Animal (2019), **13:10**, pp 2114 – 2124 © The Animal Consortium 2019
doi:10.1017/S1751731119000430

animal

Invited review: Piglet survival: benefits of the immunocompetence

E. M. Heuß, M. J. Pröll-Cornelissen, C. Neuhoff, E. Tholen and C. Große-Brinkhaus†

Institute of Animal Science, University of Bonn, Endenicher Allee 15, 53115 Bonn, Germany

(Received 18 July 2018; Accepted 12 February 2019; First published online 15 March 2019)

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 programmes. 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 programme 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 programmes. 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.

Keywords: pig immunity, robustness, piglet survivability, piglet vitality, animal welfare

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.

Introduction

General implications

The number of weaned piglets per sow is the main determiner of the profitability of piglet production. Therefore, breeding organizations have focussed 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 programmes so far (Clapperton *et al.*, 2008). 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 programmes to improve piglet survivability.

† E-mail: cgro@itz.uni-bonn.de

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 2 to 3 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*., 2014). 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 ($G \times E$) 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, *postpartum*, 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, crossbreeds as well as with current and changing housing conditions.

In recent years, various authors (Clapperton *et al*., 2009; Flori *et al*., 2011) 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.

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 $G \times E$ interactions (Knap, 2005). Thereby, reaction norm models quantify $G \times E$ 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

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press

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).

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. However, the authors found the selection responses to be higher if the pathogen challenge is recorded (Mulder and Rashidi, 2017).

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).

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 NBA 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 1st 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 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).

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press

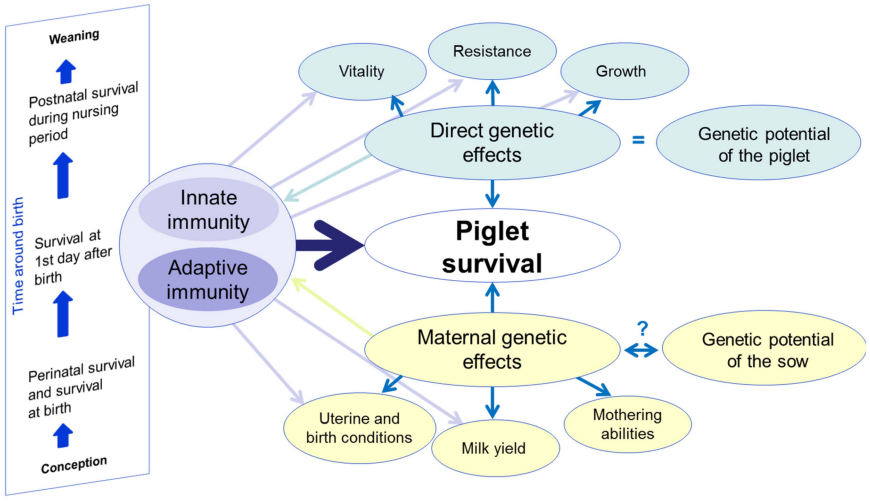

Figure 1 The connection between piglet survival and immunity. This figure captures the questions and knowledge gaps behind the relationships of the immunocompetence and piglet survival described in this review. Piglet survival is considered within the timeframe between conception and weaning. Thereby, 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 new-born to survive (modified according to Roehe *et al.*, 2009).

Relationship between immunity and piglet survival

The primary immune response of the piglet needs 7 to 10 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 *postpartum*. 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 1 to 4 days *postpartum*. 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, for example, 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 concentrations in piglets that were born later (Le Dividich *et al.*, 2017).

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.*, 2008). 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.

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press

Table 1 *Heritabilities ($h^2 \pm SEM$) in blood parameters of the porcine immune system (full table in Supplementary Material (Supplementary Table S3))*

Parameters	Henryon *et al.* (2006)	Clapperton *et al.* (2008)	Clapperton *et al.* (2009)	Flori *et al.* (2011)	Mpetile *et al.* (2015)	Ponsuksili *et al.* (2016)
Breed	Duroc, Landrace, Yorkshire	Large White	Large White, Landrace	Large White	Yorkshire	Landrace
n	4204	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)	
Platelets				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
Haematocrit				0.57 (0.03)	0.06 (0.14)	0.34

The relationships between the innate and adaptive immune response were estimated by Flori *et al.* (2011) 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.*, 2011). 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.

To our knowledge, only Clapperton *et al.* (2008 and 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.*, 2002; 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.

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press

Table 2 *Heritabilities (h² ± SEM) for survival traits in pigs (dam lines and crossbreds) (full table in Supplementary Material (Supplementary Table S4))*

Parameters	h_t2	h_d2	h_m^2	Breed
Number of piglets born alive	0.12 (0.04)[1]			Yorkshire[1]
	0.08 (0.02)[2]			Large White[2]
	0.10 (0.03)[3]			Landrace[3]
Number of stillborn piglets	0.19 (0.02)[2]			Large White[2]
	0.05 (0.03)[3]			Landrace[3]
Proportion of stillborn piglets	0.13 (0.04)[1]			Yorkshire[1]
Stillbirth		0.04[4a]	0.10[4a]	Large White[4]
Individual survival at birth	0.01 to 0.04[5]	0.00 to 0.02[5]	0.04 to 0.12[5]	Dam lines[5]
		0.21[6]	0.15[6]	Crossbreds[6]
Total pre-weaning mortality		0.03[4b]	0.09[4b]	Large White[4]
Pre-weaning survival		0.24[6]	0.14[6]	Crossbreds[6]
Individual birth weight		0.04[4b]	0.15[4b]	Large White[4b]
		0.36[6]	0.28[6]	Crossbreds[6]
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]Canario *et al.* (2006).
[3]Hellbrügge *et al.* (2008).
[4]Arango *et al.* (2006) ([4a]Model 3, [4b]Model 1).
[5]Kapell *et al.* (2011).
[6]Roehe *et al.* (2010).

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 focusses 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.

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).

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. Genome-wide association studies for domestic animals largely focussed 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 (Supplementary Table S1).

Immunity

Few publications focussing 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) (Supplementary 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 haemopoietic system. Interestingly, Rohrer *et al.* (2014) measured the colostrum intake of 5312 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.

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press

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).

Genome-wide association studies on traits related to piglet survival (Supplementary Table S2) were conducted for, for example, 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 QTL for litter size and its variability in Large White. The results of the mentioned studies above ranged from 1 to 65 associations comprising breed-specific QTL and revealed overlapping QTL 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, for example, 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).

Breeding strategies

Pig breeding programmes classically apply selection indexes based on estimated breeding values and the marginal economic value of each trait using multivariate BLUP 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 programmes (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 programmes using different approaches in northern Europe. However, most breeding strategies focussed 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 3 (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.*, 2002). The advantages of selecting for higher birth weights were regarded critically (Knol *et al.*, 2002). Roehe *et al.* (2009 and 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

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press

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 programme 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-optimized 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 focussed 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 interest 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*. (2011) discussed that selection for response to a specific pathogen 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 programme. 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.

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

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press

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 $G \times E$ 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.

Acknowledgements

This review is based on an invited presentation at the 68th Annual Meeting of the European Association for Animal Production held in Tallinn, Estonia, August 2017. Esther Heuß is funded by the 'pigFit' project which is supported by funds of German Government's Special Purpose Fund held at Landwirtschaftliche Rentenbank (FKZ28-RZ-3-72.038). The authors want to thank our project partners Dr Hubert Henne and Dr Anne Appel at Bundeshybridzuchtprogramm (BHZP GmbH) for providing their support. Furthermore, the authors thank Klemens Schulz at the Bundesverband Rind und Schwein e.V. (BRS e.V.) for providing important information on German pig production. In conclusion, many thanks to Katharina Roth and Christina Dauben for their huge support regarding table and figure design within this review as well as Mikhael Poirier and Dennis Miskel for their linguistic revision.

Declaration of interest

There is no potential conflicts of interest.

Ethics statement

None.

Software and data repository resources

None.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1751731119000430

References

Alonso-Spilsbury M, Ramirez-Necoechea R, Gonzalez-Lozano M, Mota-Rojas D and Trujillo-Ortega ME 2007. Piglet survival in early lactation: a review. Journal of Animal and Veterinary Advances 6, 76–86.

Arango J, Misztal I, Tsuruta S, Culbertson M, Holl JW and Herring W 2006. Genetic study of individual preweaning mortality and birth weight in Large White piglets using threshold-linear models. Livestock Science 101, 208–218.

Baxter EM, Jarvis S, D'Eath RB, Ross DW, Robson SK, Farish M, Nevison IM, Lawrence AB and Edwards SA 2008. Investigating the behavioural and physiological indicators of neonatal survival in pigs. Theriogenology 69, 773–783.

Baxter EM, Rutherford KMD, D'Eath RB, Arnott G, Turner SP, Sandøe P, Moustsen VA, Thorup F, Edwards SA and Lawrence AB 2013. The welfare implications of large litter size in the domestic pig II. Management factors. Animal Welfare 22, 219–238.

Blasco A, Martínez-Álvaro M, García M-L, Ibáñez-Escriche N and Argente M-J 2017. Selection for environmental variance of litter size in rabbits. Genetics, Selection, Evolution 49, 48.

Boddicker N, Waide EH, Rowland RRR, Lunney JK, Garrick DJ, Reecy JM and Dekkers JCM 2012. Evidence for a major QTL associated with host response to porcine reproductive and respiratory syndrome virus challenge. Journal of Animal Science 90, 1733–1746.

Canario L, Cantoni E, Le Bihan E, Caritez JC, Billon Y, Bidanel JP and Foulley JL 2006. Between-breed variability of stillbirth and its relationship with sow and piglet characteristics. Journal of Animal Science 84, 3185–3196.

Chase CCL and Lunney JK 2012. Immune system. In Diseases of swine, 10th edition (ed. JJ Zimmerman), pp. 227–250. Wiley-Blackwell, Chichester, UK.

Clapperton M, Bishop SC and Glass EJ 2005. Innate immune traits differ between Meishan and Large White pigs. Veterinary Immunology and Immunopathology 104, 131–144.

Clapperton M, Diack AB, Matika O, Glass EJ, Gladney CD, Mellencamp MA, Hoste A and Bishop SC 2009. Traits associated with innate and adaptive immunity in pigs: heritability and associations with performance under different health status conditions. Genetics Selection Evolution 41, 54.

Clapperton M, Glass EJ and Bishop SC 2008. Pig peripheral blood mononuclear leucocyte subsets are heritable and genetically correlated with performance. Animal 2, 1575–1584.

Colditz IG 2009. Allocation of resources to immune responses. In Resource allocation theory applied to farm animal production (ed. WM Rauw), pp. 192–209. CAB International Publishing, Wallingford, UK.

Colditz IG and Hine BC 2016. Resilience in farm animals: biology, management, breeding and implications for animal welfare. Animal Production Science 1961–1983.

Collins AM 2014. On-farm measures to monitor the health and immune status of pig. In Breeding focus 2014 – improving resilience (ed. S Hermesch and S Dominik), pp. 31–49. University of New England, Animal Genetics and Breeding Unit, Armidale, Australia.

Damgaard LH, Rydhmer L, Lovendahl P and Grandinson K 2003. Genetic parameters for within-litter variation in piglet birth weight and change in within-litter variation during suckling. Journal of Animal Science 81, 604–610.

Dekkers J, Rowland RRR, Lunney JK and Plastow G 2017. Host genetics of response to porcine reproductive and respiratory syndrome in nursery pigs. Veterinary Microbiology 209, 107–113.

Doeschl-Wilson AB, Villanueva B and Kyriazakis I 2012. The first step toward genetic selection for host tolerance to infectious pathogens. Obtaining the tolerance phenotype through group estimates. Frontiers in Genetics 3, 265.

Dyck MK and Swiersta EE 1987. Causes of piglet death from birth to weaning. Canadian Journal of Animal Science 67, 543–547.

Edwards SA 2002. Perinatal mortality in the pig: environmental or physiological solutions? Livestock Production Science 78, 3–12.

Edwards SA and Baxter EM 2015. Piglet mortality: causes and prevention. In The gestating and lactating sow (ed. C Farmer), pp. 253–278. Wageningen Academic Publishers, Wageningen, The Netherlands.

erzeugerring.info 2018. Erzeugerringdatenbank des Bundesverbandes Rind und Schwein e.V. Retrieved on June 26, 2018 from https://erzeugerring.info/.

Fay RA, Dey PL, Saadie CM, Buhl JA and Gebski VJ 1991. Ponderal index. A better definition of the 'at risk' group with intrauterine growth problems than

birth-weight for gestational age in term infants. The Australian & New Zealand Journal of Obstetrics & Gynaecology 31, 17–19.

Fix JS 2010. Relationship of piglet birth weight with growth, efficiency, composition, and mortality. PhD Thesis. North Carolina State University, Raleigh, NC, USA.

Flori L, Gao Y, Laloë D, Lemonnier G, Leplat J-J, Teillaud A, Cossalter A-M, Laffitte J, Pinton P, Vaureix C, de, Bouffaud M, Mercat M-J, Lefèvre F, Oswald IP, Bidanel J-P and Rogel-Gaillard C 2011. Immunity traits in pigs: Substantial Genetic Variation and Limited Covariation. PLos One 6, e22717.

Friggens NC, Blanc F, Berry DP and Puillet L 2017. Review: Deciphering animal robustness. A synthesis to facilitate its use in livestock breeding and management. Animal 11, 2237–2251.

Gluckman PD and Hanson MA 2005. The fetal matrix. Evolution, development, and disease. Cambridge University Press, Cambridge, UK.

Grandinson K, Lund MS, Rydhmer L and Strandberg E 2002. Genetic parameters for the piglet mortality traits crushing, stillbirth and total mortality, and their relation to birth weight. Acta Agriculturae Scandinavica, Section A – Animal Science 52, 167–173.

Guo X, Christensen OF, Ostersen T, Wang Y, Lund MS and Su G 2015. Improving genetic evaluation of litter size and piglet mortality for both genotyped and nongenotyped individuals using a single-step method. Journal of Animal Science 93, 503–512.

Guo X, Su G, Christensen OF, Janss L and Lund MS 2016. Genome-wide association analyses using a Bayesian approach for litter size and piglet mortality in Danish Landrace and Yorkshire pigs. Bio Med Central Genomics 17, 468.

Gutiérrez J, Nieto B, Piqueras P, Ibáñez N and Salgado C 2006. Genetic parameters for canalisation analysis of litter size and litter weight traits at birth in mice. Genetics Selection Evolution 38, 445.

Guy SZY, Thomson PC and Hermesch S 2012. Selection of pigs for improved coping with health and environmental challenges: breeding for resistance or tolerance? Frontiers in Genetics 3, 281.

Harper J, Bunter K, C Hine B, Hermesch S and M Collins A 2018. The association between measures of immune competence of boars and survival of their purebred progeny. In Proceedings of the World Congress on Genetics Applied to Livestock Production Volume Species - Porcine 2, 7–16 February 2018, Auckland, NZ, p. 368.

Hellbrügge B, Tölle K-H, Bennewitz J, Henze C, Presuhn U and Krieter J 2008. Genetic aspects regarding piglet losses and the maternal behaviour of sows. Part 1. Genetic analysis of piglet mortality and fertility traits in pigs. Animal 2, 1273–1280.

Henryon M, Heegaard PMH, Nielsen J, Berg P and Juul-Madsen HR 2006. Immunological traits have the potential to improve selection of pigs for resistance to clinical and subclinical disease. Animal Science 82, 597–606.

Hermesch S 2014. Breeding disease resilient pigs. In Breeding focus 2014 - improving resilience (ed. S Hermesch and S Dominik), pp. 5–18. University of New England, Animal Genetics and Breeding Unit, Armidale, Australia.

Hermesch S and Luxford BG 2018. Genetic parameters for white blood cells, haemoglobin and growth in weaner pigs for genetic improvement of disease resilience. In Proceedings of the World Congress on Genetics Applied to Livestock Production, 7–16 February 2018, Auckland, New Zealand, p. 384.

Hu Z-L, Park CA and Reecy JM 2016. Developmental progress and current status of the Animal QTLdb. Nucleic Acids Research 44, D827–D833.

Jonas E and Rydhmer L 2018. Effect of candidate genes for maternal ability on piglet survival and growth. Livestock Science 207, 83–90.

Kanis E, van den Belt H, Groen AF, Schakel J and Greef KH de 2004. Breeding for improved welfare in pigs: a conceptual framework and its use in practice. Animal Science 78, 315–329.

Kapell DNRG, Ashworth CJ, Knap PW and Roehe R 2011. Genetic parameters for piglet survival, litter size and birth weight or its variation within litter in sire and dam lines using Bayesian analysis. Livestock Science 135, 215–224.

Kause A 2011. Genetic analysis of tolerance to infections using random regressions. A simulation study. Genetics Research 93, 291–302.

Knap PW 2005. Breeding robust pigs. Australian Journal of Experimental Agriculture 45, 763–773.

Knap PW 2009. Robustness. In Resource allocation theory applied to farm animal production (ed. WM Rauw), pp. 288–301. CAB International Publishing, Wallingford, UK.

Knap PW 2014. Pig breeding goals in competitive markets. In Proceedings of 10th World Congress of Genetics Applied to Livestock Production, 18–22 August 2014, Vancouver, Canada, pp. 007.

Knap PW and Su G 2008. Genotype by environment interaction for litter size in pigs as quantified by reaction norms analysis. Animal 2, 1742–1747.

Knol EF 2001. Genetic aspects of piglet survival. PhD thesis, Wageningen University, Wageningen, The Netherlands.

Knol EF, Leenhouwers JI and van der Lende T 2002. Genetic aspects of piglet survival. Livestock Production Science 78, 47–55.

Knol EF, Nielsen B and Knap PW 2016. Genomic selection in commercial pig breeding. Animal Frontiers 6, 15–22.

Le Dividich J, Charneca R and Thomas F 2017. Relationship between birth order, birth weight, colostrum intake, acquisition of passive immunity and pre-weaning mortality of piglets. Spanish Journal of Agricultural Research 15, e0603.

Le Dividich J, Rooke JA and Herpin P 2005. Nutritional and immunological importance of colostrum for the new-born pig. Journal of Agricultural Science 143, 469–485.

Lu X, Liu J-F, Gong Y-F, Wang Z-P, Liu Y and Zhang Q 2011. Mapping quantitative trait loci for T lymphocyte subpopulations in peripheral blood in swine. Bio Med Central Genetics 12, 79.

Magnusson U, Wilkie B, Mallard B, Rosendal S and Kennedy B 1998. Mycoplasma hyorhinis infection of pigs selectively bred for high and low immune response. Veterinary Immunology and Immunopathology 61, 83–96.

Mallard BA and Wilkie BN 2007. Phenotypic, genetic and epigenetic variation of immune response and disease resistance traits of pigs. Advances in Pork Production 18, 139–146.

Mallard BA, Wilkie BN, Kennedy BW and Quinton M 1992. Use of estimated breeding values in a selection index to breed Yorkshire pigs for high and low immune and innate resistance factors. Animal Biotechnology 3, 257–280.

Mangino M, Roederer M, Beddall MH, Nestle FO and Spector TD 2017. Innate and adaptive immune traits are differentially affected by genetic and environmental factors. Nature Communications 8, 13850.

Merks JWM, Mathur PK and Knol EF 2012. New phenotypes for new breeding goals in pigs. Animal 6, 535–543.

Mormede P and Terenina E 2012. Molecular genetics of the adrenocortical axis and breeding for robustness. Domestic Animal Endocrinology 43, 116–131.

Mpetile Z, Young JM, Gabler NK, Dekkers JCM and Tuggle CK 2015. Assessing peripheral blood cell profile of Yorkshire pigs divergently selected for residual feed intake. Journal of Animal Science 93, 892–899.

Mulder HA 2016. Genomic selection improves response to selection in resilience by exploiting genotype by environment interactions. Frontiers in Genetics 7, 178.

Mulder HA, Hill WG and Knol EF 2015. Heritable environmental variance causes nonlinear relationships between traits: application to birth weight and stillbirth of pigs. Genetics Research 199, 1255–1269.

Mulder HA and Rashidi H 2017. Selection on resilience improves disease resistance and tolerance to infections. Journal of Animal Science 95, 3346–3358.

Nielsen B, Su G, Lund MS and Madsen P 2013. Selection for increased number of piglets at d 5 after farrowing has increased litter size and reduced piglet mortality. Journal of Animal Science 91, 2575–2582.

Onteru SK, Fan B, Du Z-Q, Garrick DJ, Stalder KJ and Rothschild MF 2012. A whole-genome association study for pig reproductive traits. Animal Genetics 43, 18–26.

Ponsuksili S, Reyer H, Trakooljul N, Murani E and Wimmers K 2016. Single- and Bayesian multi-marker genome-wide association for haematological parameters in pigs. PLoS One 11, e0159212.

Popescu L, Gaudreault NN, Whitworth KM, Murgia MV, Nietfeld JC, Mileham A, Samuel M, Wells KD, Prather RS and Rowland RRR 2017. Genetically edited pigs lacking CD163 show no resistance following infection with the African swine fever virus isolate, Georgia 2007/1. Virology 501, 102–106.

Raberg L, Graham AL and Read AF 2009. Decomposing health: tolerance and resistance to parasites in animals. Philosophical Transactions of the Royal Society B: Biological Sciences 364, 37–49.

Rashidi H, Mulder HA, Mathur P, van Arendonk JAM and Knol EF 2014. Variation among sows in response to porcine reproductive and respiratory syndrome. Journal of Animal Science 92, 95–105.

Rauw WM 2012. Immune response from a resource allocation perspective. Frontiers in Genetics 3, 267.

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press

Reiner G 2016. Genetic resistance - an alternative for controlling PRRS? Porcine Health Management 2, 27.

Roehe R and Kalm E 2000. Estimation of genetic and environmental risk factors associated with pre-weaning mortality in piglets using generalized linear mixed models. Animal Science 70, 227–240.

Roehe R, Shrestha NP and Mekkawy W 2009. Genetic analyses of piglet survival and individual birth weight on first generation data of a selection experiment for piglet survival under outdoor conditions. Livestock Science 121, 173–181.

Roehe R, Shrestha NP, Mekkawy W, Baxter EM, Knap PW, Smurthwaite KM, Jarvis S, Lawrence AB and Edwards SA 2010. Genetic parameters of piglet survival and birth weight from a two-generation crossbreeding experiment under outdoor conditions designed to disentangle direct and maternal effects. Journal of Animal Science 88, 1276–1285.

Rohrer GA, Rempel LA, Miles JR, Keele JW, Wiedmann RT and Vallet JL 2014. Identifying genetic loci controlling neonatal passive transfer of immunity using a hybrid genotyping strategy. Animal Genetics 45, 340–349.

Rootwelt V, Reksen O, Farstad W and Framstad T 2013. Postpartum deaths: piglet, placental, and umbilical characteristics. Journal of Animal Science 91, 2647–2656.

Rutherford KMD, Baxter EM, D'Eath RB, Turner SP, Arnott G, Roehe R, Ask B, Sandoe P, Moustsen VA, Thorup F, Edwards SA, Berg P and Lawrence AB 2013. The welfare implications of large litter size in the domestic pig I: biological factors. Animal Welfare 22, 199–218.

Rydhmer L 2000. Genetics of sow reproduction, including puberty, oestrus, pregnancy, farrowing and lactation. Livestock Production Science 66, 1–12.

Rydhmer L 2005. Swine breeding programmes in the Nordic countries. Retrieved on June 18, 2018 from http://www.nsif.com/conferences/2005/pdf%5CBreeding NordicCountries.pdf.

Schalm OW, Jain NC and Caroll EJ 1975. Veternity haematology, 3rd edition. Lea and Fabiger, Philadelphia, PA, USA.

Schneider JF, Rempel LA, Snelling WM, Wiedmann RT, Nonneman DJ and Rohrer GA 2012. Genome-wide association study of swine farrowing traits. Part II: Bayesian analysis of marker data. Journal of Animal Science 90, 3360–3367.

Sell-Kubiak E, Duijvesteijn N, Lopes MS, Janss LLG, Knol EF, Bijma P and Mulder HA 2015a. Genome-wide association study reveals novel loci for litter size and its variability in a Large White pig population. Bio Med Central Genomics 16, 1049.

Sell-Kubiak E, Wang S, Knol EF and Mulder HA 2015b. Genetic analysis of within-litter variation in piglets' birth weight using genomic or pedigree relationship matrices. Journal of Animal Science 93, 1471–1480.

Seutter U 1995. Einfluss von Rasse, Haltung, Fütterung, Management, Alter und Reproduktionsstadium auf hämatologische und klinisch-chemische Parameter beim Schwein. Ludwig-Maximilians-University, Munich, Germany.

Simms EL 2000. Defining tolerance as a norm of reaction. Evolutionary Ecology 14, 563–570.

Stear MJ, Bishop SC, Mallard BA and Raadsma H 2001. The sustainability, feasibility and desirability of breeding livestock for disease resistance. Research in Veterinary Science 71, 1–7.

Theil PK, Lauridsen C and Quesnel H 2014. Neonatal piglet survival. Impact of sow nutrition around parturition on fetal glycogen deposition and production and composition of colostrum and transient milk. Animal 8, 1021–1030.

Tizard IR 2013. Veterinary immunology, 9th edition. Elsevier/Saunders, St. Louis, MI, USA.

Trujillo-Ortega ME, Mota-Rojas D, Olmos-Hernández A, Alonso-Spilsbury M, González M, Orozco H, Ramírez-Necoechea R and Nava-Ocampo AA 2007. A study of piglets born by spontaneous parturition under uncontrolled conditions: could this be a naturalistic model for the study of intrapartum asphyxia? Acta Bio-Medica: Atenei Parmensis 78, 29–35.

van der Lende T and de Jager D 1991. Death risk and preweaning growth rate of piglets in relation to the within-litter weight distribution at birth. Livestock Production Science 28, 73–84.

Wang Y, Ding X, Tan Z, Ning C, Xing K, Yang T, Pan Y, Sun D and Wang C 2017. Genome-wide association study of piglet uniformity and farrowing interval. Frontiers in Genetics 8, 194.

Wang Y, Ding X, Tan Z, Xing K, Yang T, Pan Y, Mi S, Sun D and Wang C 2018. Genome-wide association study for reproductive traits in a Large White pig population. Animal Genetics 49, 127–131.

Watson H 2015. Biological membranes. Essays in Biochemistry 59, 43–69.

Wilkie B and Mallard B 1999. Selection for high immune response: an alternative approach to animal health maintenance? Veterinary Immunology and Immunopathology 72, 231–235.

Zhang F, Zhang Z, Yan X, Chen H, Zhang W, Hong Y and Huang L 2014. Genome-wide association studies for hematological traits in Chinese Sutai pigs. Bio Med Central Genetics 15, 41.

https://doi.org/10.1017/S1751731119000430 Published online by Cambridge University Press