Breeding for general disease resistance: a selection experiment in rabbits

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Abstract
We performed a selection experiment to investigate the possibility to improve resistance to non-specific diseases in rabbits. The selection criterion was a binary trait (healthy versus sick or dead) obtained from clinical signs of diseases occurring naturally on farm. A herd of 116 to 132 does and 30 bucks was bred based on this selection criterion. The heritability of the trait was 0.035 ± 0.009. After four generations of selection, the genetic progress was 1.5 genetic standard deviation, indicating that breeding for general disease resistance is feasible.

Introduction
Livestock populations are exposed to a variety of pathogens, not always identified, resulting in multifactorial diseases that are difficult to eradicate. For this reason, animal breeders and farmers are searching for robust strains of animals, able to cope with environmental stresses and to resist epizootics. However, a measure of individual responses to diseases resistance that is accurate, cheap, heritable and easy to perform on farm is difficult to obtain (Davies et al., 2009; Bishop and Woolliams, 2014). In this study, we performed a selection experiment to improve the general resistance of animals to the various diseases they may encounter. The selection criterion was a binary trait (healthy versus sick or dead) based on clinical signs of diseases occurring naturally on farms. The aim of our project was to investigate if selection for non-specific disease is possible based on this criterion in rabbits.

Materials & Methods

Trait.
The selection criterion was a binary trait (0 = morbid, sick or dead from digestive, respiratory, or other diseases, mostly from infectious origin; 1= healthy). Clinical signs were recorded at the INRAE experimental rabbit farm at a single time point toward the end of growth (63 days of age). The most likely cause of death was also recorded for rabbits that died between weaning and the end of the test. Clinical signs of diseases were recorded once in the young rabbit life, at 63 days of age, but not between weaning and the end of the test. Thus, rabbits categorized as healthy at 63 days of age might have been sick (exposed) individuals which recovered before recording (resistant or tolerant individuals). During the two years of the experiment, 10169 rabbits were recorded individually.

Animals.
A foundational herd of 132 females and 30 males was constituted from the INRA1777 rabbit line, a maternal line selected for litter size and for direct and maternal effects on weaning

weight. Throughout the experiment, animals were not exposed to any sort of antibiotic treatments. Reproducers were vaccinated against myxomatosis and Rabbit Hemorrhagic Disease (RHD). The herd was conducted with overlapping generations. The number of reproducing does varied between 116 to 132, while the number of available bucks was kept to 30. The reproduction interval was of 42 days. Between 300 to 900 kits were born in each batch. They were weaned at 35 days old and reared in groups of 5 kits during the fattening period. Litters were split after weaning to mix the genetic origins in each group. Weaned rabbits were fed *ad libitum* a commercial diet for growing rabbits (STABI-GREEN G, Terrya, Rignac, France).
The first 2 generations (10 batches) were reared in old facilities with standard cages (38*90*32 or 40*100*38). Then, the herd was moved to new facilities (renovated buildings, new housing systems: 46*90*70 or 46*90*60) from the eleventh batch.
Every 42 days, the best 30 females and 10 males were selected based on our selection criterion to become reproducers, with a constraint to limit inbreeding increase at 1% per generation, by using the Gencont software (Meuwissen, 2002). The selection was based on the genetic merit of the individuals, estimated from the information collected on all relatives tested in the pedigree to achieve the best possible accuracy.

Genetic analyses.
Variance components were computed with a restricted maximum likelihood method, using a single-trait animal linear model and a threshold model with a logit link function. Breeding values were estimated with the BLUP method using the linear model. Variances components and genetic values were estimated together with the ASReml 3.0 software (Gilmour et al., 2009). The models included a random additive polygenic effect and a random common litter effect. The significant fixed effects were the batch, parity of the dam, and gestation length. The estimated breeding values were used to estimate the genetic gain on the selection criterion. The linearity of the relationship between the means of the estimated breeding value per batch and the batch number was tested using a Fischer test from the Proc Reg of the SAS software.

Ethics.
All experiments were conducted in accordance with the guidelines of the Directive 2010/63/EU of the European Parliament and of the Council and were approved by the ethical review board (N° 115, under the code APAFIS#1812-201812121652792 v4).

Results & Discussion
In total, 14.9% of the rabbit showed clinical signs of diseases. The proportion of the main syndromes are shown in Table 1. Animals mostly suffered from digestive symptoms (in 68% percent of the cases), which could be related to Epizootic Rabbit Enteropathy (a gastrointestinal disorder of unknown aetiology) or to other digestive diseases caused by various pathogens.

The heritability of the selection criterion was low (Table 2), with a low genetic variance. This value was in the same range as previous studies in other rabbit lines (Gunia et al., 2015; Gunia et al., 2018), where the heritability estimates ranged from 0.03±0.003 to 0.10±0.02.

Table 1. Main disease syndromes recorded.

Syndromes	Number of rabbits	Proportion
Digestive symptoms	1024	68 %
Poor body condition	324	21 %
Rabbit Haemorrhagic Disease (RHD)	139	9 %
Other clinical signs	28	2 %
Total	1512	100 %

Table 2. Genetic components of the non-specific disease status.

	Threshold model (underlying scale)		Linear model (observed scale)	
	Value	Standard-error	Value	Standard-error
Genetic Variance	0.140	0.068	0.003	0.001
Heritability	0.027	0.013	0.032	0.009
Common litter effect	0.152	0.012	0.128	0.006

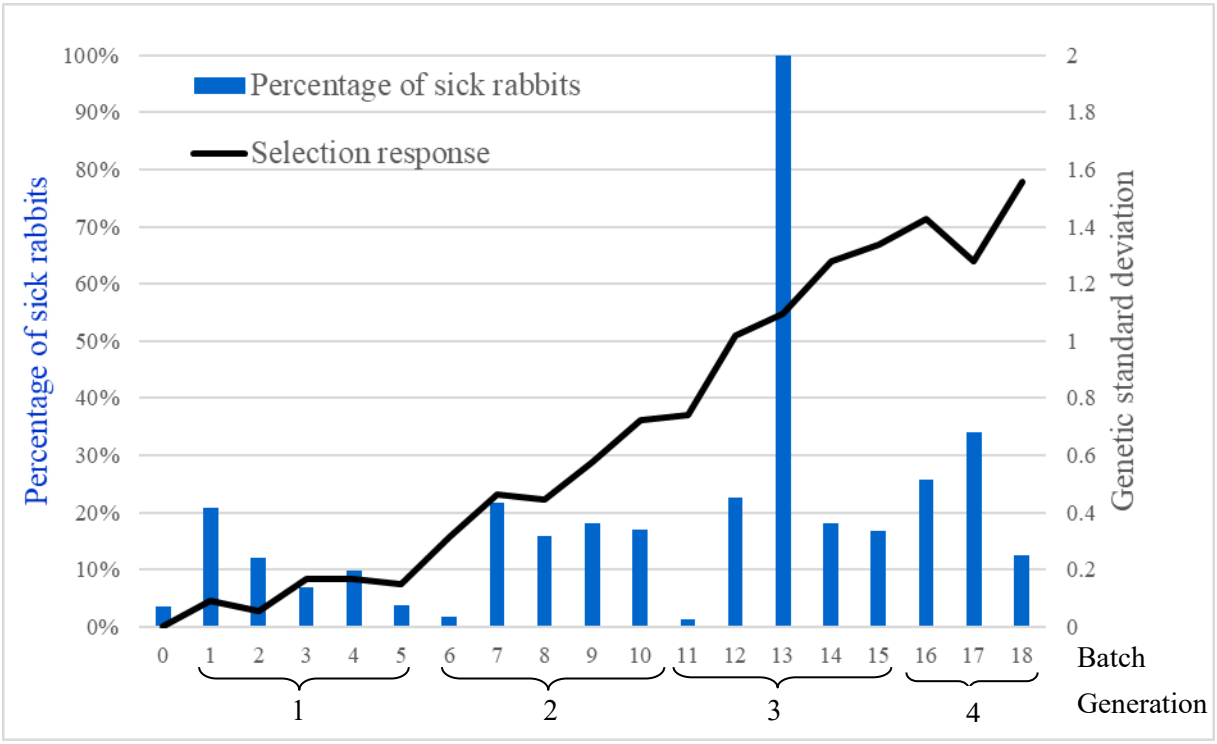

Figure 1. Proportion of sick rabbits (in percentage) per batch and predicted selection response for the proportion of healthy rabbit (in genetic standard deviation units).

We observed a linear ($p<0.001$) increase of the estimated selection response (Figure 1), reaching 1.5 genetic standard deviation after 18 batches (approximately 2 years, a batch being 42 days). The first generation (batch 1 to 5) was a transition from the foundational herd (batch 0) conducted with separated generation to the herd selected on disease resistance with overlapping generation. It explains why the genetic level remained stable from batch 1 to 5, before increasing at batch 6.

The percentage of sick or dead rabbits was on average 14.9% per batch. The very low percentage of sick rabbit in batch 11 (0.1%) was related to the installation of the herd to the renovated facilities. In batch 13, an outbreak of RHD occurred. This disease is lethal and

highly contagious. Sick rabbits were euthanised and all the other rabbit of this batch were culled to prevent contamination risk between batches and herds at the experimental facility. The culled rabbits were not considered in the experiment. The room and parcs were disinfected before introducing the next batch, and all fattening rabbits were vaccinated against RHD from batch 14.

Phenotypically, we did not see any progress or reduction in the number of sick rabbits (Figure 1). It is probably be due to the various pathogens that rabbits encountered in each batch. In addition, the type of pathogen and the pathogen loads may vary from batch to batch.

The first results of the selection experiment are promising. We did not perform a divergent section for ethical reasons. However, a comparison with a control herd is planned by the end of 2022. Embryos of the founder herd (before selection) were frozen. This final experiment will allow assessing the effect of selection by comparing the selected and control groups together in the same environment. Two contrasted environments (indoor in cages and outdoor on pasture) will be tested. Selected and control groups will be naturally exposed to the same pathogens within the same environment and thus will be able to express their various degree of disease resistance and/or tolerance.

Our results show that selection for health, without targeting any specific disease, is possible. We will assess if the results of selection in a specific environment are also validated in a different environment with different pathogens challenges.

Analyses on immune response traits and gut microbiota will now be performed to get a first insight into the mechanisms underlying this general disease resistance.

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