,590	4,290
Sows	1,834	366	1,140	1,302
Litters	4,381	246	2,292	2,923

NBA=Number born alive, SB=Stillbirth, PWL=Pre-weaning loss, BW=Individual birth weight, NBT=Number born total, SB=Stillbirth, PWL=Pre-weaning loss, BW=Individual birth weight, *=Due to the missing phenotypes for stillborn piglets and their respective birth weights in farms B and C, analyses of SB were conducted only including farms A and D. Sows and litters analysed included only litters with the respective birth weight records available.

Statistical analysis of individual piglet traits – single-trait analysis

SB, PWL and BW were analysed testing different univariate models. The analysis of BW based on a normal distribution. SB and PWL were investigated using a logit link function. Thereby, the continuous liability to the binary observations of SB and PWL is linked through a threshold, which is crossed if the trait is expressed (Falconer and Mackay, 1996). According to Gilmour et al. (2015) the residual variance on the underlying scale was fixed to $\pi^2/_3 \sim 3.29$ in all SB and PWL (co)variance analyses. The results for the variance components for SB and PWL are given on the underlying liability scale. The general structure of the applied models is given in the following equation 1:

$$\mathrm{y} = \mathrm{X}\beta + \mathrm{Za} + \mathrm{Zm} + \mathrm{Zc} + \mathrm{e}, \quad (1)$$

where y contains the underlying continuous variable for SB and PWL or the observed phenotypic observations of BW for each piglet. The vector β includes the fixed effects parity (1-5, >5), sex (♂,♀,unknown) and (herd-)year-season in LR (HYS: 1-226) and LW (HYS: 1-333).

It is well known, that BW has an important influence on SB and PWL (Roehe and Kalm, 2000). In order to determine the importance of BW as an environmental effect, the genetic variances of PWL and SB were analysed including and excluding BW as fixed covariate in the model, respectively. All analyses were carried out within line. In addition, as has been shown in table 3, BW of stillborn piglets are only recorded consistently in one herd within the LR (farm A) or LW (farm D) population. Because of this limitation all univariate as well as multivariate analysis within the LR or LW population which include SB as dependent trait are based on the data of farm A or D only.

All models comprised following random effects: additive genetic (a), m^2 and c^2 effects. The vector e contains the residual effects. X and Z are the incidence matrices linking the fixed and random effects with the observations in y.

The (co)variance structure presumed was as follows:

$$V\begin{bmatrix} a \\ m \\ c \\ e \end{bmatrix} = \begin{bmatrix} A_a \otimes \sigma_a^2 & A_{am} \otimes G_{am} & 0 & 0 \\ A_{ma} \otimes G_{ma} & A_m \otimes \sigma_m^2 & 0 & 0 \\ 0 & 0 & I \otimes C & 0 \\ 0 & 0 & 0 & I \otimes R \end{bmatrix} \quad (2)$$

Where A is the numerator relationship matrix of the piglets (A_a), their respective dams (A_m), or of the piglets and their respective dams (A_{ma}, A_{am}). The additive genetic and maternal genetic variances are σ_a^2 and σ_m^2. G is the (co)variance matrix of the random additive genetic (a) and maternal genetic (m) effects, which allows the estimation of the genetic correlations between the maternal and the additive genetic effect (r_{AM}). The random common environment effects litter (c) and residual (e) were assumed to be independently distributed with the (co)variance structures $I \otimes C$ and $I \otimes R$. Litter effects were defined by a concatenation of dam and parity information. For SB and BW, the biological dam and the biological litter were appropriate to model the litter effect.

For PWL m^2 and c^2 can be defined as the effect of the B or CF dam, which is different in case of cross-fostering. Theoretically, both effects can be modeled, but due to the low proportion of cross-fostered piglets a clear separation of both effects is not possible. In order to obtain at least some information of the consequences, alternative models with the different litter effect definitions were applied and the results were compared.

In order to identify the best fitting model, likelihood-ratio test statistics (LRT) were used to test log-likelihood differences between the complete model and models, which were reduced by one random effect. Although the logit models reflect the binary distribution of SB and PWL best, this LRT approach cannot be used. Hence, the likelihoods of the standard normal models were used to find the most appropriate model for all traits.

Multi-trait analysis of individual piglet traits

Variances and covariances of the piglet based traits SB and BW as well as PWL and BW were estimated simultaneously by a bivariate generalized linear mixed model (GLMM). This model contains a liability threshold submodel for the binary traits SB or PWL and a standard linear submodel for BW. The general structure of the models followed equation 1. For PWL, the B dam and CF litter were considered as random effects based on the results of the single-trait analysis. For PWL and SB, BW was not modeled as a covariate. As mentioned above, the multi-trait analysis of SB and BW was conducted only for one farm due to missing BW records for piglets born dead. For the bivariate analysis of PWL and BW, the litter effect of the CF dam and the B litter were considered, respectively. The (co)variance structure presumed was as follows:

$$V\begin{bmatrix} a \\ m \\ c \\ e \end{bmatrix} = \begin{bmatrix} A_a \otimes G_a & 0 & 0 & 0 \\ 0 & A_m \otimes G_m & 0 & 0 \\ 0 & 0 & I \otimes C & 0 \\ 0 & 0 & 0 & I \otimes R \end{bmatrix} \quad (3)$$

where A is the numerator relationship matrix and G is the (co)variance matrix of the random additive genetic (a) and maternal (m) effects. The random environmental effects litter (c) and residual (e) were assumed to be independently distributed with a (co)variance structures $I \otimes C$ and $I \otimes R$. Because of the different litter effect definition of PWL (CF dam) and SB or BW

(B dam) the covariance component in C was set to 0. The r_{AM} correlations were not estimated in the bivariate models due to their missing significances for the univariate models.

Statistical analysis of litter based reproduction traits

(Co)variance components for the litter based traits NBT, NBA, NBD, PWM, MBW and VBW were analysed using first a single-trait analysis and subsequently a series of multi-trait analyses with the following underlying linear model (equation 4):

$$\mathrm{y} = \mathrm{X}\beta + \mathrm{Za} + \mathrm{Zpe} + \mathrm{e}\ , \quad (4)$$

where y contains the observations for the traits named above for each litter of a sow. The vector β includes the fixed effects parity (1-5, >5) and HYS (1-132 (LR), 1-121 (LW)). In addition the fixed covariates age at first conception or days between conceptions were considered as nested effects in the submodels for first or later parities, respectively. As (co)variance structure for the random effects genetic (a), permanent environment of the sow (pe) and residual (e) was modeled. The following co(variance) structure was assumed:

$$V\begin{bmatrix} a \\ pe \\ e \end{bmatrix} = \begin{bmatrix} A_a \otimes G_a & 0 & 0 \\ 0 & I \otimes PE & 0 \\ 0 & 0 & I \otimes R \end{bmatrix} \quad (5)$$

The A_a, G_a and I, PE and R matrices are designed as described above. Significance of the random environmental effects (pe^2) were tested via LRT based on previously conducted single-trait analyses. VBW and MBW include the aggregated birth weights of piglets born alive and therefore only sows were included in the analyses where the respective BW were available. Significance of the estimated genetic correlations (r_g) was determined by the extent of the respective standard error (SE).

4.3. Results

The descriptive statistics of phenotypic measurements of the investigated pigs is given in tables 4 and 5. The proportion of stillborn piglets was 7.8 % in the LR and 6.4 % in the LW population. However, stillborn piglets were weighted consistently only in farms A (LR) and D

(LW). Pre-weaning losses had a prevalence of 13.1 % in LR and of 10.9 % in LW. Levels of cross-fostering (including non-nucleus dams) were 31 % and 6 % in the LR and 8 % and 23 % in the LW population. The mean BW was higher in LR (1.33 kg) compared to the LW population (1.28 kg).

Table 4: *Descriptive statistics of the traits analysed (individual piglet traits)*

Trait	**Landrace**		**Large White**	
	Frequency		**Frequency**	
SB* (%)	7.8		6.4	
PWL (%)	13.1		10.9	
	Mean	**SD**	**Mean**	**SD**
BW (kg)	1.33	0.37	1.28	0.35

SB=Stillbirth, PWL=Pre-weaning loss, BW=Individual birth weight (the mean includes the birth weights of complete litters including stillborn piglets), *=Due to the missing phenotypes and birth weights of stillborn piglets in farms B and C, analyses of SB were conducted only including farms A and D.

Table 5: *Descriptive statistics of the traits of the sows analysed*

Trait	**Landrace**		**Large White**	
	Mean	**SD**	**Mean**	**SD**
NBT	15.03	3.51	15.02	3.73
NBA	13.91	3.23	14.35	3.50
NBD	1.13	1.55	0.67	1.15
PWM	1.75	1.83	1.48	1.79
VBW (kg)*	0.28	0.08	0.27	0.08
MBW (kg)*	1.38	0.25	1.32	0.23

NBT=Number of piglets born total per litter, NBA=Number of piglets born alive per litter, NBD=Number piglets born dead per litter, PWM=Pre-weaning mortality per litter, MBW=Medium birth weight within litter, VBW=Variance of birth weights within litter. *VBW and MBW are the aggregated birth weights of piglets born alive per litter.

Table 5 contains the descriptive statistics for all litter traits investigated here. The average NBT was similar in both populations (15.03 (±3.51) (LR), 15.02 (±3.73) (LW)). The NBA was somewhat lower in LW (13.91 (±3.23)) compared to LR (14.35 (±3.50)) population. In LR, the NBD and PWM were on average higher (NBD 1.13 (±1.55), PWM 1.75 (±1.83)) than in LW (NBD 0.67 (±1.15), PWM 1.48 (±1.79)). However, the mean values of VBW were at a comparable level in both populations. The MBW per litter was also higher in LR compared to LW.

Variance components for piglet survival traits

Table 6 presents the results of the variance components as well as the r_{AM} for the survival traits and BW obtained by the single-trait analyses. As has been described in the material and methods part, different definition of the maternal and common environmental litter effects can be used. However, the estimated parameter of these alternative model definitions were very similar. Therefore, table 6 contains only the parameter estimates of models including maternal and litter effects of the B dams, except for PWL, where c^2 are defined on basis of the CF dam. For SB, low h^2 of 0.014 to 0.019 were estimated for LR, whereas for LW, h^2 was close to zero. For PWL, the estimated h^2 were lower for LW (0.009 - 0.015) compared to those for LR (0.016 - 0.027). For both traits, the BW modeled as covariate increased the genetic variance (σ_a^2) and h^2, especially for LW. For PWL, h^2 were higher when the litter effect was modeled as the litter of the foster dam. Similar observations were made when the genetic effect of the CF dam was modeled. In both populations, low h^2 were observed with 0.037 (±0.009) for LW and 0.057 (±0.009) for LR.

Maternal genetic effects (m^2) for SB and PWL ranged from 0.020 to 0.077 and were a little higher for LR compared to LW. Stronger m^2 effects were observed for BW which reached 0.191 (±0.009) in the LR and was marginally lower than for the LW (0.175 (±0.009)) population.

The c^2 revealed the highest variance ratio for SB and PWL with 0.059 up to 0.125. The highest c^2-values were found in LR for SB as well as for the CF-dam/CF-litter model for PWL. These estimates are indicators of the relatively high environmental influence of the litter environment (e.g. litter size) on piglet survival traits. Estimates for c^2-effects for BW were lower than the corresponding m^2-effects (0.128 and 0.132 for LR and LW, respectively). However, it should be mentioned that the separation of m^2 and c^2-effects is problematic, because the datasets comprise many sows (605 (LR), 897 (LW)) with only one litter. The r_{AM} were widely ranging for the two lines when performing the single-trait analyses (-0.444 to 0.044 for LR and -0.603 to 0.205 for LW). The correlations between the additive and the maternal genetic effect were not significant using LRT on a linear model basis for testing). Hence, there are no clear indicators that m^2 of these traits would be negatively influenced by a direct selection on piglet survival or BW. Therefore, the r_{AM} was not modeled in the bivariate models. In addition, the models containing r_{AM} showed convergence problems.

In table 7, the results of the bivariate analyses considering the binary expression of SB and PWL are presented. SB and BW exhibited a positive genetic (r_g) (0.221 (±0.0300) for LR) and negative phenotypic correlations (r_p) (-0.204 for LR and -0.215 for LW). In LW, no r_g was estimable due to the missing direct genetic variance for SB. However, PWL showed a clear antagonistic relationship to BW with a genetic r_g of -0.497 (±0.156) (LR) and -0.700 (±0.120) (LW). Phenotypic correlations were -0.381 and -0.356 for LR and LW, respectively. These relationships indicate that higher BW increases the probability for the piglet to be stillborn. However, if the piglet is born alive, the odds to survive until weaning are increased by a higher BW.

Table 6: *Estimated variance components for piglet traits - Univariate models*

Breed	BW (y/n)	Dam	Litter	σ_p^2	h^2±SE	m^2±SE 1)	c^2±SE 2)	r_{AM}±SE 3)
SB								
LR	yes	B	B	4.097 (±0.049)	0.019 (±0.009)	0.074 (±0.001)	0.104 (±0.009)	0.044 (±0.264)
	no	B	B	3.980 (±0.041)	0.014 (±0.008)	0.043 (±0.008)	0.116 (±0.009)	-0.293 (±0.253)
LW	yes	B	B	3.912 (±0.056)	0.009 (±0.009)	0.059 (±0.010)	0.108 (±0.011)	-0.383 (±0.278)
	no	B	B	3.795 (±0.043)	0.000 (±0.000)	0.042 (±0.010)	0.091 (±0.097)	-0.603 (±0.669)
PWL								
LR	yes	CF	CF	3.893 (±0.036)	0.027 (±0.007)	0.046 (±0.007)	0.082 (±0.007)	-0.218 (±0.156)
		B	CF	3.861 (±0.033)	0.022 (±0.006)	0.041 (±0.006)	0.085 (±0.006)	-0.325 (±0.141)
		B	B	3.753 (±0.031)	0.023 (±0.007)	0.042 (±0.007)	0.057 (±0.006)	-0.289 (±0.155)
LW	yes	CF	CF	3.921 (±0.032)	0.015 (±0.006)	0.042 (±0.007)	0.100 (±0.007)	0.091 (±0.199)
		B	CF	4.002 (±0.036)	0.011 (±0.005)	0.077 (±0.008)	0.090 (±0.006)	0.103 (±0.176)
		B	B	3.927 (±0.033)	0.009 (±0.005)	0.062 (±0.008)	0.091 (±0.007)	0.205 (±0.213)
LR	no	CF	CF	4.011 (±0.034)	0.016 (±0.006)	0.039 (±0.006)	0.125 (±0.007)	-0.123 (±0.209)
		B	CF	3.802 (±0.028)	0.018 (±0.005)	0.020 (±0.004)	0.097 (±0.005)	-0.444 (±0.150)
		B	B	3.674 (±0.026)	0.020 (±0.006)	0.026 (±0.005)	0.059 (±0.006)	-0.431 (±0.160)
LW	no	CF	CF	3.776 (±0.028)	0.013 (±0.005)	0.020 (±0.005)	0.119 (±0.006)	-0.422 (±0.194)
		B	CF	3.851 (±0.028)	0.013 (±0.005)	0.038 (±0.005)	0.095 (±0.005)	-0.055 (±0.206)
		B	B	3.780 (±0.026)	0.012 (±0.005)	0.031 (±0.005)	0.087 (±0.006)	-0.083 (±0.243)
BW								
LR	no	B	B	0.132 (±0.001)	0.037 (±0.009)	0.191 (±0.009)	0.128 (±0.005)	-0.280 (±0.113)
LW	no	B	B	0.127 (±0.001)	0.057 (±0.009)	0.175 (±0.009)	0.132 (±0.004)	-0.232 (±0.010)

BW=Individual birth weight, PWL=Pre-weaning loss, SB=Stillbirth, σ_p^2=Total phenotypic variance, h^2=Heritability, m^2=Maternal genetic effects, c^2=Common environment effects. CF=Cross-foster dam/litter, B=Biological dam/litter. LRT significance test: LogL complete model (CM) vs. LogL-reduced model=CM minus factor: 1) CM vs. CM-dam and r_{AM}, 2) CM vs. CM-litter, 3) CM vs CM-r_{AM}. m^2 and c^2 effects were significant in all models tested and r_{AM} not significant in all CM models tested. *P< 0.05. Results for SB and BW are given for farms A and C due to missing phenotypes and birth weights for stillborn piglets in farms B and D.

Table 7: *Estimated (co)variance components for individual piglet traits – Bivariate models*

Landrace				Correlations with BW	
Trait	h^2	m^2	c^2	r_g	r_p
5SB	0.015(±0.008)	0.045(±0.008)	0.120(±0.009)	0.221(±0.300)	-0.204
BW	0.026(±0.007)	0.200(±0.010)	0.123(±0.005)		
PWL	0.022(±0.006)	-0.002(±0.001)	0.074(±0.005)	-0.497(±0.156)	-0.381
BW	0.024(±0.007)	0.240(±0.010)	0.128(±0.006)		
Large White					
SB	0.000(±0.000)	0.042(±0.008)	0.095(±0.009)	n.e.	-0.215
BW	0.038(±0.005)	0.092(±0.010)	0.151(±0.005)		
PWL	0.019(±0.004)	-0.003(±0.001)	0.081(±0.005)	-0.700(±0.120)	-0.356
BW	0.036(±0.006)	0.223(±0.009)	0.138(±0.005)		

BW= Individual birth weight, PWL= Pre-weaning loss, SB = Stillbirth, h^2=Heritability, m^2=Maternal genetic effects, c^2=Common environment effects (biological litter in SB and BW and foster litter in PWL), r_g=Genetic correlation, r_p=Phenotypic correlation. Results for SB and BW are given for farms A and C due to missing phenotypes and birth weights for stillborn piglets in farms B and D. n.e.=not estimable. Results for SB and PWL are presented on the underlying liability scale.

(Co)variance components reproduction traits

The h^2 for reproduction and litter related traits (table 8) were in a low range of 0.035 to 0.168 for both populations except for the MBW with 0.443 (±0.035) and 0.381 (±0.034) for LR and LW, respectively. In LW, all h^2 estimates were slightly lower compared to those estimated for LR. The pe^2-effects for the reproduction traits ranged for LR between 0.008 (±0.021) for VBW and 0.096 (±0.025) for NBA. In LW, the pe^2 ranged in a comparable magnitude. Permanent environment effects were estimated for both breeds. Table 9 presents the r_g and r_p estimates using a multivariate model. As expected, a strong r_g was expressed for LR and LW for the traits NBT and NBA (0.965 (±0.014) in LR and 0.986 (±0.006) in LW). Generally, the r_g of NBT to NBD and PWM was unfavorably high, ranging from 0.249 to 0.641 for both breeds. The corresponding r_g between NBA and NBD or PWM were in the same direction, but slightly less distinct in a range of 0.223 to 0.444. However, these results indicate that breeding for more piglets will automatically increase the number of stillbirths as well as PWM in a substantial manner. In addition, for LR litter size (NBA, NBT) had a negative genetic impact on the MBW of the same magnitude (r_g: -0.289) in comparison to the LW breed (r_g: -0.241 (NBT) and -0.231 (NBA)).

Table 8: *Variance components for the reproduction traits in Landrace and Large White*

Breed	Trait	σ_p^2	h^2±SE	pe^2±SE
LR	NBT	11.483(±0.276)	0.151(±0.028)	0.084(±0.026)
	NBA	10.097(±0.236)	0.128(±0.026)	0.096(±0.025)
	NBD	2.256(±0.049)	0.082(±0.034)	0.061(±0.021)
	PWM	3.103(±0.068)	0.072(±0.020)	0.077(±0.022)
	VBW	0.006(±0.001)	0.169(±0.024)	0.008(±0.021)
	MBW	0.051(±0.001)	0.443(±0.035)	0.069(±0.027)
LW	NBT	12.758(±0.283)	0.137(±0.026)	0.069(±0.024)
	NBA	11.706(±0.255)	0.124(±0.024)	0.052(±0.024)
	NBD	1.152(±0.023)	0.104(±0.047)	0.051(±0.019)
	PWM	3.029(±0.061)	0.035(±0.014)	0.042(±0.021)
	VBW	0.006(±0.001)	0.107(±0.021)	0.042(±0.021)
	MBW	0.051(±0.001)	0.381(±0.034)	0.089(±0.027)

NBA=Number of piglets born alive per litter, NBD=Number of piglets born dead per litter, PWM=Pre-weaning mortality per litter, VBW=variance of birth weight within litter, MBW=Mean birth weight within litter. σ_p^2=Total phenotypic variance, h^2=Heritability, pe^2=permanent environment effects of the sows. VBW and MBW do only include the birth weights of piglets born alive.

The estimated r_g between NBT or NBA and VBW were considerably different between LR and LW. While the correlations were higher (r_g: 0.327/0.351) for the LW breed, the r_g estimates for LR were 0.195 and 0.243. Furthermore, the strong genetic relationships between PWM and MBW for LR (r_g: -0.650(±0.095)) and LW (r_g: -0.488 (±0.137)) indicates the clear antagonistic impact of MBW on piglet mortality in both breeds. Additionally, the r_g showed a lower impact of lower MBW on the NBD (r_g: -0.155 (±0.122) for LR and LW. The r_g between NBD and VBW showed a higher r_g for LR (r_g: 0.272 (±0.148) compared to LW (r_g: 0.043 (±0.181). However, both indicate a low negative effect of varying birth weights within litter on NBD. The relationship between PWL and VBW showed diverse results. For the LR breed, a negative correlation was observed (r_g: -0.135 (±0.152)), whereas for the LW population this relationship was positive but negligible (0.067 (±0.202)). Furthermore, the genetic relationship between NBD and PWM was expressed substantially higher for LW (r_g: 0.562 (±0.222)), compared to the results for the LR breed (r_g: 0.211 (±0.193).

Table 9: *Genetic and phenotypic correlations for the reproduction traits in Landrace (1st line) and Large White (2nd line)*

Trait	NBT	NBA	NBD	PWM	VBW	MBW	Breed
NBT	-	0.965(±0.014)*	0.641(±0.121)*	0.249(±0.151)	0.243(±0.116)	-0.289(±0.087)*	LR
	-	0.986(±0.006)*	0.557(±0.144)*	0.507(±0.171)*	0.327(±0.131)	-0.241(±0.096)*	LW
NBA	0.897	-	0.419(±0.173)*	0.223(±0.163)	0.195(±0.125)	-0.289(±0.094)*	LR
	0.954	-	0.411(±0.175)*	0.444(±0.184)*	0.351(±0.133)	-0.231(±0.099)*	LW
NBD	0.358	-0.091	-	0.211(±0.193)	0.272(±0.148)	-0.155(±0.122)	LR
	0.287	-0.014	-	0.562(±0.222)*	0.043(±0.181)	-0.166(±0.136)	LW
PWM	0.334	0.175	0.129	-	-0.135(±0.152)	-0.650(±0.095)*	LR
	0.254	0.142	0.123	-	0.067(±0.202)	-0.488(±0.137)*	LW
VBW	0.151	0.156	0.010	0.121	-	0.412(±0.085)*	LR
	0.238	0.240	0.026	0.161	-	0.402(±0.107)*	LW
MBW	-0.500	-0.452	-0.171	-0.385	0.016	-	LR
	-0.510	-0.480	-0.167	-0.289	-0.128	-	LW

r_p (=Phenotypic correlation) under the diagonal, r_g (=Genetic correlation) above the diagonal, NBA=Number of piglets born alive per litter, NBD=Number of piglets born dead per litter, PWM=Pre-weaning mortality per litter, VBW=variance of birth weight within litter, MBW=Mean birth weight within litter. $^*P< 0.05$. The significance was determined using the height of the SE of the respective r_g.

4.4. Discussion

The observed phenotypes

All data analysed here, originated from two intensively managed nucleus populations kept on four farms of the breeding company BHZP GmbH. Datasets were recorded by specialized technicians and adequate recording equipment so that the available datasets provide detailed and accurate information about all common reproduction traits including the binary traits SB and PWL as well as individual BW of all born piglets (NBA and SB (only in farms A and D)). It has been stated by Arango *et al.* (2006) and Knol *et al.* (2002b), that analyses of binomial distributed traits require large datasets and benefit from a high level of accurate recording. All pigs investigated in this study were housed under nucleus breeding farm conditions. These farms provided high levels of supervision on their animals, especially around birth. The observed rates of SB and PWL here are at a comparable level as described in literature, where Ibanez-Escriche *et al.* (2009) reported similar rates of losses in LR (9.9 %) and LW (14.3 %). This result is remarkable, because the mean values for NBT in LR (15.03) and in LW (15.02) are higher in the present study compared to the results of Ibanez-Escriche *et al.* (2009) with 13.29 and 11.58 piglets in both breeds. One major reason for the differences in mortality rates between both studies could be attributed to the genetic and environmental variability between the populations investigated or the different recording schemes for stillborn piglets and those died in the first hours after birth (Ibanez-Escriche *et al.*, 2009).

In the analysed LR and LW populations, average BWs differ up to 6 g, which is in accordance with the study of Kapell *et al.* (2011), where average BWs of different dam lines range from 1.39 to 1.45 kg. However, for LW the average BWs (1.28kg) were lower in comparison to results of previous studies. For example, Arango *et al.* (2006) and Roehe and Kalm (2000) reported average BWs of about 1.40 kg in a LW population. Similar to PWL, it can be assumed that the differences in the average BWs of specific breeds are caused by selection processes within the breeding programs influenced by changing breeding objectives.

Significance testing of binary models based on the log-likelihood in ASReml

The selection of the best fitting model for the traits under investigation was conducted using a LRT. To our knowledge, applying ASReml, which uses the penalized quasi-likelihood (PQL), a comparison of log-likelihoods, based on a logistic regression while analysing a binary trait, is not feasible (Gilmour *et al.,* 2015; Mulder *et al.,* 2015). We therefore conducted the LRT based on the not logistically transformed traits and chose the model to be significant if the distance between the different models exceeded three. Significance tests analysing genetic correlations at a continuous level were not possible, because the bivariate analysis, SB or PWL being defined as continuous traits, did not converge. However, due to the use of these approximated values and the low stringency about the performance of PQL, significances have to be considered carefully when it comes to hypothesis testing for binary traits.

4.4.1 Heritabilities of piglet survival traits and individual birth weight

Stillbirth and PWL

The h^2 estimates for SB found in literature (Arango *et al.*, 2006; Ibanez-Escriche *et al.*, 2009; Roehe *et al.*, 2010) spanned a high range from 0.02 to 0.21. This variation was not found in the present study applying single-trait and multi-trait analyses (0.014 to 0.019 in LR and 0.00 to 0.009 in LW).

Similar to our approach, all h^2 were estimated on the liability scale. Arango *et al.* (2006) applied a threshold-linear model using a Markov Chain Monte Carlo (MCMC) algorithm. These authors have found direct and maternal h^2 of 0.04 and 0.14, respectively. In comparison to our results, the direct h^2 and m^2 effects in this study are substantially higher. Arango *et al.* (2006) have not included the random litter effect in the statistical model, which might serve as an explanation for the higher m^2 estimates. Roehe *et al.* (2010) have reported higher h^2 of 0.21 for SB in crossbred piglets born and weaned under outdoor conditions. These authors applied a multivariate linear-threshold model using a Bayesian approach. The m^2-effects were higher (0.15) compared to the present study, although additionally c^2-effects (0.13) were considered here. These litter effects will presumably withdraw considerable variance from the maternal genetic variance resulting in lower m^2-effects. Ibanez-Escriche *et al.* (2009) have found higher h^2 for piglet survival at birth for a LR population (0.08 (±0.02)) and lower estimates for a LW population (0.02 (±0.01)). Based on these results, the authors recommended to align a selection strategy for SB to the respective populations (Ibanez-Escriche *et al.*, 2009). Hence, Ibanez-Escriche *et al.* (2009) have concluded that in LR and Piétrain populations, farrowing survival is a trait of the piglet, whereas in LW farrowing survival should be seen as a trait of the sow. Maternal genetic and c^2-effects within the LR and LW ranging from 0.02 to 0.05 and 0.06 to 0.11, respectively, which corresponds to our results. The missing genetic variance for SB in the LW population appears to be caused by the high effect of the litter. Reasons for the low h^2 of SB is according to Ibanez-Escriche *et al.* (2009) is the high prolificacy of maternal lines.

In the present study, low h^2 were observed for the single-trait analyses of PWL ranging from 0.016 to 0.027 for LR and 0.009 to 0.013 for LW. Similar observations have been made by Knol *et al.* (2002a), who reported h^2 for pre-weaning survival of 0.02 (±0.01) for dam lines. Roehe and Kalm (2000) have found a h^2 for pre-weaning mortality of 0.018 (±0.028) on the underlying liability scale applying a sire model for crossbred piglets under the condition of an experimental testing station. Maternal genetic effects (0.077 (±0.038)) on the logit scale were similar (Roehe and Kalm, 2000) compared to the results of the present study, where m^2-effects of 0.020 up to 0.077 were estimated for LR and LW. The estimated c^2-effects with 0.059 to 0.119 were in the same range as reported by Roehe and Kalm (2000), who found c^2 of 0.119 (±0.43).

In comparison to our analyses and the above mentioned studies of Knol *et al.* (2002a) and Roehe and Kalm (2000), PWL analysed by Arango *et al.* (2006) and Su *et al.* (2008) covered different parts of the suckling period. Arango *et al.* (2006) have observed h^2 for early pre-weaning mortality (until day 5 after birth) of 0.05 (±0.02) and maternal genetic effects of 0.08 (±0.01) for LW. In the study of Su *et al.* (2008), piglet survival has been analysed following the national Danish pig breeding program, where the traits were defined as follows: (1) survival from birth to day 5 and (2) from day five until weaning. The data sets of a Danish Landrace and a Danish Yorkshire population have been analysed using a liability threshold model and a Bayesian approach. h^2 of 0.056 (±0.010) for survival up to day five and of 0.027 (±0.011) for survival until weaning have been reported for the Danish Landrace. In the Danish Yorkshire, the estimates were slightly lower with 0.030 (±0.009) and 0.025 (±0.011) for survival to day 5 and from day 5 until weaning, respectively (Su et al. 2008).

Piglet mortality at farrowing and until weaning is highly influenced by maternal genetic as well as environmental factors. Under the condition of cross-fostering, these effects are difficult to consider in the statistical model. The m^2-effect of the biological dam affects the piglets during pregnancy due to uterine effects and the influence during the expulsion phase during farrowing Knol *et al.* (2002b). Nurse dams affects the piglet before weaning with their mothering ability based on milk quality and quantity as well as behavioral characteristics (Knol *et al.*, 2002b; Rydhmer *et al.*, 2008). However, Su *et al.* (2007) have shown that the nursing sow has only a small effect on the piglet during the first days after birth, which are crucial, since the highest colostrum doses are taken by piglets in this period from the biological dam. The rates of cross-fostering in the present study (6-31 % (LR); 8-23 % (LW)) are higher in farms A and D compared to the levels described in the studies of Knol *et al.* (2002a), Arango *et al.* (2006) and Roehe *et al.* (2010). Cross-fostering ranging from 4.9 % to 18 % in different dam lines were classified as low rates by all authors. Knol *et al.* (2002a) evaluated the thresholds for the number of foster dams per population and reported proportions about 10 to 15 % to be significant. Lower amounts of cross-fostering make a precise fractionation and distinction of the maternal and cross-fostering dam effects as well as the respective litter effects for PWL difficult (Knol *et al.*, 2002a). Arango *et al.* (2006) have also described the difficulties in separating these random effects. These authors have also postulated that for assessing PWM, using the nursing litter seems to be more appropriate.

Based on this suggestion, we have tested here the effect of cross-fostering on PWL by comparing the effect of the biological or CF dam as the maternal (m^2) and/or litter effect (c^2) results of two alternative models. The LRT statistic (tested on a linear scale) of the m^2 and c^2-effects in the model showed that the CF dam and the respective litter affect PWL significantly ($P<0.05$). The results of these analyses only showed marginal differences in variance ratios for h^2, m^2 and c^2-effects (table 6). From this, we conclude that even if the CF litter effect shows the best model fit, it does not have a substantial influence on the results of the estimated variance components. However, an impeccable bivariate analysis of PWL and BW would not be possible due to the differentially analysed maternal genetic component which would be based on separated pedigree information.

In the present study, the binary character of SB and PWL was investigated with a liability threshold model. Several previous studies have analysed piglet survival as a continuous trait (Högberg and Rydhmer, 2000; Grandinson *et al.*, 2002; Knol *et al.*, 2002a; Knol *et al.*, 2002b) where maternal genetic effects were not modeled (Roehe and Kalm, 2000; Grandinson *et al.*, 2002). According to Knol *et al.* (2002b) and Roehe *et al.* (2010), it is important to take the binary character of SB and PWL into account to have a more precise analysis, even though the additive genetic variance will remain the same. Linear models tend to underestimate the heritability of binary traits, especially for low frequencies in one of the two categories (Knol *et al.*, 2002b; Roehe *et al.*, 2010). This was not observed consistently in the present study while finding an appropriate model for variance component estimation. The results ranged in general in a similar parameter space. Other studies have applied Bayesian and MCMC based methods to analyze mortality traits as a binary trait on the liability scale (Arango *et al.*, 2006; Ibanez-Escriche *et al.*, 2009).

The traits SB and PWL were not analysed within a bivariate analysis here. It is known from previous studies that both traits should be analysed separately (Knol *et al.*, 2002b; Roehe *et al.*, 2010) due to strong negative r_{AM} correlations. Furthermore, this fact stresses that the maternal genetic effects should be included in a model to analyze these traits (Arango *et al.*, 2006; Ibanez-Escriche *et al.*, 2009). In most of the previous studies, it has been shown that direct-maternal-models fit best (Arango *et al.*, 2006; Su *et al.*, 2008; Roehe *et al.*, 2010). Arango *et al.* (2006) analysed SB and PWL with a bivariate model and found a r_g of 0.45 (±0.02) for LW. This result can also be found in this study with a r_g between NBD and PWM at sow level for LW (r_g: 0.562 (±0.222)). The proportion of environmental variance was at the same level as reported by Roehe *et al.* (2010) and Su *et al.* (2008). Roehe *et al.* (2010) concluded that associations of a common environment among traits can be found at the individual piglet level rather than at the litter level. In accordance with the studies of Ibanez-Escriche *et al.* (2009) and Roehe *et al.* (2010), the c^2-effect was fitted as the identity matrix of the dam with the corresponding parity. Analysing the LW population, the additive genetic variance was taken in by the c^2.

Individual BW

For individual BW, heritability estimates (single-trait analysis) were 0.037 (±0.009) for LR and 0.057 (±0.009) for LW. These results are low but in accordance with earlier studies, where h^2 did not exceed 0.10 (Roehe and Kalm, 2000; Knol *et al.*, 2002b; Arango *et al.*, 2006; Rosendo *et al.*, 2007). Higher h^2 have been estimated in LW by Kerr and Cameron (1995) of 0.16 (±0.02), by Roehe *et al.* (2010) of up to 0.36 (±0.31 to 0.41) for crossbred piglets and by Kapell *et al.* (2011) up to 0.19 (±0.09 to 0.30) in dam lines. According to Fix (2010), the h^2 for BW in populations kept under conventional conditions is low and therefore breeding via a direct selection for birth weight is expected to be difficult. Maternal h^2 for BW of the present study were in accordance with previous studies (Roehe and Kalm, 2000; Knol *et al.*, 2002a;

Arango *et al.*, 2006). Common environment effects were in the same range (0.13 (±0.01)) for both populations and with the study of (Roehe *et al.*, 2010) (0.15).

Correlations between additive genetic and maternal genetic effects

The r_{AM} were widely ranging for the two lines while performing single-trait analyses (-0.444 to 0.044 for LR and -0.603 to 0.205 for LW). Positive r_g were estimated for SB in LR as well as for PWL in LW when BW was considered, respectively. Ibanez-Escriche *et al.* (2009) have found r_{AM} for farrowing survival of -0.56 (±0.13) for LR and 0.15 (±0.12) for LW using univariate models without BW as covariate. Their results are partly in accordance with our estimated r_{AM}, which were moderate and negative in LR. However, our results showed strong negative r_{AM} also in LW. The low standard errors (SE) of the r_{AM} for BW and PWL (table 6: B CF, B B in LR with and without BW as covariate and CF CF in LW without BW as covariate) indicate a significant relationship. However, the estimated r_{AM} were not significant (tested using the LRT) in the complete models or not estimable like in LW due to the missing genetic variance for SB. In addition, r_{AM} models showed convergence problems. Hence, the r_{AM} was not modeled for the bivariate models. According to Roehe *et al.* (2010), a weak relationship between additive and maternal genetic effects has shown that a direct selection for survival traits does not influence the maternal response for these traits. Reasons for strong and negative estimates of r_{AM} could be explained by environmental covariances between dam and offspring records or due to misidentification of the systematic effects structure (Bijma, 2006). However, Bijma (2006) stated that (co)variances of direct and maternal genetic effects are not feasible to estimate in a population including multiple litters and multiple offspring per litter.

Genetic and phenotypic correlations for piglet survival and birth weight

For the investigated LR population, a positive r_g of 0.221 (±0.300) and a negative r_p of -0.204 were found between BW and SB (table 3). However, in the LW population no r_g was estimable due to the missing genetic variance for the trait SB. Our results for r_g contradict most previous studies showing antagonistic relationships between SB and BW (Roehe and

Kalm, 2000; Quiniou *et al.*, 2002; Arango *et al.*, 2006). This antagonistic relationship was found in previous explorative analyses of the datasets, when the c^2-effect was modeled considering only the dam (without the corresponding parity) as an identity matrix into the model. These results support the observations made by Zaleski and Hacker (1993), showing that lower average BWs within litter increase the risk of a piglet being stillborn. Knol *et al.* (2002a) also reported that BW has a negative effect on SB. The weak positive r_g between SB and BW in this study indicates that piglets with a higher birth weight have a higher probability to be stillborn. Edwards and Baxter (2015) explained that heavy piglets can prolongate the farrowing process by being too heavy and clog the parturient canal resulting in a higher risk of asphyxia for themselves and their littermates. The increasing risk of piglets with higher BW being more susceptible to being stillborn was already described by Grandinson *et al.* (2002) who identified a positive genetic correlation between SB and the individual BW.

However, the expected antagonistic relationship was found at a genetic level between PWL and BW for both populations. Strong negative r_g of -0.497 (±0.156) for LR and -0.700 (±0.120) for LW were found. Phenotypic correlations were negative and higher compared to the results for SB and PWL (-0.381 for LR; -0.356 for LW). These associations show clearly that low birth weight piglets are more prone to die before weaning and are in accordance with literature (Roehe and Kalm, 2000; Quiniou *et al.*, 2002; Arango *et al.*, 2006).

In general, individual BW has been discussed to supply substantially more information in a bivariate analysis due to its continuous character and it has been stated that even a low correlation will improve survival traits leading to more accurate genetic parameters from a threshold-continuous trait model (Roehe *et al.*, 2010). Roehe and Kalm (2000) have suggested that BW would be an appropriate trait to improve piglet survival traits, because they observed positive r_g between individual BW and survival traits. Arango *et al.* (2006) have found r_g between BW and SB of -0.43 (±0.01) for LW. In addition, they estimated a r_g for early piglet mortality of -0.41 (±0.01) and their results have shown that the probability of piglet mortality decreases if the individual BW is higher. However, Knol *et al.* (2002a) have indicated that a selection for higher BWs will not or only to a limited extend improve the survivability. Therefore, uniform piglets are favourable for increased survivability. In addition, Roehe *et al.* (2010) have shown not only that survival during farrowing and before weaning are under different genetic control, but also that piglet survival is only slightly positively influenced by the individual BW. In the present study, the results showed that increasing BWs increase the probability of a piglet to be stillborn. Increasing litter sizes result in reduced BW due to the uterine capacity possibly limiting the total litter weight (Fix *et al.*, 2010). According to Alonso-Spilsbury *et al.* (2007), the main way BW is influencing piglet survival is the higher risk of asphyxia during farrowing. Mulder *et al.* (2015) have reported that this risk increases as well if the piglet is very heavy and not only if the piglet is light weighted. On the other hand, low BW piglets are less vital, resulting in less colostrum intake and a higher risk of pre-weaning mortality (Edwards, 2002). Even though a light BW is associated with a reduced potential for future growth, the relationship between BW and future weight is not linear per se (Fix, 2010). Fix (2010) has shown that this non-linear relationship arises because a decrease in BW below the mean value leads to a higher decrease of the future weight. Piglets with low BWs do not only suffer from reduced vitality, but their development and future weight gain is decreased whilst the impact of postnatal environmental factors increases (Le Dividich *et al.*, 2005; Fix, 2010). Light BWs result in lighter pigs at harvest or longer fattening periods (Fix *et al.*, 2010). Similar results have been shown by Knol (2001) who has reported moderate positive r_g between survivability and finishing traits indicating that a selection on survival traits will affect finishing traits, such as leanness, negatively and vice versa.

4.4.2. Heritabilities of reproduction traits

Heritabilities estimated for reproduction traits were within expectations and low for NBT, NBA, NBD, PWM and VBW for both populations. Furthermore, h^2 for MBW were higher with 0.443 (±0.035) and 0.381 (±0.034) for LR and LW, respectively. Overall, the results for all traits investigated are in accordance with literature (Hermesch *et al.*, 2001). For NBT, the h^2 Kapell *et al.* (2011) estimated a mean h^2 of 0.16 (±0.06 to 0.26) and Täubert and Henne (2003) estimated a mean h^2 of 0.119 (±0.011) and 0.114 (±0.010) for LR and LW. For NBA, Hellbrügge *et al.* (2008) have found a h^2 of 0.10 which are lower than in the present study. The h^2 for NBD ranged between 0.03 (±0.03) and 0.08 (±0.008) for different LR lines (Hanenberg *et al.*, 2001; Hellbrügge *et al.*, 2008; Bidanel, 2011), which is comparable to the present study, where h^2 of 0.082 (±0.034) for LR and 0.104 (±0.047) for LW were found. The results for VBW here are mainly in accordance with h^2 estimations from previous studies in LW populations (Damgaard *et al.*, 2003; Täubert and Henne, 2003), but higher for the LR population analysed (0.169 (±0.024)). For MBW, Täubert and Henne (2003) found h^2 of 0.354 (±0.024) and 0.276 (±0.019) for LR and LW which is supported by our findings. Kapell *et al.* (2011) have estimated pe^2 of 0.09 (±0.01 to 0.18) for NBT which were somewhat higher than found in the present study, with 0.084 (±0.026) for LR and 0.069 (±0.024) for LW. Pe^2-effects were lower for MBW (0.069 (±0.027) for LR and 0.089 (±0.027) for LW) compared to those estimated by Täubert and Henne (2003) (0.106 (±0.023)). Hanenberg *et al.* (2001) have found permanent environment effects for Dutch Landrace pigs for NBA of 0.085 (±0.005) and NBD of 0.055 (±0.004) and were only marginally lower than those estimated in the present study of 0.096 (±0.025) for LR and 0.052 (±0.024) for LW for NBA and 0.061 (±0.021) for LR and 0.051 (±0.019) for LW) for NBD. In summary, estimations of h^2 and pe^2-effects were of comparable magnitude as reported in previous studies.

Genetic correlations among reproduction traits

In the present study, NBT showed a strong antagonistic relationship to NBD and PWM, especially for LR. In LW, the r_g between NBT and NBD was similar as for LR and higher for NBT and PWM. Furthermore, the r_g of NBT and NBD was significant for LR (according to the low SE of the correlation). In the study of Lund *et al.* (2002), a correlation of -0.39 (±0.069) for LR between the maternal genetic effects of litter size and the proportion of piglets surviving for three weeks after birth was found. Also, Damgaard *et al.* (2003) have reported a positive correlation between litter size and the proportion of dead piglets pre-weaning. The relationship between the survival rate and NBA has been investigated by Hellbrügge *et al.* (2008) and a direct correlation of -0.60 (±0.19) was estimated. Kapell *et al.* (2011) and Täubert and Henne (2003) have estimated negative direct correlations between NBT and the MBW of -0.254 (±0.072) for LR and -0.661 (±0.057) for the LW population. The results for r_g between NBT and MBW showed here were -0.289 (±0.087) and -0.241 (±0.096) for LR and LW, respectively, which is contrary to their findings. However, the direct correlation between PWM and the MBW was strongly significant in both populations (-0.650 (±0.095) in LR and -0.488 (±0.137) in LW). This result confirmed the strong relationship between PWL and BW at the piglet level. In addition, Edwards and Baxter (2015) have described that low BW piglets are less vital and thereby more likely to be crushed or die due to hypothermia before weaning. The high r_g for NBD and PWM for LW (0.562 (±0.222)) here was not observed for LR (0.211 (±0.193)). However, Su *et al.* (2008) have found strong positive correlations for LR and LW, showing that in litters including stillborn piglets, a higher pre-weaning mortality may occur, especially for LR. The r_g between the NBT (0.243 (±0.116)), NBA (0.195 (±0.125)) and NBD (0.272 (±0.148)) with regards to VBW were of low magnitude for LR. However, for the LW population, opposing results were observed, where genetic correlations were higher for the relationships between VBW and NBT (0.327 (±0.131)) and NBA (0.351 (±0.133)), but not for NBD (0.043 (±0.181)) and VBW. Hence, the influence of NBT and NBA on VBW was stronger for LW. Furthermore, the r_g between PWM and VBW showed opposing results in the two populations. The weak negative relationship for LR (-0.135 (±0.152)) revealed that PWM decreases with a higher VBW. However, for LW this relationship was weaker and positive (0.067 (±0.202)). The negative effect of the VBW on PWM has been described by several authors (Roehe and Kalm, 2000; Milligan *et al.*, 2002b; Wolf *et al.*, 2008), whereas other studies have not found a strong relationship between the individual BW and its variation within litter and mortality traits (Leenhouwers *et al.*, 1999; Knol *et al.*, 2002b). Comparing the results for the r_g between MBW and the reproduction traits a contrary picture was shown for the investigated populations here. Apparently, the MBW was not influenced that strongly by NBT (-0.241 (±0.096)) and NBA (-0.231 (±0.099)) for LW, except for PWM (-0.488 (±0.137)) and we found a weak influence of MBW on NBD (-0.166 (±0.136)) for LW. For the LR population, similar results were observed and showed that larger litters (NBT and MBW -0.289 (±0.187)) decreased the MBW. Furthermore, PWM (-0.650 (±0.095)) was influenced unfavorably by lower MBW. These results oppose the results for r_g between BW and SB, but emphasized the relationship between BW and PWL at the individual piglet level, estimated in the present study.

4.4.3. Implementability of piglet survival and birth weight in breeding programs

The integration of piglet survival traits into breeding programs is of special interest for pig breeding organizations worldwide. The feasibility of using the BW related traits has been discussed by Roehe and Kalm (2000) as well as Knol *et al.* (2002b) due to the r_g between BW and piglet survival. Following Knol and Bergsma (2003), a selection index of piglet survival and litter size would be the most appropriate tool to gain an increased level of litter size, survival, more uniform litters of light weight piglets and an increased level of weaned piglets. Ibanez-Escriche *et al.* (2009) have concluded that a selection strategy has to be implemented population specific based on the (co)variance structure given in line under investigation. Su *et al.* (2007) have investigated Danish Landrace and Yorkshire populations and described that most losses can be observed at birth and during the first five days after farrowing. Therefore, Danish breeding organizations have introduced the breeding goal of litter size at day 5 (LS5) after birth to decrease the amount of stillbirths and the mortality of piglets in the first days after birth (Nielsen *et al.*, 2013). This trait is a combination of litter size and mortality at day 5 after birth. Due to the unavailable dates for the weaning losses in our data set, a more fractionated division of mortality was not possible. These authors have reported in their study the success of finding genetic gain in the litter size and LS5 and a simultaneous decrease in mortality regardless of the litter size category.

4.5. Conclusion

Based on data collected in LR and LW populations here, (co)variance components were investigated for traits of piglet survival, individual BW for piglets and selected reproduction and litter traits in their respective dams. Heritability estimates for the investigated mortality traits and BW were low, within expectations and mostly similar for both populations analysed. The application of the ASReml software for the analysis of binary distributed traits especially in a bivariate model with the individual birth weight was discussed critically in previous studies. However, the present results are in accordance with biological relationships, previous study results and expectations. Genetic correlations between SB and BW were weak, but positive in LR, whereas negative r_p was observed between these traits. The r_p and r_g showed antagonist associations PWL and BW. The results for litter traits were as expected and showed unfavourable relationships between litter size and piglet mortality as well as the average BW within litter and pre-weaning mortality, especially in the LR population. The implementation of piglet survival traits within breeding programs is crucial in order to reduce the number of early piglet losses and help to decrease ethical criticisms. However, it is questionable that breeding for higher BWs is only feasible to decrease SB or PWL. Further steps based on genomic studies, like genome-wide association studies are needed to clarify the genetic background of these traits.

Chapter 5. General discussion

5.1 Modelling genetic and environmental effects in the analysis of piglet survival traits

The key to maximizing the productivity of piglet producers is to increase the number of healthy piglets weaned per litter (Högberg and Rydhmer, 2000). The complexity of piglet survival is presented thoroughly in chapters 1 and 2. The number of piglets weaned depends on the ovulation rate as well as embryonic, foetal, farrowing and weaning survival (Lund et al., 2002). This shows that survivability is an intricate trait complex influenced by direct and maternal genetic effects as well as the common environment (figure 1, page 8) (Högberg and Rydhmer, 2000; Roehe *et al.*, 2009). The possibilities to improve farm management measures for increased survivability are exhausted (Baxter and Edwards, 2018). Thereby, the emphasis lies on finding breeding-based solutions to improve piglet survivability.

Genetic modelling: linearity vs. non-linearity for quantitative genetic analyses of individual piglet survival

Analysing individual piglet survival traits is demanding because of the large amount of data needed and the binary character of the trait. Moreover, the quality of the data may be impaired if recorded under production conditions. Against this background, the data used in our study presented a high level of accuracy due to the sophisticated standards of the technical equipment applied in routine data recording, processing and storage. Nevertheless, piglet mortality traits in nucleus populations are usually lower due to the high level of management applied on these farms.

As described in chapter 4, the survival traits SB and PWL were analysed using univariate threshold models (table 6, page 62). In addition, their respective relationship to the continuously distributed BW was investigated applying a bivariate GLMM, which models a threshold for SB and PWL (table 7, page 63). This is in accordance with Knol *et al.* (2002a) who ascertained that binary distributed survival traits should be analysed with adequate models such as the threshold model. Apart from the inefficient use of information incorporated in the data, convergence problems occurred if binary traits were analysed assuming a continuous distribution. This observation was already reported by Knol *et al.* (2002a).

In our study, h^2 were ranged in a similar parameter space whether SB and PWL were analysed assuming a continuous distribution or estimated on the underlying scale (table 6, page 62 and appendix table S7). However, Dempster and Lerner (1950) and Roehe *et al.* (2010) reported higher h^2 estimated on the underlying scale than on the observed scale. Various authors described that the amount of overestimation on the underlying scale or underestimation on the linear scale depend on the relationships between the animals, the selection pressure, the trait and the correlations between the residual variances (Dempster and Lerner, 1950; Gianola, 1982; Sorensen *et al.*, 1995). Knol *et al.* (2002b) discussed that the exploitable genetic variance remains the same. The results for our study showed that the additive genetic variance is higher in all threshold models compared to the continuous models for SB and PWL. Apart from a theoretically more efficient exploitation of the information incorporated in the data, univariate and bivariate threshold models showed a much better convergence and all results remain in a biologically reasonable parameter space. These aspects are discussed in chapter 4 in more detail.

Genetic modelling: Variance components for piglet survival traits

In our study, m^2 and c^2 effects for the binary traits PWL and SB exceed the estimated h^2 in all model variants applied (table 6, page 62). Knol et al. (2002a) reported accordingly that in the genetic analysis of piglet survival traits it is essential to differentiate between the quality of the piglet and the mothering ability of the sow. The authors emphasized that apart from general mothering ability the random litter effect additionally accounts for infectious diseases in piglets or udder infections of the dam. Thereby, this effect includes potential influences affecting all piglets in a litter because it represents their common environment. According to Knol et al. (2002a), it is feasible to adequately estimate the different random effects if large and well-defined data sets are available. In order to verify the consequences of the different model approaches, various reasonable model runs were carried out and the parameter estimates as well as the resulting Log-Likelihoods were compared and tested via a LRT using the linear models (appendix table S5 and S6). For all traits, the results clearly showed the necessity of modelling the m^2 and c^2 effects due to their main share that is redistributed among the estimated variance components if these random effects are fitted (table 6, page 62). Furthermore, convergence problems occurred if they were not modelled. Based on the findings presented in chapter 4, it is essential for the traits of individual piglet survival and BW to model m^2 and c^2 effects to define their determinants, appropriately.

Genetic modelling: Correlations between direct and maternal genetic effects?

Moreover, it was possible to include a covariance between maternal and direct genetic effects into the univariate models for SB, PWL and BW. Direct-maternal correlations (r_{AM}) show whether and how strong m^2 effects would be influenced if direct selection would be performed within a trait or between traits (Grandinson *et al.*, 2002; Roehe *et al.*, 2010). The results of the study presented in chapter 4, showed that r_{AM} caused convergence problems, were not significant and ranged massively between testing the various full univariate models for SB, PWL and BW (table 6, page 64). Thereby, r_{AM} were not modelled in the bivariate models. This was in accordance with the study of Roehe *et al.* (2010) in which only weak r_{AM} were found within traits. According to Bijma (2006), an estimation of (co)variances between direct and maternal effects is not feasible in populations with multiple litters and multiple offspring per litter. Considering the r_{AM} between traits, the results of Knol *et al.* (2002a) showed a positive correlation between the direct component of BW and the maternal component of SB, indicating a negative influence on SB if selection on the direct component of the individual BW occurs. In addition, Knol *et al.* (2001) reported decreased litter BW if selecting directly for individual piglet survival. These findings show that r_{AM} can be indicatory when it comes to designing a model to breed for improved piglet survival, especially between traits.

Genetic modelling: Biological and/or cross-fostering dam as random maternal or litter effect?

In our study, all statistical models used to analyse SB and BW included the m^2 of the biological dam (B), reflecting the quality of the uterus of the sow, and the common environment of the piglets during gestation defined as c^2 effects. Because of the availability of cross-fostering information in our data sets, m^2 and c^2 effects can be modelled for PWL on the basis of the B or the cross-fostering dam (CF). Even though both effects (B and CF) are characterized by mothering abilities, those effects differ in case of cross-fostering. The B effect incorporates uterus qualities during gestation, colostrum production, farrowing and mothering abilities. The CF effect represents mostly the milk production capacity of a sow and mothering abilities (Knol *et al.*, 2002a; Roehe *et al.*, 2009). However, these effects become indistinct depending on the amount of cross-fostering applied in the population and the time range considered in the analysis. Thereby, for PWL the integration of m^2, c^2 and cross-fostering effects into the statistical model would be reasonable because it would represent the actual contributing effects on survivability for a substantial proportion of piglets in most nucleus populations. However, because of the relatively small amount of cross-fostered piglets in two of the four farms analysed (6-31 % (LR); 8-23 % (LW)) the simultaneous inclusion of all these effects could possibly make precise fractionation and distinction between the B and the CF effects difficult (Knol *et al.*, 2002a).

However, even though the model fit was best for the nurse dam effect (m^2 and c^2) according to the LRT (appendix table S5 and S6), estimations of variance components showed no relevant differences between models (table 6, page 64). Arango et al. (2006) described the difficulties emerging from the confounding due to the B and the CF dam existing pre-weaning. Thereby, as described thoroughly in chapter 4, such effects can be accurately considered only if the amount of cross-fostering is sufficient (Knol et al., 2002a; Arango et al., 2006). In summary, if individual pre-weaning survival is incorporated into a breeding goal, the CF dam should be recorded and taken into account for the accurate consideration of this trait. However, if the cross-fostering rate is similar as in our data set, practical consequences of ignoring the cross-fostering effects seem to be low.

Genetic modelling: Birth weight as covariate in models for survival traits?

The consideration of the individual BW as covariate for PWL and SB was investigated in the study presented in chapter 4. BW had a significant effect and influenced the magnitude of the variance components in SB by slightly increasing the additive genetic variance in both lines (table 6, page 62). Considering the non-linear relationship with BW, Knol *et al.* (2002a) reported that BW indirectly covers the impact of intrauterine crowding if modelled as a fixed effect for survival traits in 100 g classes. Knol and Bergsma (2004) analysed PWL as a binary trait. Their statistical model includes BW as a correcting covariate. Consequently, the authors reported that the inclusion of the covariate BW may have an undesirable genetic impact on BW itself. A genetic reduction of BW can be expected because the piglet with the smallest BW that survived had the highest EBV for survival. In order to avoid this negative consequence, the authors suggested using a sire and dam model rather than an animal model including a direct genetic effect. Against this background, it should be critically analysed how the inclusion of BW as a fixed effect influences the genetic progress of individual BW and LS. The possibilities to consider survivability and BW in breeding programs are discussed in chapter 5.2.

5.2 Integration of piglet survival into breeding programs

Considering the different approaches found in literature it seems to be very challenging to find the appropriate breeding strategy to improve piglet survival. The main reasons are (1) this trait complex is determined by maternal and direct genetic effects with mostly low variance proportions (h^2, m^2, c^2), and (2) the genetic relationships between piglet survival and production traits are mostly unfavourable (Knol, 2001; Roehe *et al.*, 2009; Fix, 2010). Furthermore, the breeding goal should be balanced and include important production traits as well as animal welfare aspects (Rydhmer, 2000). However, causes for piglet mortality are complex and their exact individual recording is mostly not applicable in farm routines. In order to separate genetic from environmental effects and to achieve sustainable genetic progress in piglet survivability, technical improvements in on-farm data recording (e.g. mortality reasons, BW) are targeted and rewarding investments. The following sections describe various approaches to integrate piglet survivability into a breeding program and summarize existing approaches applied in pig breeding.

Piglet survival: Trait of the piglet or a trait of the dam?

In the study presented in chapter 4, analysing piglet survival (SB, PWL and BW) as a trait of the piglet itself resulted in h^2 estimates ranging between 0.00 and 0.04. There have been few studies, which have analysed piglet survival as a trait of the piglet itself. But the results published are mostly in accordance with our findings (e.g. Arango *et al.*, 2006; Ibanez-Escriche *et al.*, 2009; Roehe *et al.*, 2010). Clearly, under the conditions of low h^2 or m^2 estimates, sufficient genetic progress is hard to achieve. However, the large amount of data can compensate the deferring effect of low genetic variances, because the different effects can be estimated with enhanced accuracy. Nevertheless, in case of h^2 not exceeding 0.00 - as has been shown in LW for SB - this aspect can be neglected because it does not provide any advantage if direct genetic variance is missing. It is advantageous when modelling survival at the piglet level to include individual BW and mortality reasons, if recorded. Based on our results, the question if PWL, SB and BW should be modelled as separate traits or if BW should be a covariate of survival traits cannot be answered clearly.

Furthermore, h^2 for reproduction traits defined as a trait of the dam were low, except for MBW (table 9, page 68). This is in accordance with the results presented in literature (e.g.

Högberg and Rydhmer, 2000; Täubert and Henne, 2003; Kapell *et al.*, 2009). However, the example for the trait NBA showed that improvement is possible apart from its low h^2, because a genetic variation existed (Bergfelder-Drueing *et al.*, 2015). In chapter 4, SB did not show any or low genetic variability in LW, but at sow level it did (table 6, page 64). In LR, direct genetic variation was found at piglet and dam level. This indicates breed or population differences affecting the degree of direct genetic effects on piglet mortality (Grandinson *et al.*, 2002; Lund *et al.*, 2002). Selection for direct and m^2 effects of piglet survival was very successful in a cross-breeding experiment under outdoor conditions reported by Roehe *et al.* (2009) and Roehe *et al.* (2010) with increased genetic variation and h^2. As previously described by Ibanez-Escriche *et al.* (2009), differences exist between lines when it comes to the determining genetic effects on piglet survival. According to the correlations between direct and m^2 effects, Ibanez-Escriche *et al.* (2009) reported that survivability is a trait of the piglet in LR and Piétrain, but a trait of the sow in LW. Knol *et al.* (2002a) found that the direct components for PWL are stronger in the dam line, whereas m^2 effects dominate in the sire line. Grandinson *et al.* (2002) reported a negligible genetic variation for total piglet mortality in Yorkshire piglets and Su *et al.* (2008) found lower h^2 for LW. These results indicate that the selection strategy has to be designed line specific (Ibanez-Escriche *et al.*, 2009; Kapell *et al.*, 2011). Kapell *et al.* (2009) underlined this proposition after investigating a sire and a dam line originated from one LW population selected for production and reproduction traits, respectively. In the sire line, survival was required to be included into a SI whereas in the dam line reproduction traits were improved without an additional focus on production traits. The findings presented here and from literature reveal that a direct selection against SB would be feasible in LR. Due to the missing additive genetic variability for SB in the LW population the improvement of this trait should be considered at litter level when designing a breeding goal.

Piglet survival: Direct or indirect indicators?

SB and PWL are two genetically separate traits and their relationship with BW is contradictory (table 7, page 65, chapter 4). Already Knol *et al.* (2002a) found a negative impact of BW on farrowing survival and a positive effect on pre-weaning survival. The individual BW is a crucial determinant for piglet survival (Roehe and Kalm, 2000). To only breed for increased BW to improve direct piglet survival is complex, especially if large LS should be maintained (Knol, 2001). Fix (2010) reported that an incremental decrease in BW results in a greater increase of the likelihood to die, especially during the pre-weaning phase. Several studies show that simply increasing the individual BW raises the probability for SB because the relationship of these traits is not linear (Roehe and Kalm, 2000; Knol *et al.*, 2002a). Hellbrügge *et al.* (2008) also found a high negative correlation ($r_g = -0.57$) between NBD and underweight at litter level, showing that light piglets are actually favourable for parturition. Nevertheless, a minimum BW of 1 kg has to be realized for the vitality of the piglet whilst keep LS stable (Roehe and Kalm, 2000; Knol *et al.*, 2002a). Grandinson *et al.* (2003) and Hellbrügge *et al.* (2008) found that heavier piglets have improved chances to survive pre-weaning and a lower risk to be crushed. Therefore, a balancing act has to be realized when it comes to using BW to increase piglet survival indicating a uniform and ideal BW as suggested by Mulder *et al.* (2015).

Piglet survival: Correlation to other traits

NBT and NBA showed unfavourable correlations to NBD and PWM at litter level (table 9, page 68) in both breeds indicating that mortality rates increase in larger litters. This relationship was already described in the literature (Högberg and Rydhmer, 2000; Grandinson *et al.*, 2003). In addition, Sorensen *et al.* (2000) concluded that the individual piglet BW and viability as well as reproduction traits should be monitored to prevent unfavourable genetic changes when breeding for NBT. Lund *et al.* (2002) stated that a selection for NBT alone would cause a deterioration of maternal abilities of sows and other components due to unfavourable direct-maternal correlations within and between reproduction traits. The quadratic relationship of piglet survival and LS shows that piglets from intermediate litter sizes have a higher chance of survival compared to those from extreme small or large litters (Li et al., 2018). The findings presented in chapter 4 and from literature, show that a breeding goal has to be well balanced if the focus remains on high LS. The negative influence of large litters on piglet survival and especially uniformity raises the question if medium sized litters are more favourable if LS remains mostly the same until weaning. Management efforts would be reduced and uniformity increased.

Here, NBT and NBA showed unfavourable correlations in both breeds with the MBW. Furthermore, the VBW was positively correlated to NBT and NBA for both populations (table 9, page 68). Quesnel *et al.* (2008) reported 1.8 piglet extra per litter in LW dams and a reduction of the mean BW per litter by 180 g within ten years. Moreover, the authors found an increased variability in BW with increased LS as already described by Milligan *et al.* (2002b). Hellbrügge *et al.* (2008) found high correlations between underweight, runting and NBD and NBT, respectively. These results emphasize the negative impact of LS on prenatal growth due to rivalry in the uterus and again emphasizes the need for a balanced breeding goal if large LS should be maintained. Therefore, including traits related to BW into a SI for improved survivability should be considered.

Piglet survival: Existing approaches for selection indexes

To develop a SI, it is crucial to consider which traits are measurable within given performance testing conditions, the costs of their recording and their marginal economic value (Täubert and Henne, 2003; Knap, 2014). According to Knol *et al.* (2002b), PWL is the easiest and most economical trait to record to be included into breeding programs. The number of weaned piglets (NWP) is the essential trait to improve due to its economic relevance for piglet production (chapter 1). However, cross-fostering methods complicate the selection process because the trait will not be recorded with the needed accuracy in most breeding programs (Täubert and Henne, 2003). This problem potentially holds also for PWL, as presented in chapter 4. Nevertheless, in our study it showed a higher genetic variability for both breeds compared to SB (table 6, page 64). Various approaches to include piglet survival into breeding goals are presented in table 10.

Dutch pig breeders have mainly investigated breeding for the direct component of piglet survival and various approaches to integrate BW into the SI. However, the direct selection for BW result in negative effects for LS and meat quality traits. Using BW as a correcting covariate BW may have an undesirable genetic impact on BW itself (chapter 5.1: Birth weight as covariate in models for survival traits?). An improved uniformity can be expected from breeding for the direct component of piglet survival alone, however, runts or giants will still occur and cause pre-weaning losses or farrowing difficulties (Knol, 2001; van der Lende et al., 2001). A selection experiment in the Netherlands showed high potential if underlying mechanisms responsible for the remarkable reproductive performance of the Meishan breed are considered as traits in a LW line. Their SI showed that even though BW is expensive and elaborate to record, it is essential for a balanced breeding program for improved survivability (Knap, 2014). In addition, the results showed that breeding for increased LS is successful if survival traits and BW are included in the SI as well. Swedish pig breeders have compiled considerable research in the holistic treatment at litter level and considered that uniformity of BW would result in improved piglet survival (Damgaard et al., 2003). In France, selection for absolute BW resulted in increased proportions of small piglets and the proportion of heavier piglets increased when selecting for the categorized BW in combination with LS (Quesnel et al., 2008). German pig breeders created a SI for a simulated breeding structure, with the help of using NBA versus including NBA, MBW and VBW simultaneously. The authors found that with the inclusion of MBW and VBW, the NBA decreases but the NWP increases due to lower amounts of piglet losses. In addition, the MBW increased the accuracy of the SI by at least 17 %. If only NBA was considered piglet losses increased by 0.1 piglets, MBW was reduced and VBW enhanced. Therefore, additional information on MBW and VBW reduced the losses (Täubert and Henne, 2003).

Table 10: *Approaches to include piglet survival into breeding programs*

Trait	Covariate	Consequence	Reference
PS (direct)		⬇VBW →⬆uniformity	Knol (2001)
PS (direct)		⬇VBW (runts/giants occur) → ⬆ uniformity	van der Lende *et al.* (2001)
PS (direct), NBT		⬆ survivability,⬆ uniformity, ⬆ NPW	Knol (2003)
PS (direct)	BW in 100g classes	⬇ intrauterine crowding	Knol *et al.* (2002a)
PS (direct)	BW	⬇ BW	Knol and Bergsma (2004)
LS,PS, BW, VBW, GL		⬆ NBA (+2), ⬆PS (+8), ⬇ MBW (-400 g),⬇ LW (-2.9 g), ⬇ BW (-71 g)	Knol *et al.* (2002b)
BW		⬇ meat quality	Knol (2001)
BW		⬆proportions of small piglets	Quesnel *et al.* (2008)
VBW		⬆PS	Damgaard *et al.* (2003)
MBW,VBW		⬆uniformity	Sell-Kubiak *et al.* (2015b)
NBD, MA		⬆LS	Hanenberg *et al.* (2001)
NBA	MBW,VBW	⬇ NBA,⬆NWP, ⬆PS, ⬆ accuracy of SI	Täubert and Henne (2003)
LS5		⬆ NBT,⬇ MORT	Nielsen *et al.* (2013)

PS=Piglet survival, NBT=Number of piglets born total, VBW=Variance of birth weights within litter, NPW=Number of weaned piglets, BW=Birth weight, LS=Litter size, GL=Gestation length, MBW=Mean birth weight within litter, NBD=Number of piglets born dead, MA=Mothering abilities, LS5=Litter size at day 5 after farrowing, MORT=Piglet mortality rate until day 5 after farrowing

In Denmark, breeding organizations worked with the trait LS5 and achieved a successful increase in the NBT and piglet survival rates until day five after farrowing in Danish LR and LW nucleus herds (Nielsen *et al.*, 2013). These examples show that selection for improved survivability and uniformity is possible while remaining LS if the SI is balanced according to the genetic prerequisites the population provides. However, breeding organizations have to invest into accurate and large-scale phenotyping, which has to be justified by the economic values it returns.

Piglet survival: Benefit of the immunocompetence

Although the analyses presented in chapter 4 only cover survival traits as well as BW, immunocompetence is discussed to be a crucial and rarely considered determinant for piglet survivability. Based on chapter 3, in which this relationship is reviewed thoroughly, the following section aims to resume important points of this debate. Restricted performance or piglet losses due to impaired health create economic damage for piglet producers. Clinical disease is observable, whereas, health or immunocompetence is difficult to quantify (Wilkie *et al.*, 1998), also economically. As described in chapter 2, the sow rarely influences the immune system of the piglets during gestation. The epitheliochorial placenta results in the naïve immune system of new-born piglets, which is challenged immensely after birth (Tizard, 2013). Colostrum, rich in immunoglobulins, is therefore essential for the passive immunization of the piglet (Klobasa *et al.*, 1987). Moreover, the nutritional components of colostrum are crucial for the thermoregulation and energy supply of the piglet, because piglets do not possess brown fat tissue or any other energy reserves (Quesnel *et al.*, 2012; Theil *et al.*, 2014). Thereby, sows have to produce an appropriate amount of high quality colostrum for their litter, recover quickly from birth and stay healthy until weaning as well as for the next conception. Piglets have to be vital, quickly stand, move to the udder of the sow and take in colostrum (Edwards and Baxter, 2015). Hypoxia, reduced physiological development and low BW are the main causes for missing vitality (Edwards, 2002). Thereby, the critical period after birth is influenced by complex relationships between the sow and the piglet, which can only be addressed by a balanced breeding goal (Rydhmer, 2000). However, it is crucial to investigate the actual decisive relationships between survival, immunocompetence and robustness. Piglet vitality and its complex causes, mothering abilities as well as colostrum production play a role in this sensitive interaction of trait complexes. In addition, the quality of the dams' immune system, and how it influences the piglets' immunity, has to be investigated.

As described in chapter 3, general immunocompetence does also represent robustness. For piglets and growing pigs, this would suggest that the immune system of the piglet has to react rapidly and to an appropriate extent to various environments as well as pathogens. Furthermore, the piglet should show unrestricted growth and performance (Knap, 2005; Colditz and Hine, 2016). That means that no resources intended for growth should be allocated to the immune reaction because it utilizes resources that would be available for performance (Rauw, 2012). But as described by Kvidera *et al.* (2017) an accurate quantification of the energetic requirements of the immune system is difficult because, during its activation, immune cells are found in every tissue and leukocyte distribution as well as flux changes dynamically. Huntley *et al.* (2017) estimated that an immunoactivation increases maintenance demands by approximately 25 % in growing pigs. Kvidera *et al.* (2017) quantified that the amount of the activated immune system uses “approximately 116 g of glucose within 480 min” in growing pigs and stated that this is underestimated because it was not possible to estimate all utilization or contribution processes. Hence, immune reactions like inflammatory responses claim nutrients that are not available for productive purposes anymore (Kvidera *et al.*, 2017). Therefore, the burden of an immune activation or response is dangerous for a piglet around birth and until weaning because of its very limited resources. Especially inflammatory processes, fever and acute-phase-protein reactions incur metabolic costs. High immune responses might be too expensive when it comes to the physiological costs for the body (Rauw, 2012).

SI for increased porcine immunocompetence were mostly conducted via categorizing animals into high (HIR) or low immune response groups (LIR) (Mallard *et al.*, 1992). Subsequent studies on these selected animals showed that selection for “multiple immune response traits representing both antibody and cell-mediated immune response” (Magnusson *et al.*, 1998) resulted in high and low response lines which differed significantly in their response to antigens they were bred for but also to other antigens (Magnusson *et al.*, 1999). However, Stear *et al.* (2001) questioned this approach, because animals which are bred for a specific immune response are more prone for other diseases. Pluske *et al.* (2018a), who found that the capacity for an animal to mount a substantial immune response is crucial, confirmed this. However, the negative effects of pro-inflammatory cytokines have to be minimized because they substantially reduce animal health and performance (Pluske *et al.*, 2018a). According to Black and Pluske (2011), both, under- and over-responsiveness of the immune system will influence animal health and productivity negatively. Clapperton *et al.* (2009) measured parameters of the immune system after challenging pigs in two different environmental categories according to the hygiene status of the farms. Results from these studies and from Flori *et al.* (2011), as presented in chapter 3 (table 1, page 37), showed that immune parameters show distinct genetic variation and could be bred for. However, immune traits underlie huge GxE interactions indicating that the SI has to be created population specific (Black and Pluske, 2011). In addition, uniformity should be considered critically when it comes to the immune system. Fundamental knowledge on the relationships within the immune system is missing. The genetic variation of immune traits is very susceptible to age, infection pressure, life phase and number of animals analysed. Furthermore, the relationships to important production traits were only rarely investigated (Clapperton *et al.*, 2008a; Clapperton *et al.*, 2008b). Due to the high expenses that are related to the measurement of immune traits and the missing knowledge about the appropriate direction to select for, it is difficult to include these traits into a useful SI at this point.

5.3 Perspectives

The findings presented in chapters 3 and 4 as well as the results from literature show that a selection for improved survivability is feasible via individual piglet and litter traits. However, these observations raise the question whether or not it might be more useful to accept smaller litters with uniform piglets if the consequence is that LS stay the same until weaning and the management effort will be reduced. Furthermore, it would be interesting to further investigate the respective causes of PWL and the relationships between them. Even though those traits are of high importance, they are difficult to record accurately in on-farm routines. Thereby, it is important to determine phenotypes that represent various positive individual features for survivability at piglet and dam level. Li *et al.* (2018) used a single trait threshold model for ten different traits representing pre-weaning survival. The results of the h^2 estimation doubled when the authors used not only the pedigree information but additional genotypic information as well. The genomic analysis of the phenotypes discussed with regards to survivability, BW, growth and the immune system would be of particular interest. GWAS of the respective traits would have to be conducted in order to identify potential candidate genes that can be included into a breeding program. GS is promising because it provides a more accurate way of selection (Knol *et al.*, 2016). However, genomic analyses must also be modelled according to the binomial character of piglet individual survival traits with the help of case-control studies.

When it comes to immunocompetence, the question arises whether individual immune parameters are a proxy for survival or if breeding for survival directly includes the genetic potential for a general robustness. This is particularly interesting because phenotyping of immune parameters are extremely costly and survival traits as well as the individual BW would be easier to record in on-farm routines. In addition, fundamental research has to be pursued when it comes to the useful inclusion of immune parameters into breeding programs. Although uniformity appears to be crucial for the improvement of piglet survivability, it may create problems if applied on the immune system. The role of colostral immunity (e.g. Bandrick *et al.*, 2011; Bandrick *et al.*, 2014) as well as the gut of the piglet (e.g. Pluske *et al.*, 2018b) on the development of the immune system need to be investigated. In addition, the influence of maternal genetic effects (e.g. Salmon *et al.*, 2009) on piglet immunocompetence are important fields that have to be studied thoroughly, if we consider the influence of maternal stress on the immune system of the piglet as described in chapter 1.

Chapter 6. Conclusion

Uniform low piglet birth weights appear to be the key to help to improve piglet survival. Piglets from uniform litters create less problems during farrowing, are well developed and more vital. According to literature, piglets with an adequate individual BW also show good growth rates. Survival, BW and LS can be simultaneously included into a SI as individual piglet or litter traits, considering the relationships to performance traits and fitted for the respective breed. Regarding the results presented above, which indicate the need for line specific inclusion of survival traits, the question arises if MBW and VBW should be included in a SI for LW, but for LR individual piglet traits would favourably be included in form of PWL and VBW. Apart from litter uniformity and optimum BW, mothering abilities, parturition performance scores and colostrum amount may be potential solutions to improve piglet survival at all levels. However, the costs for phenotyping these traits have to be evaluated towards their actual profit and on-farm applicability. Breeding for piglet survival is possible and can be even more efficient if genotypic information is included in the analyses via GWAS and GS.

Immunocompetence is another intricate trait complex that is only rarely defined, especially when it comes to measurable traits representing it. Even though various studies found considerable genetic foundations for immune parameters, a substantial knowledge gap exists on their impact on survivability and robustness. Selection traits have to be carefully evaluated considering their consequences for all (re)production traits and the immune system before incorporating them into a breeding program. The specificity of immune parameter concentrations under various life conditions, GxE interactions and missing reference values complicate this situation. Furthermore, it has to be carefully evaluated if breeding for a specific immune reaction with the help of challenge tests is the right step towards a general immunocompetence requiring a flexible reaction pattern towards pathogens and diseases.

Chapter 7. Summary

Piglet survival determines the success of piglet production because it majorly influences the number of piglets weaned. Moreover, restricted performance or piglet losses due to impaired health create economic impacts for piglet producers. Apart from financial losses, decreased piglet survivability raises animal welfare concerns. This situation was intensified by increasing LS in the last decades, because they resulted in lower BW and increased VBW in occidental pig breeds. In addition, light BW piglets show decreased growth rates. Piglet survivability is an intricate trait complex influenced by additive genetic, m^2 and environmental effects. However, it was reported that management strategies are exhausted. Various studies of immune traits revealed profound genetic variability, but it remains unclear which traits represent a robust immune system. Furthermore, the consequences for survival and performance remains unclear if immune traits are included into a breeding program. In this context, it would be beneficial to establish a SI to additionally select for improved piglet survival and general immunocompetence.

The aim of this thesis was to analyse the prospects to select for improved piglet survival. Therefore, the complex determinants of survivability were also evaluated with respect to the immune system. In addition, traits representing piglet survival were analysed genetically in the maternal lines LR and LW. For this purpose, comprehensive data sets including 168,823 piglets and their respective 4,642 dams were provided by a German breeding organization. Apart from individual BW for stillborn as well as live born piglets, the data sets included accurately recorded cross-fostering information.

In chapter 3, the intricate trait complexes piglet survival and immunocompetence that are highly influenced by G×E interactions were summarized. Thereby, knowledge gaps and potential selection strategies to improve survivability and robustness were discussed. In order to design reasonable breeding programs for improved survivability and robustness, appropriate immune parameters have to be evaluated considering their mode and direction of

effectiveness. This holds especially for reference values that need to be updated for an adequate characterization of current pig populations as well as the critically discussed selection for specific immune responses. Moreover, it is important to keep in mind that while clinical disease is observable, health or immunocompetence is difficult to quantify. Thereby, the relationships between survivability, immune parameters and production parameters have to be investigated to actually improve robustness. Due to the high costs of phenotyping immune parameters it would be interesting to investigate whether or not survival would be a proxy for immunocompetence.

In the second study (chapter 4), the piglet traits SB, PWL and BW as well as their representative litter traits were investigated using univariate, bivariate and multivariate generalized linear mixed models. The analysis focused especially on the binary character of SB and PWL applying threshold models and a logit link function. Due to the large data sets available and high levels of cross-fostering the m^2 effect of the CF dam could be investigated. Piglet survival and BW traits showed low h^2 at piglet and litter level, except for the mean BW within litter. In addition, the genetic r_g between SB, PWL and BW revealed distinct relationships between the traits indicating that uniform individual BW are required to reduce the odds for a piglet to be stillborn but to ensure the vitality needed to survive until weaning. Moreover, the litter traits representing survival and BW revealed unfavourable r_g to LS. Breed differences were found at the individual piglet and litter level. Considering the CF dam showed the best model fit for PWL but had no considerable effect on the magnitude of the variance components.

In conclusion, the consideration of piglet survival and the immune system in a SI is possible but complex. Furthermore, it should generally be designed population specific. Considering piglet survival as well as growth, uniform individual BW appear to be ideal for farrowing and pre-weaning survival. However, when it comes to the immune system, uniformity and

specific immune responses are discussed critically. Furthermore, the costs for phenotyping these traits have to be evaluated towards their actual profit and on-farm applicability. Breeding for piglet survival is possible and can be even more efficient if genotypic information is included in the analyses via GWAS and GS.

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Chapter 9. Appendix

Table S1: *Genomic analyses for haemopoetic traits in pigs*

Method	Traits	Breed	Reference
Transcriptome analysis	Total white blood cells, lymphocyte counts, proportions of various leucocyte subsets, cells harbouring IgM, γδTCR, CD4/CD8, CD16/CD2 and CD16/CD172a/MHCII, phagocytosis & *in vitro* production of IL1B, IL6, IL8, TNF, IL12 and IFNα after blood stimulation, lymphocyte proliferation, *in vitro* production of IL2, IL4, IL10 and IFNγ after blood stimulation, total IgG, IgA, IgM, specific IgG levels, C-reactive protein, haploglobin	French Large White	Flori *et al.* (2011b)
GWAS & LONG-GWAS	Hematocrit, hemoglobin, HBE, MCHC, MCV, erythrocytes, RDW, granulocytes (%), amount of granulocytes, monocytes (%), amount of monocytes, lymphocytes (%), amount of lymphocytes, leucocytes, thrombocytes, PCT, PDW, MPV	White Duroc × Erhulian F2	Zhang *et al.* (2013)
GWAS of DNA pools	γ-Immunokrit	Landrace x (Duroc x Yorkshire)	Rohrer *et al.* (2014)
GWAS & haplotype analysis	Hematocrit, hemoglobin, HBE, MCHC, MCV, erythrocytes, RDW-SD, lymphocytes (%), amount of lymphocytes, leucocytes, thrombocytes, PDW, MPV, P-LCR	Chinese Sutai	Zhang *et al.* (2014a)
GWAS & multi-marker analysis	Leucocytes, lymphocytes, erythrocytes, hemoglobin, hematocrit, MCV, HBE, MCHC, thrombocytes, RDW, MPV, PCT	German Landrace	Ponsuksili *et al.* (2016)

Method	Traits	Breed	Reference
GWAS & LDA & PCA	Leucocytes, neutrophils, neutrophils (%), lymphocytes, lymphocytes (%), monocytes, monocytes (%), erythrocytes, MCV, hemoglobin, hematocrit, HBE, MCHC, RDW, thrombocytes, MPV, PDW, PCT	Landrace, Large White, Songliao Black	Wang *et al.* (2013)
GWAS	Hematocrit, hemoglobin, HBE, MCHC, MCV, erythrocytes, RDW	Large White × Minzhu F2	Luo *et al.* (2012)
GWAS & LDA	IFNγ, IL 10, IFNγ-IL10-ratio, IgG	Landrace, Yorkshire, Songliao Black	Lu *et al.* (2013)
Linkage analysis/QTL mapping with microsatelites	T lymphocyte subpopulations: proportions of CD4+, CD8+, CD4+CD8+, CD4+CD8-, CD4-CD8+, and CD4-CD8- T cells and the ratio of CD4+:CD8+ T cells	Landrace, Large White, Songalio Black pig	Lu *et al.* (2011)

GWAS=Genome-wide association studies, QTL=Quantitative trait loci, LONG-GWAS=longitudinal GWAS, LDA=Linkage disequilibrium analysis, PCA=Principle component analysis, HBE=Hemoglobin concentration in blood, MCHC=Mean corpuscular hemoglobin concentration, MCV=Mean corpuscular volume, RDW=Red cell distribution width, RDW-SD= Red cell distribution width – standard deviation, PCT=Volume occupied by platelets, PDW=Platelet distribution width, MPV=Mean platelet volume, P-LCR=Platelet large cell ratio, IFN=Interferone, IL=Interleukin, IgG=Immunoglobulin G, TNF=Tumor necrosis factor.

Table S2: *Genome-wide association studies (GWAS), candidate gene and linkage analyses for traits associated with piglet survival*

Method	Traits	Breed	Reference
Candidate gene analysis	TNB, NBA	Meishan	Rothschild *et al.* (1996)
QTL mapping via microsatellites	TNB, NSB, NBA	Large White, Yorkshire	Tribout *et al.* (2008)
Candidate gene analysis	TNB, NSB, PM	American Large White, Landrace	Sironen *et al.* (2010)
GWAS (BM)	TNB, NBD, NSB, MUM, LBW, ABW	Crossbreds	Schneider *et al.* (2012)
Whole-genome association study	TNB, NSB, PM	Finnish Landrace	Uimari *et al.* (2011)
Whole-genome association study	TNB, NBA, NSB, MUM	Large White x Landrace	Onteru *et al.* (2012)
Genome-wide linkage analysis	TNB, NBA, PS	Large White x Meishan F2	Hernandez *et al.* (2014)
GWAS	HEBV and LEBV for IBW	Crossbreds	Zhang *et al.* (2014b)
GWAS	NSBIL, NSBL, PCSPIL	Crossbreds	Schneider *et al.*, 2015
GWAS	NBA	Landrace, Large White	Bergfelder-Drueing *et al.* (2015)
GWAS	TNB, varTNB	Large White	Sell-Kubiak *et al.* (2015a)
GWAS (BM)	TNB, LS 5, MORT	Danish Landrace	Guo *et al.* (2016)
GWAS (BM) & generation of gene-transcription factor networks	NSB, NT	Large White	Verardo *et al.* (2016)

Method	Traits	Breed	Reference
Candidate SNP analysis	TNB, NBA, ABW, PM	Large White	Sato *et al.* (2016)
GWAS	PU	Large White	Wang *et al.* (2017)
GWAS	NBT, NBA	Erhualian	Ma *et al.* (2018)
GWAS	NBT, NBA, LBW, ABW	Large White	Wang *et al.* (2018)
Candidate gene analysis	NBT, NPD, NSB, NBDA, ABW	Yorkshire	Jonas and Rydhmer (2018)

GWAS=Genome-wide association studies, SNP=Single nucleotide polymorphism, QTL=Quantitative trait loci, BM=Bayesian models, TNB=Total number of piglets born, NSB=Number of stillborn piglets, NBA=Number of piglets born alive, NBD=Number of piglets born dead, MUM=Number of mummies, LBW=Total litter birth weight, ABW=Average birth weight, PM=Piglet mortality between birth and weaning, PS=Prenatal survival, HEBV=High estimated breeding values for the individual birth weight, LEBV=Low estimated breeding values for the individual birth weight, IBW=Individual birth weight, NSBIL=Number of stillborn piglets ignoring the last piglet born per litter, NSBL=Number of stillbotn in the last birth position, PCSBIL=Percent stillborn ignoring the last piglet, LS 5=Litter size at day 5, MORT=Mortality rate before day 5, PU=Piglet uniformity, NPD=Dead piglets of total born, NBDA=Dead piglets of live born, varTNB=Variability of TNB, NT=Number of teats, NBT=Number of piglets born total.

Table S3: *Heritabilities (h^2 ± SEM) in blood parameters of the porcine immune system (full table)*

Parameters	Edfors-Lilja *et al.* (1994)	Henryon *et al.* (2006)	Clapperton *et al.* (2008b)	Clapperton *et al.* (2009)	Flori *et al.* (2011a)	Mpetile *et al.* (2015)	Ponsuksili *et al.* (2016)
n	220	4204	500	606	443	518	591
Breed	Swedish Yorkshire	Duroc, Landrace, Yorkshire	Large White	Large White, Landrace	Large White	Yorkshire	Landrace
Leukocytes	0.44 (0.29)	0.25 (0.05)	0.24 (0.15)	0.28 (0.11)	0.73 (0.20)	0.23 (0.19)	0.23
Neutrophiles		0.22 (0.04)			0.61 (0.20)	0.31 (0.21)	
Lymphocytes	0.24 (0.21)	0.24 (0.05)			0.72 (0.21)	0.15 (0.19)	0.49
Monocytes		0.22 (0.04)	0.52 (0.17)	0.26 (0.13)	0.38 (0.20)	0.36 (0.20)	
Eosinophils		0.30 (0.05)			0.80 (0.21)	0.58 (0.12)	
Basophils						0.12 (0.19)	
Thrombocytes					0.56 (0.19)	0.11 (0.23)	0.39
Erythrocytes					0.43 (0.20)	0.62 (0.25)	0.41
Haemoglobin						0.56 (0.13)	0.40
Hematocrit					0.57 (0.03)	0.06 (0.14)	0.34
MCV						0.47 (0.24)	0.69
HBE						0.37 (0.24)	0.67
MCHC						0.04 (0.16)	0.67
IFNγ					0.00 (0.17)		
IL10					0.35 (0.19)		
IL12					0.51 (0.20)		
IL1beta					0.12 (0.19)		
IL4					0.15 (0.18)		
IL6					0.11 (0.19)		
IL8					0.00 (0.17)		

Parameters	Edfors-Lilja *et al.* (1994)	Henryon *et al.* (2006)	Clapperton *et al.* (2008b)	Clapperton *et al.* (2009)	Flori *et al.* (2011a)	Mpetile *et al.* (2015)	Ponsuksili *et al.* (2016)
n	220	4204	500	606	443	518	591
Breed	Swedish Yorkshire	Duroc, Landrace, Yorkshire	Large White	Large White, Landrace	Large White	Yorkshire	Landrace
TNFalpha					0.00 (0.19)		
Haptoglobin		0.14 (0.07)		0.20 (0.11)	0.55 (0.21)		

MCV=Mean corpuscular volume, HBE=Hemoglobin concentration in blood, MCHC=Mean corpuscular hemoglobin concentration, IFN=Interferone, IL=Interleukin, TNF=Tumor necrosis factor

Table S4: *Heritabilities* (h^2 ± SEM) *for survival traits in pigs (dam lines and crossbreds)*

Parameter	h_t^2	h_d^2	h_m^2	Breed
Number of piglets born alive	0.12 (0.04)[2]			Yorkshire[2],
	0.08 (0.02)[4]			Large White[4],
	0.10 (0.03)[5]	0.11 (0.02)[8]		Landrace[5 8]
Number of stillborn piglets	0.05 (0.03)[1]			3 dam lines[1]
	0.19 (0.02)[4]			Large White[4]
	0.05 (0.03)[5]			Landrace[5]
Proportion of stillborn piglets	0.13 (0.04)[2]			Yorkshire[2]
Stillbirth		0.04[3a]	0.10[3a]	Large White[3]
Individual survival at birth	0.042 (0.009)[6]	0.035 (0.006)[6]	0.057 (0.009)[6]	Landrace[6]
	0.01-0.04[10]	0.00-0.02[10]	0.04-0.12[10]	Dam lines[10]
		0.21[9]	0.15[9]	Crossbreds[9]
Total pre-weaning mortality		0.03[3b]	0.09[3b]	Large White[3]
Pre-weaning survival		0.24[9]	0.14[9]	Crossbreds[9]
Survivability to day 5	0.093 (0.012)[6]	0.056 (0.010)[6]	0.04 (0.008)[6]	Landrace[6]
Survivability from day 6 to weaning	0.015 (0.007)[6]	0.027 (0.011)[6]	0.03 (0.011)[6]	Landrace[6]
Individual birth weight	0.147 (0.016)[6]	0.090 (0.012)[6]	0.160 (0.016)[6]	Landrace[6]
		0.04[3b]	0.15[3b]	Large White[3b]
		0.36[9]	0.28[9]	Crossbreds[9]
Mean birth weigth	0.31 (0.05)[1]	0.32 (0.06)[8]		3 dam lines[1]
	0.39 (0.05)[2]			Yorkshire[2]
Mean body weight at 3 weaks of age	0.19 (0.04)[2]			Yorkshire[2]
		0.17 (0.02)[8]		Landrace[8]
Piglet mortality		0.02 (0.02)[7]	0.05 (0.01)[7]	Large White[7]
		0.06 (0.01)[7]	0.13 (0.02)[7]	Landrace[7]

h_t^2=total heritability; h_d^2=direct heritability; h_m^2=maternal heritability; [1]Hermesch *et al.* (2001); [2]Damgaard *et al.* (2003); [3]Arango *et al.* (2006) ([3a]Model 3, [3b]Model 1); [4]Canario *et al.* (2006); [5]Hellbrügge *et al.* (2008); [6]Su *et al.* (2008); [7]Ibanez-Escriche *et al.* (2009); [8]Canario *et al.* (2010); [9]Roehe *et al.* (2010); [10]Kapell *et al.* (2011)

Table S5: *Complete models tested for the single-trait analysis of piglet traits (linear results – for Landrace)*

			PWL						SB		BW
Model			1	2	3	4	5	6	1	2	1
			B B		CF CF		B CF				
Fixed effects	Parity		x	x					x	x	x
	Parity of foster dam				x	x	x	x			
	HYS[a]/Season[b]		x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[b]	x[b]	x[ab]
	Sex* only in LR		x	x	x	x	x	x	x*	x*	x
	BW		x		x		x		x		
Random effects	Animal	h^2	x 4918.56	x 1097.45	x 2230.66	x 6396.64	x 4918.56	x 1097.45	x 4692.42	x 3609.36	x 5632.87
	Dam	m^2	x 4998.06	x 1155.50			x 4998.06	x 1155.50	x 4794.88	x 3701.49	x 6953.16
	Foster dam	cfm^2			x 6499.14	x 2347.56					
	Litter	c^2	x 5053.11	x 1249.67					x 4977.98	x 3947.48	x 8021.67
	Foster litter	cfc^2			x 6625.86	x 2448.59	x 6625.86	x 2448.59			
Random effects	Full models (h^2, m^2, c^2)		x 5088.51	x 1264.94	x 6724.26	x 2684.27	x 5237.62	x 1476.85	x 5013.10	x 3965.35	x 8362.95
	Animal – Dam correlation (r_{AM})		x 5089.56	x 1266.78	x 6724.89	x 2684.36	x 5239.07	x 1478.94	5013.03	x 3965.82	x 8365.11
	LRT ($\Delta_{LogL} > 3 \rightarrow p<0.05$)		1.05	1.84	0.63	0.09	1.47	2.09	0.02	0.47	2.16

All models for SB and PWL were tested at logit link and linear level. Results on log-likelihoods presented here are given at linear level. Each model was tested for the significance ($p<0.05$) of r_{AM} by applying a likelihood-ratio test (LRT) in the full models applied. B B=Model in which biological dam and biological litter were fitted, CF CF=Model in which foster dam and foster litter were fitted, B CF= Model in which biological dam and foster litter were fitted, x=effect was included in the respective model, digits given under x are the respective log-likelihoods which were used to test for Δ_{LogL} = difference between log-likelihoods. *Sex was only used in LR for SB because in LW no sex was recorded for stillborn piglets. [a]Phenotypes were recorded in both farms for each line and a herd-year-season effect was modeled (HYS). [b]Records of stillborn piglets were only available in one farm, hence a seasonal effect was modeled.

Table S6: *Complete models tested for the single-trait analysis of piglet traits (linear results – for Large White)*

			PWL						SB		BW
Model			1	2	3	4	5	6	1	2	1
			B B		CF CF		B CF				
Fixed effects	Parity		x	x					x	x	x
	Parity of foster dam				x	x	x	x			
	HYS^a/Season^b		x^a	x^a	x^a	x^a	x^a	x^a	x^b	x^b	x^{ab}
	Sex* only in LR		x	x	x	x	x	x	x*	x*	x
	BW		x		x		x		x		
Random effects	Animal	h^2	x 387.25	x 4933.82	x 647.09	x 5656.77	x 4918.56	x 1097.45	x 9213.99	x 8490.07	x 4988.63
	Dam	m^2	x 5094.32	x 504.64			x 4998.06	x 1155.50	x 9265.44	x 8527.66	x 1425.47
	Foster dam	cfm^2			x 5588.89	x 746.12					
	Litter	c^2	x 5223.39	x 708.64					x 9332.21	x 8615.49	x 3032.72
	Foster litter	cfc^2			x 5802.14	x 1010.04	x 6625.86	x 2448.59			
Random effects	Full models (h^2, m^2, c^2)		x 5277.71	x 729.73	x 5844.07	x 1094.83	x 5347.89	x 827.77	x 9535.24	x 8625.95	x 3364.12
	Animal – Dam correlation (r_{AM})		x 5278.08	x 729.77	x 5844.16	x 1095.97	x 5348.10	x 827.79	x 9535.88	x 8626.12	x 3365.87
	LRT ($\Delta_{LogL} > 3 \rightarrow p<0.05$)		0.37	0.04	0.09	1.14	0.21	0.02	0.64	0.17	1.75

All models for SB and PWL were tested at logit link and linear level. Results on log-likelihoods presented here are given at linear level. Each model was tested for the significance ($p<0.05$) of r_{AM} by applying a likelihood-ratio test (LRT) in the full models applied. B B=Model in which biological dam and biological litter were fitted, CF CF=Model in which foster dam and foster litter were fitted, B CF= Model in which biological dam and foster litter were fitted, x=effect was included in the respective model, digits given under x are the respective log-likelihoods which were used to test for Δ_{LogL} = difference between log-likelihoods. *Sex was only used in LR for SB because in LW no sex was recorded for stillborn piglets. ^{a}Phenotypes were recorded in both farms for each line and a herd-year-season effect was modeled (HYS). ^{b}Records of stillborn piglets were only available in one farm, hence a seasonal effect was modeled.

Table S7: *Estimated variance components for piglet traits - Univariate models without logit link for survival traits*

Breed	BW (y/n)	Dam	Litter	σ_p^2	h^2±SE	m^2±SE$^{1)}$	c^2±SE$^{2)}$	r_{AM}±SE$^{3)}$
SB								
LR	yes	B	B	0.075 (±0.001)	0.0094 (±0.003)	0.0210 (±0.001)	0.046 (±0.003)	0.044 (±0.264)
	no	B	B	0.072 (±0.001)	0.007 (±0.003)	0.012 (±0.003)	0.051 (±0.003)	-0.293 (±0.253)
LW	yes	B	B	0.058 (±0.001)	0.003 (±0.003)	0.016 (±0.003)	0.036 (±0.003)	-0.383 (±0.278)
	no	B	B	0.060 (±0.001)	0.001 (±0.003)	0.009 (±0.003)	0.038 (±0.003)	-0.603 (±0.669)
PWL								
LR	yes	CF	CF	0.010 (±0.001)	0.024 (±0.004)	0.017 (±0.003)	0.050 (±0.03)	-0.218 (±0.156)
		B	CF	0.101 (±0.001)	0.023 (±0.004)	0.020 (±0.003)	0.045 (±0.003)	-0.325 (±0.141)
		B	B	0.100 (±0.001)	0.021 (±0.004)	0.018 (±0.003)	0.029 (±0.003)	-0.289 (±0.155)
LW	yes	CF	CF	0.087 (±0.001)	0.017 (±0.004)	0.018 (±0.003)	0.050 (±0.003)	0.091 (±0.199)
		B	CF	0.088 (±0.001)	0.013 (±0.003)	0.040 (±0.003)	0.042 (±0.002)	0.103 (±0.176)
		B	B	0.088 (±0.001)	0.011 (±0.003)	0.028 (±0.003)	0.042 (±0.003)	0.205 (±0.213)
LR	no	CF	CF	0.111 (±0.001)	0.017 (±0.004)	0.015 (±0.003)	0.063 (±0.003)	-0.123 (±0.209)
		B	CF	0.111 (±0.001)	0.016 (±0.004)	0.008 (±0.002)	0.051 (±0.003)	-0.444 (±0.150)
		B	B	0.111 (±0.001)	0.015 (±0.004)	0.009 (±0.002)	0.032 (±0.003)	-0.431 (±0.160)
LW	no	CF	CF	0.095 (±0.001)	0.011 (±0.003)	0.006 (±0.002)	0.058 (±0.003)	-0.422 (±0.194)
		B	CF	0.096 (±0.001)	0.010 (±0.003)	0.019 (±0.003)	0.047 (±0.002)	-0.055 (±0.206)
		B	B	0.096 (±0.001)	0.008 (±0.003)	0.012 (±0.002)	0.046 (±0.003)	-0.083 (±0.243)

BW=Individual birth weight, PWL=Pre-weaning loss, SB=Stillbirth, σ_p^2=Total phenotypic variance, h^2=Heritability, m^2=Maternal genetic effects, c^2=Common environment effects. CF=Cross-foster dam/litter, B=Biological dam/litter. LRT significance test: LogL complete model (CM) vs. LogL-reduced model=CM minus factor: $^{1)}$ CM vs. CM-dam and r_{AM}, $^{2)}$ CM vs. CM-litter, $^{3)}$ CM vs CM-r_{AM}. m^2 and c^2 effects were significant in all models tested and r_{AM} not significant in all CM models tested. *$P < 0.05$. Results for SB and BW are given for farms A and C due to missing phenotypes and birth weights for stillborn piglets in farms B and D.

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Publications and presentations

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