SMAll RuminanTs breeding for Efficiency and Resilience

Definition of resistance to disease and resilience in small ruminant: concepts, traits and recording, and genetic basis

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Scope

Genetic purpose

Small ruminants

Out of scope today: welfare & behaviour

New challenges for livestock breeding

The selection programs on production traits have been very effective since the 1960s!

Brito et al., Animal, 2021

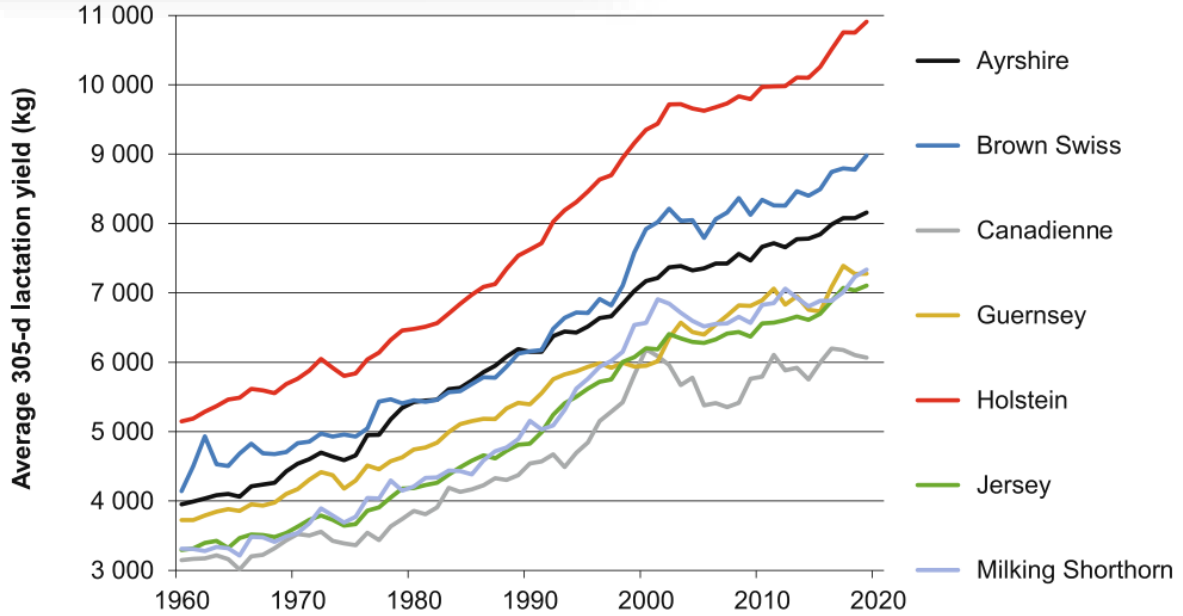


Fig. 2. Average 305-d lactation milk yield (kg) in dairy cattle breeds in Canada (thicker lines indicate the main worldwide dairy breeds). Data sou Information Centre, 2020 (www.dairyinfo.gc.ca).

New challenges

- ✓ Adverse effects on functional traits ?
- ✓ Lowering production costs
- ✓ Limiting the use of drugs
- ✓ Animal welfare
- ✓ …

Climate Change : a major challenge for livestock breeding

Different aspects of Disease Resistance and Resilience

Presentation Outline

1. **Resistance to identified diseases**
2. **Global health and adaptation capacities**
3. **Resilience as a dynamic response to stress**
4. **From discovery to application**

1. Disease resistance

Which diseases in small ruminants?

Table 4 : List and scores of infectious sheep diseases

Pathogen/disease	Industry concern	Economic impact	Public concern	Zoonotic potential	Animal welfare	International trade	Disease score	Genetic variation	OG rank within species	OG rank across species
Mastitis (dairy sheep)	3	3		1	2		9	3	4.5	6.5
GI parasites	3	3			2		8	3	4.3	6.3
Footrot	2	2			2		6	3	4	6
Mastitis (meat sheep)	2	2		1	2		7	2	3.2	5.2
Maedi visna	2	2			2		6	1	2	4
FMD	2	3	2		2	3	12		2	4
CLA	3	3		2	3		11		1.8	3.8
Sheep scab	3	2			3		8		1.3	3.3
CODD	2	2			3		7		1.2	3.2
Toxoplasmosis	2	1	1	2	1		7		1.2	3.2
Pneumonia	2	2			2		6		1	3
Chlamydial abortion	2	1	1	1	1		6		1	3

OG = operational genomics; GI = gastrointestinal; FMD = foot and mouth disease; CLA = caseous lymphadenitis; CODD = contagious ovine digital dermatitis.
[1]The scores (1, 2 or 3) indicate the relative strength of evidence, impact, concern or threat posed by each disease, with an absence of evidence indicated by no assigned value.

Davies G. et al., Animal, 2009

The main diseases in small ruminants: key figures

Mastitis

udder inflammation/infection with staphylococci (bacteria)
loss of milk due to subclinical infection, few clinical cases

Gastro-Intestinal (GI) parasites

infestation with nematodes
main constraint for grazing ruminants
lower production
resistance to anthelmintic due to extensive use

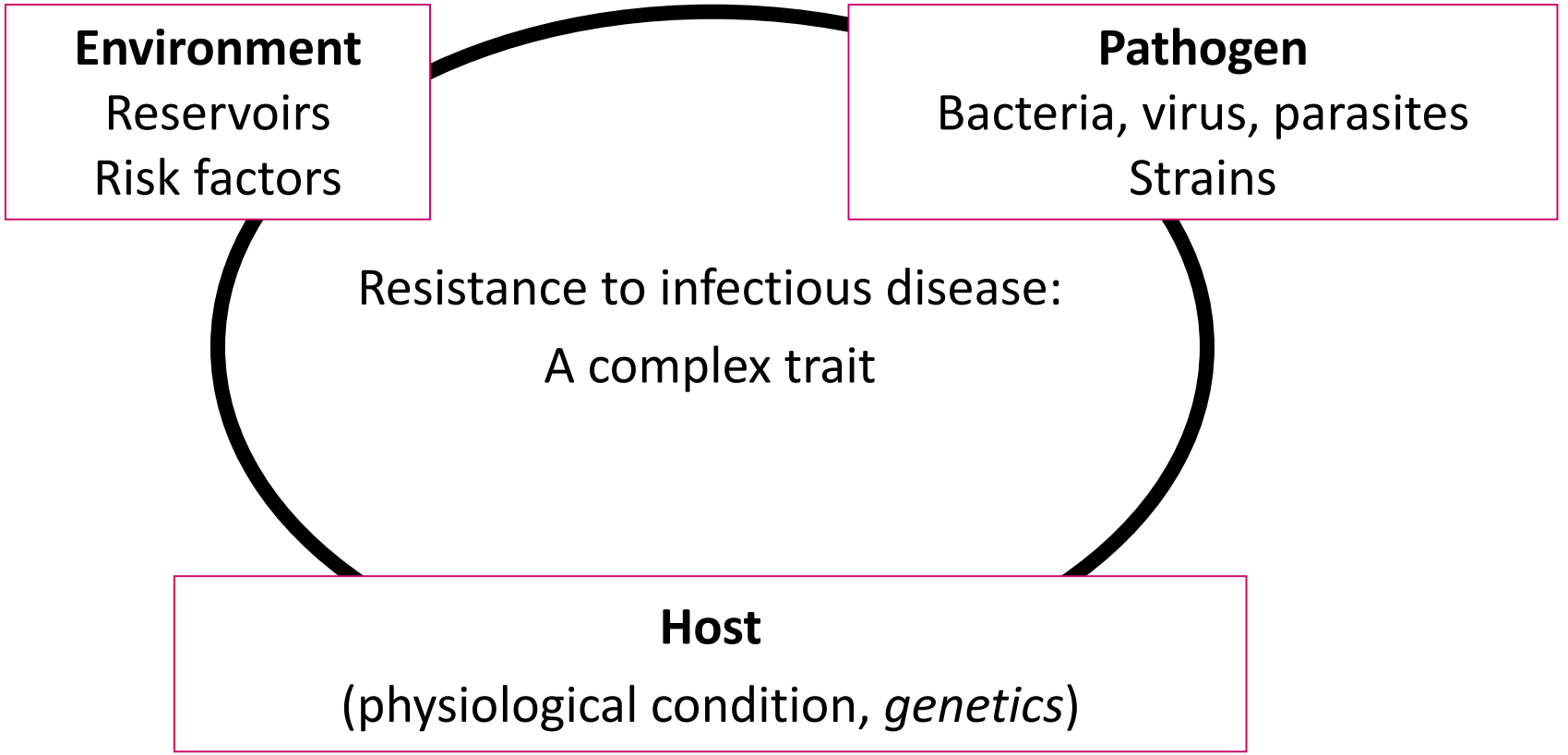
Footrot

infection of hooves with Dichelobacter nodosus bacteria
major cause of lameness in sheep
highly contagious, causes pain and welfare issues

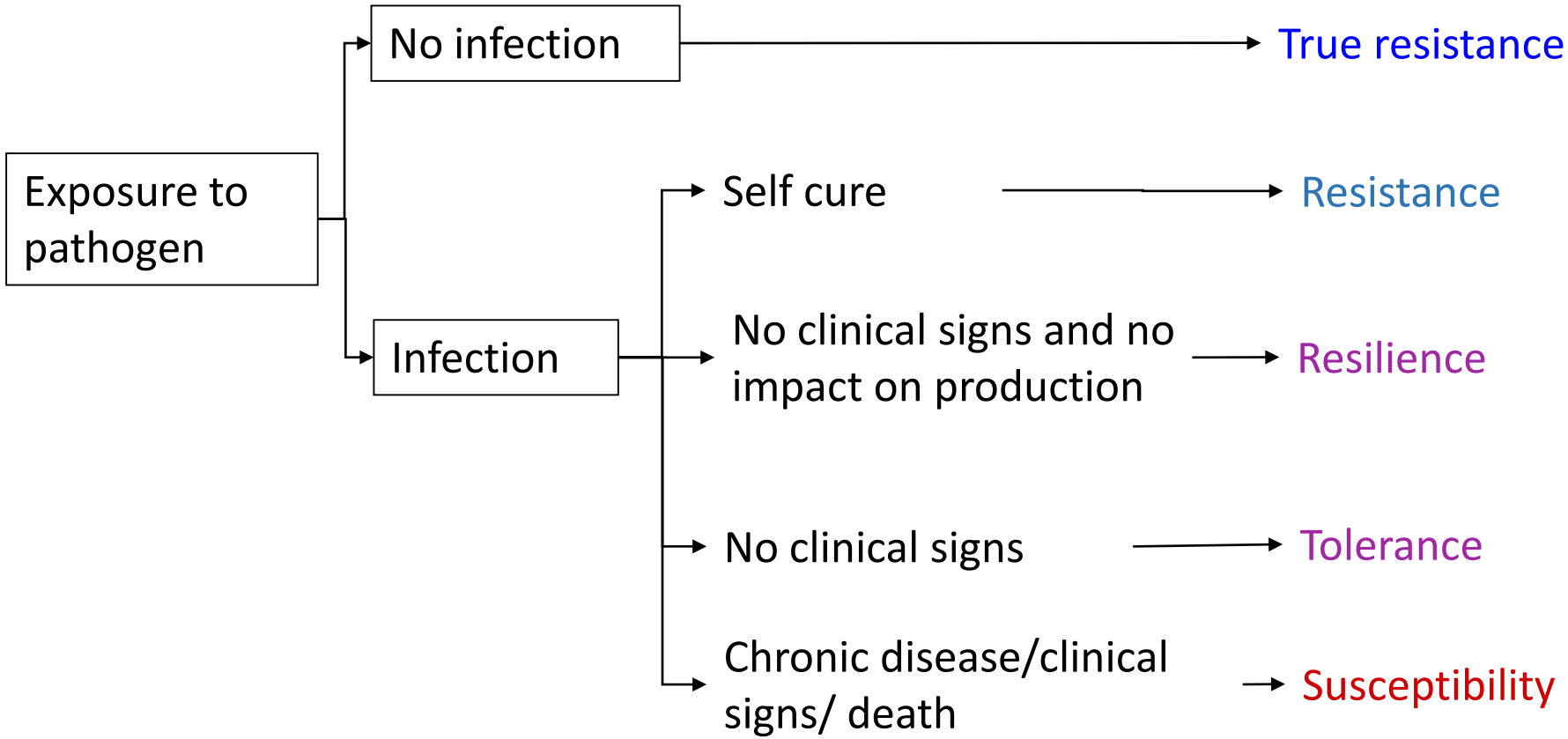
Maedi Visna & Caprine arthritis and encephalitis virus (CAEV)

general infection with lentiviruses
progressive disease
causes production loss and arthritis (mastitis)

Resistance to infectious diseases : definitions



Resistance to infectious diseases : definitions



Resistance to infectious diseases : measures

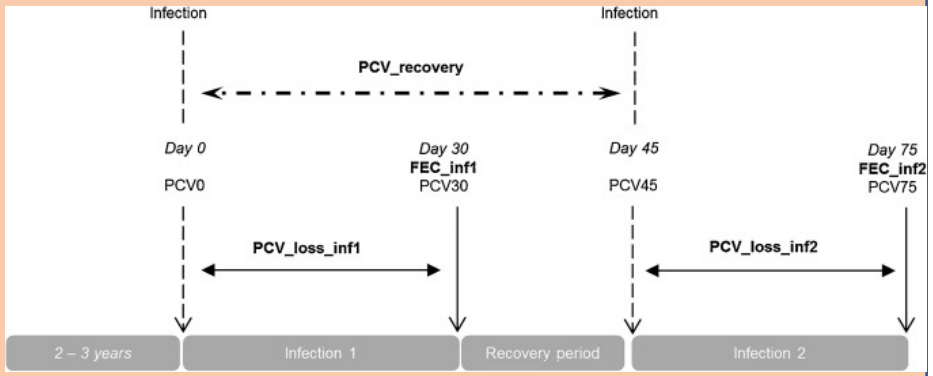
- **Natural infection condition** (field studies, experimental farms)
  - ☺ Numbers
  - ☹ Exposed/non exposed ?, limited measures

  Mastitis, footrot, lentiviruses

- **Experimental challenge / model challenge**
  - ☺ Control of pathogen strain, quantity, time
  - ☹ Workload, cost, small numbers

  GI Parasites, LPS model (mastitis)

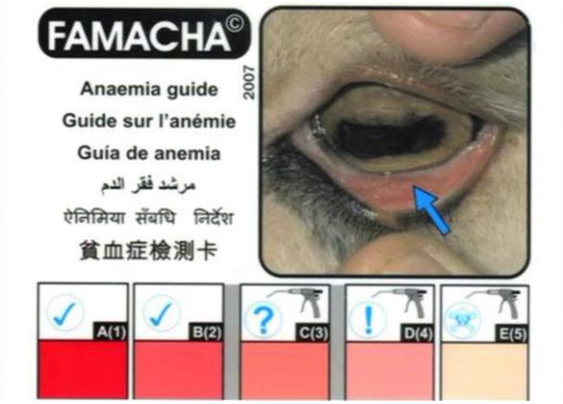
Fig. 1. Experimental design for ram infection.



Aguerre *et al., Vet. Parasitol* (2018)

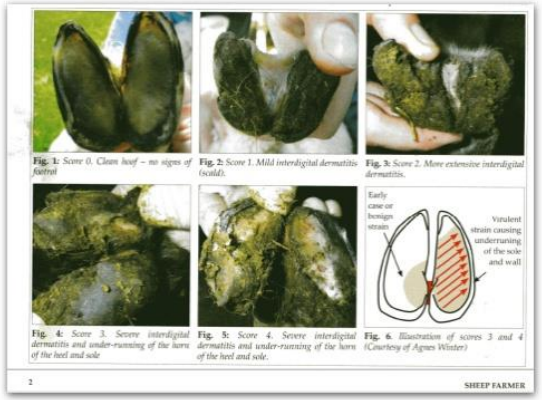
Resistance to infectious diseases : measures

- **Direct measures: diagnostic**
  - Clinical signs/death/autopsy : GI parasites, Footrot, arthitis (Caev)
  - Pathogen identification and quantification:
    - Antibody tests (Elisa): lentivirus (CAEV et VISNAE), IgA parasites
    - Observation in feces : nematodes (GI parasitism)
    - Bacteriology : Staphylococci (mastitis)

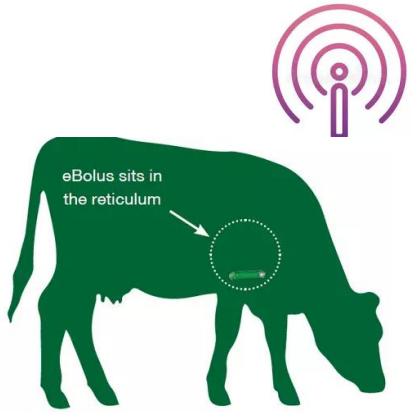


Famacha (GI parasites)

Dag score (GI parasites)



Hoove scoring (footrot)



Internal temperature (bolus)

Resistance to infectious diseases : measures

- **Indirect measures: prediction**
  - Inflammatory response : milk Somatic Cell Counts
    or California mastitis test (CMT) for mastitis
  - Immune response : cytokines, immunoglobulins (GI parasitism, mastitis)
  - Production losses: GI parasitism

Implemented in Smarter

California Mastitis Test

Genetic basis for disease resistance : heritability

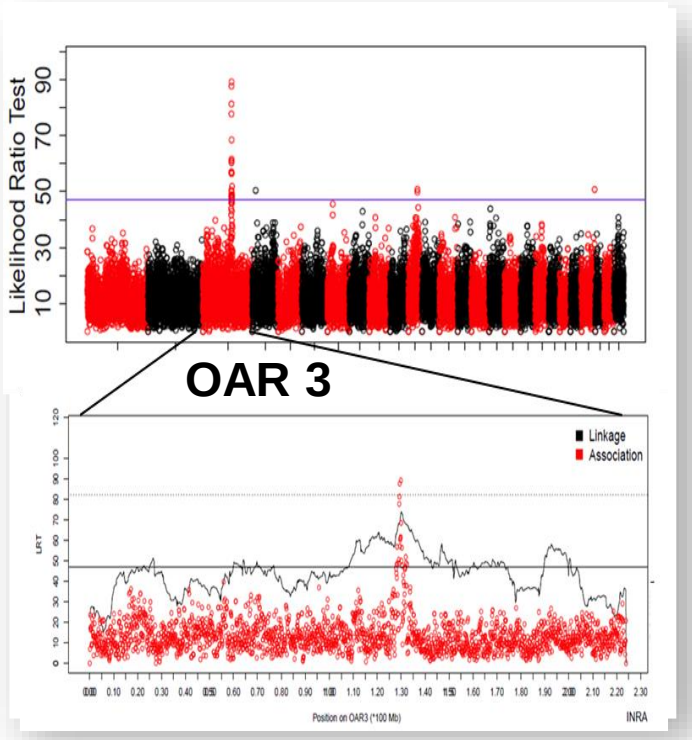
Disease	Measure	Heritability	Reference
Mastitis	Milk SCC	**0.13**±0.02– dairy sheep **0.21**±0.01– dairy goat **0.11**±0.04 – meat sheep	Mucha et al. 2022* McLaren et al. 2018
	California Mastitis Test	**0.08** ±0.04 – meat sheep **0.07** ±0.04 – meat sheep	McLaren et al. 2018 Kaseja et al. 2022*
	Clinical cases	**0.04** ±0.03 –meat sheep	O'Brien et al., 2017
GI Parasites	Faecal egg count	**0.07**±0.01 – dairy goat **0.14**±0.04 – dairy sheep **0.29**±0.03 - meat sheep	Mucha et al. 2022
	Alternative traits : Nb of worms, dagginess, Haematocrit FAMACHA© Cytokines, antibodies	**0.10**±0.02 to **0.32**±0.14 - meat sheep **0.30**±0.08 – dairy sheep **0.10** ±0.02 – meat sheep **0.14**±0.06 to **0.77**±0.09- meat sheep	Mucha et al. 2022 Werne et al. * Ciappesoni et al * Conington & Kaseja *
Footrot	Clinical scoring	**0.12**±0.02 - meat sheep	Kaseja et al. 2022*
CAEV	Elisa test	**0.026-0.128** – dairy goat	Brito et al. 2020

Throughout the presentation = In green: publications, or non published resultst from SMARTER project (*unpublished - Deliverables : D3.1, D2.3, D2.1)

Genetic basis for disease resistance : major genes from GWAS

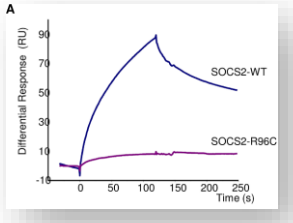
Example1. A major gene (SOCS2) associated with ovine mastitis

Lacaune sheep



- **Genome wise association study (GWAS)** for milk SCC : QTL on OAR3
- **Fine mapping** using whole genome sequencing 1 candidate mutation = a non-synonymous SNP in the ***SOCS2***
- **Functional test** : loss of link affinity

Mutation causes a defect of retro control of the inflammation and the chronic disease sets in.



The mutation explain 10% of the variance

Rupp *et al. BMC genetics* (2015)

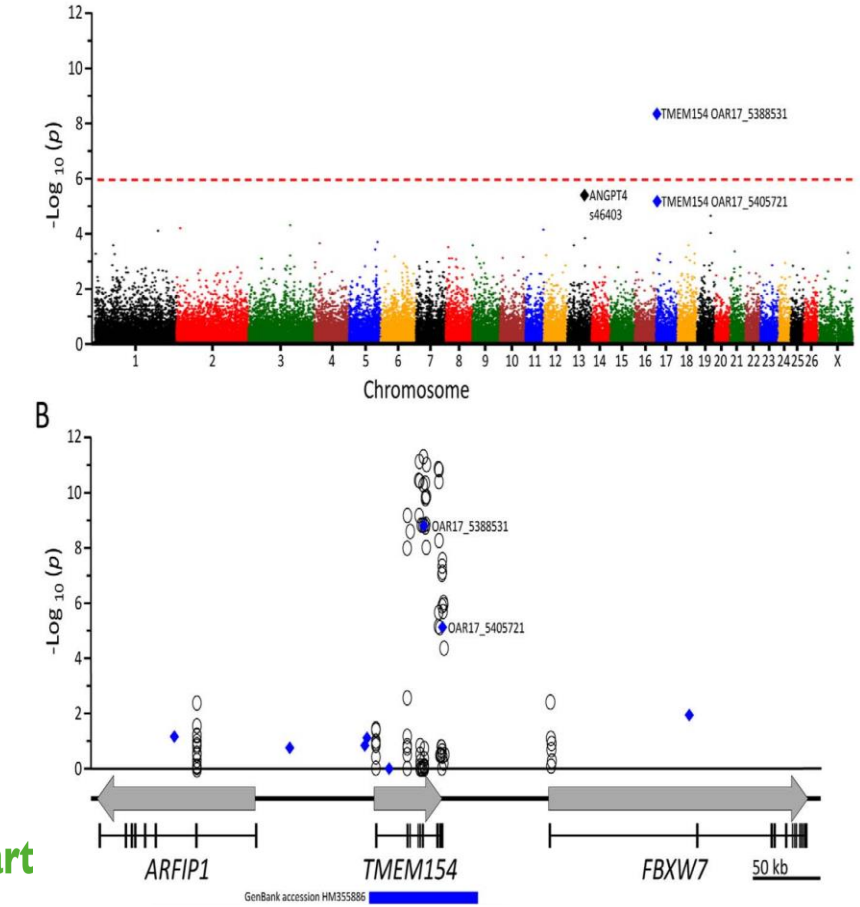
Oget *et al. BMC genetics* (2019)

- **Methods to include the major gene together with SCC in genomic evaluation**
- **Recommandation for use in breeding programmes**

Genetic basis for disease resistance : major genes from GWAS

Example2. A major gene (TMEM154) associated with Maedi-Visna in sheep

Heaton et al., PLoS Genet. 2012



69 Cas-control
(Test Elisa tests)
765 exposed sheep

!! Ancestral form of TMEM154 gene is 3X more at risk of being seropositive

Heaton et al., PLoS One 2013

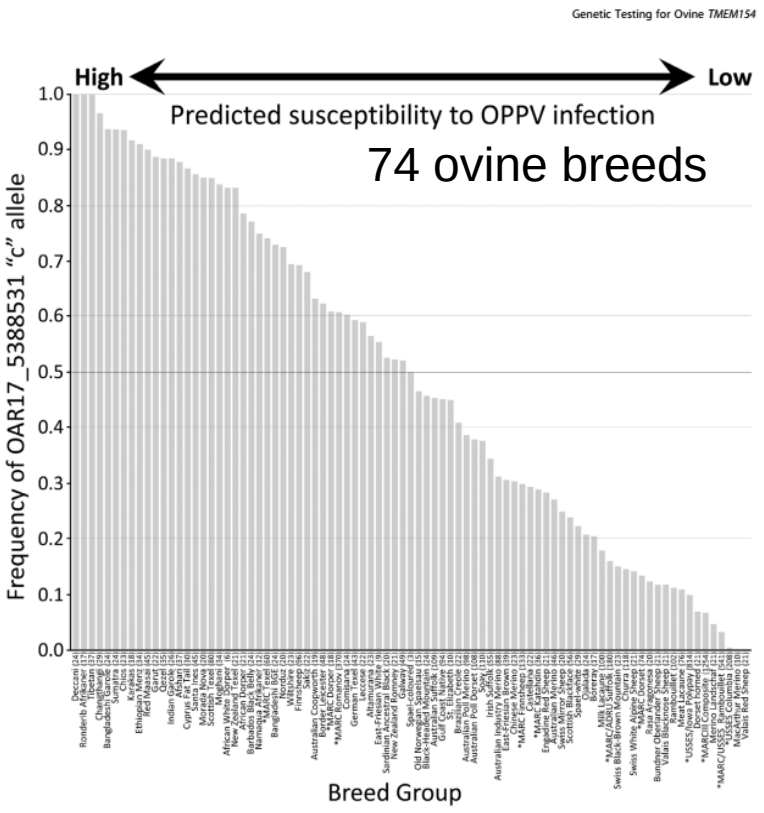


Figure 1. Estimating the frequency of highly-susceptible *TMEM154* alleles in global sheep populations. The "c" allele of SNP OAR17_5388531 is in linkage disequilibrium with the "g" nucleotide allele in codon 35 (gaa) of *TMEM154*. Genotypes for OAR17_5388531 were derived from the ISGC ovine SNP50k data set [11]. Numbers in parentheses for each breed group indicate the number of animals genotyped. The 11 breed groups with asterisks were genotyped for *TMEM154* E35 by Sanger sequencing [9] and were included for comparison with the 74 ISGC breed groups.
doi:10.1371/journal.pone.0055490.g001

What to do when you don't have an identified disease or pathogen?

2. Global Heath and Adaptation Capacities

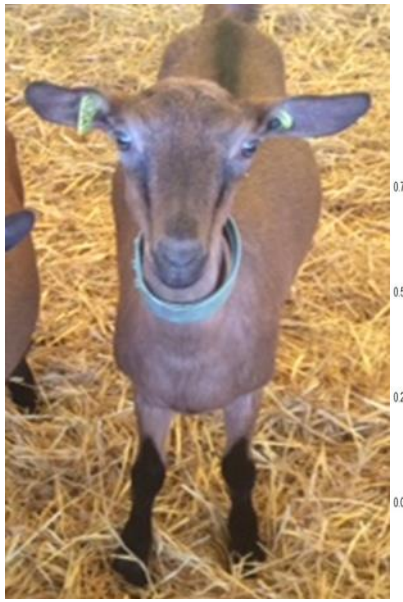
Global health : functional longevity

- **Longevity trait :** global cumulated resilience mechanisms including health
- **Measure : length of productive life** (Time interval between first lambing/kidding and culling)
- **From longevity to <u>functional</u> longevity *(correction for milk level)***

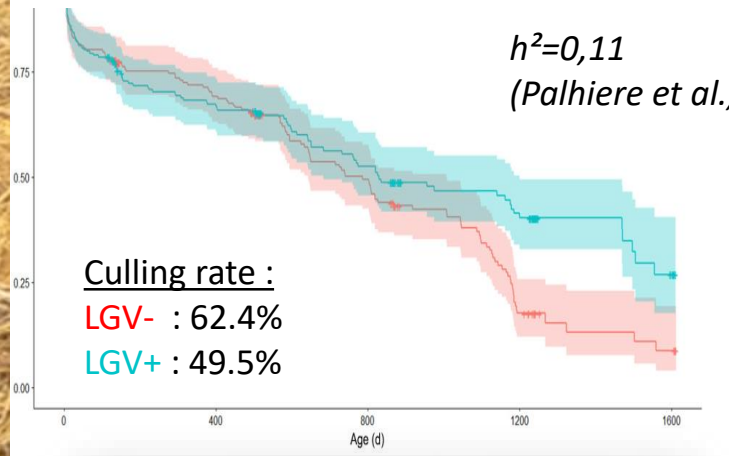
Heritability of functional longevity in dairy sheep

Chios sheep	h^2
length of productive life	0.13 ± 0.018

Vouraki et al., in prep



Results from a divergent selection experiment in Alpine dairy goat



h^2=0,11
(Palhiere et al., 2018)

<u>Culling rate :</u>
LGV- : 62.4%
LGV+ : 49.5%

Ithurbide et al.,2022

Global health : Survival of foetus and young animals

Sottish Blackface

- **Phenotypic data** : stillbirth, lamb vigour, birth assistance and suckling ability, foetus survival (pregnancy scan), lamb survival (from birth to given age)

Trait	Heritability	Reference
Stillbirth Foetal loss (Pregnancy scan to lambing) **Lamb survival** Lamb loss (lambing to weaning)	 **0.02** ±0.005 **0.02** ±0.01	Conington et al., unpublished Sottish Blackface ewes
Lamb survival Fate of maiden ewe lambs	**0.29**-**0.31**±0.03	McHugh et al., 2020 Belclare, Suffolk, Texel, and Llyen breeds
Lamb survival dead lambs/Total lambs born	0.12 **±**0,019	Vouraki et al., unpublished Chios sheep

Mine 50K SNP-chip data (without phenotype information) to identify mutations linked to embryonic death

- **Method**: reverse genetic screen method based on Homozygous Haplotype Deficiency (HHD) using 50K SNP-chip

  !! Need large genotype data sets !!

- **Results** : 13 lethal mutations linked to embryonic death, perinatal mortality and culling and created a list of 'at risk' matings for industry. Paper published GSE (Braiek et al., 2021)

- Using whole genome sequences, => 9 associated candidate lethal mutations linked to embryonic death, perinatal mortality and culling. At-risk matings to obtain homozygous lambs and to prove causality for some mutations in Lacaune (Ben Braik et al., 2022) and Manech Tete Rousse breeds (paper in draft)

Ben Braiek et al., 2021
Ben Braiek et al., 2022

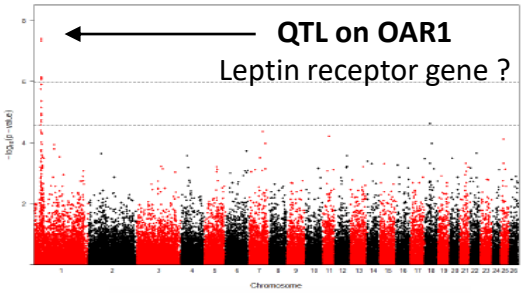
Adaptation capacity : the management of energetic body reserves

In extensive outdoor systems, the variation in nutritional intake is large and the exposure to climatic challenges is important => the animals' ability to adapt is put to the test

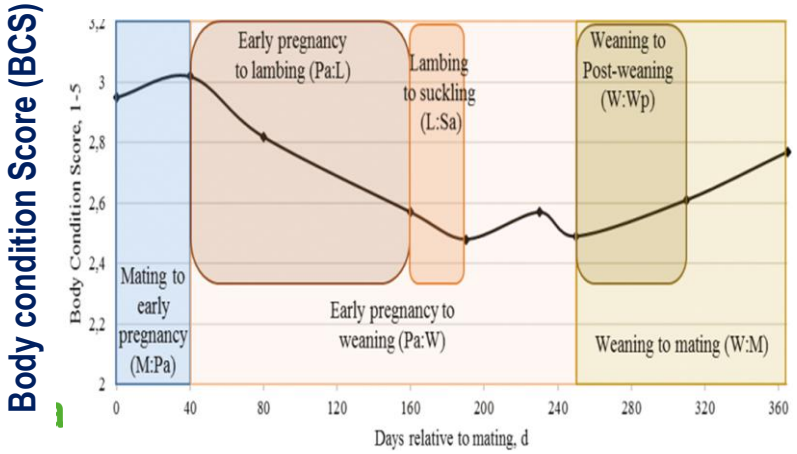
Smarter

Understand this adaptation through dynamic modeling of deposition and mobilization cycles of body reserves

Identification of a major QTL



Macé et al.,2022



The dynamics of body reserves is heritable

	h^2
mobilization	0.13 ±0.04
deposition	0.07 ±0.07

Macé et al.,2018

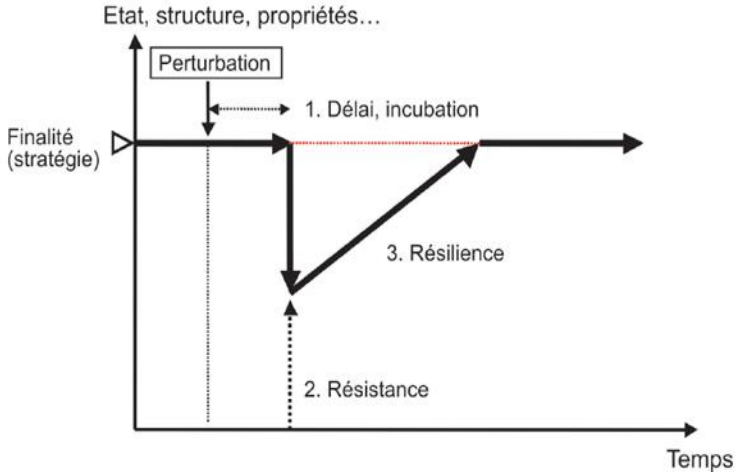
Also heritable in Scottish Blackface in extensively-managed hill farms
h^2=0,07-0,17 (*Conington et al, in prep*)

⇒adaptation predictor for selection

3. Resilience as a dynamic response to stress

Resilience

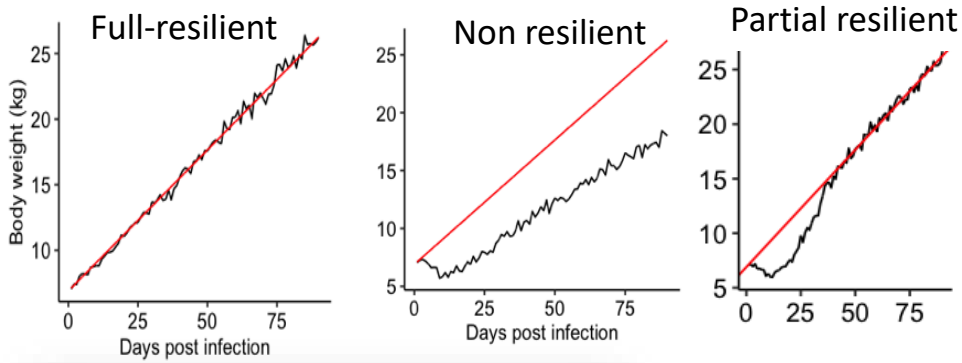
Biotic (pathogens) and abiotic (nutritional, thermal, emotional) stress



Dynamic response of a system to a disturbance

Sauvant et al., 2010

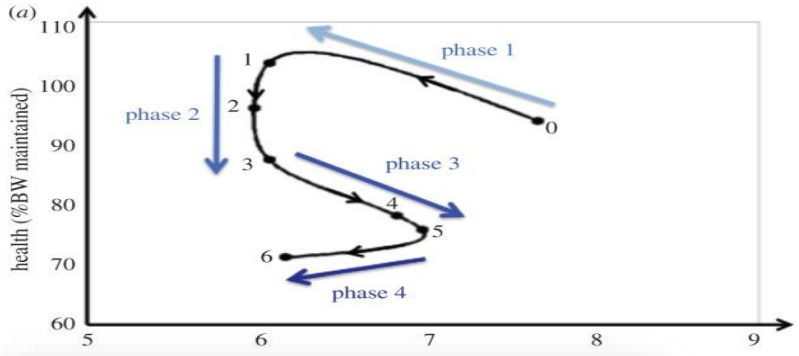
Unidimensional



Ghaderi Zefreh, in prep

Red: target trajectory
Black: real trajectory

Multidimensional trajectories



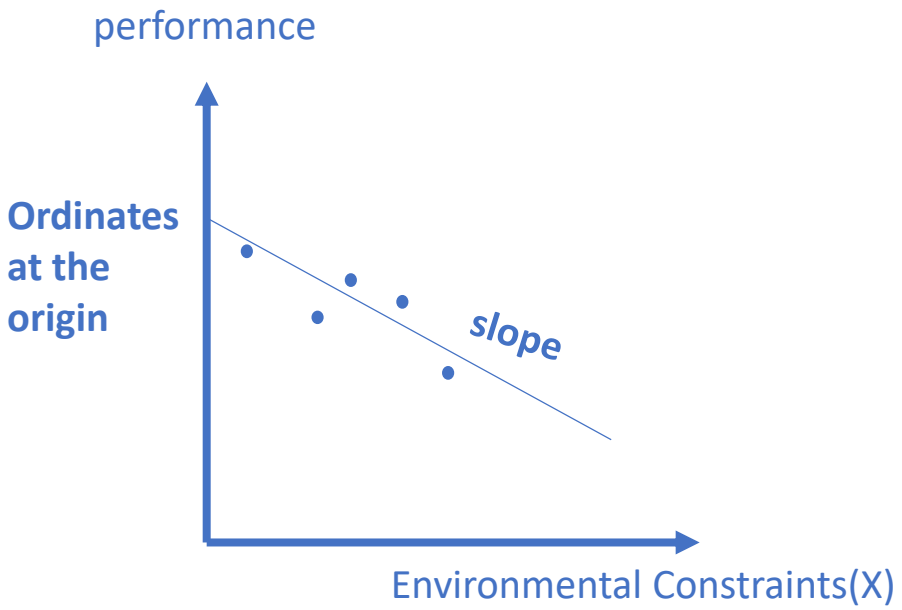
Doelsh-Wilson *et al*., 2015

Resilience vs. Robustness

Produce, reproduce, healthy in a wide variety of environments / in constrained environments

Knap, 2005 ; Friggens et al. 2017
Ducos et al. 2021

- robustness $\propto \frac{1}{|\mathbf{slope}|}$
- Production potential $\propto$ **Ordinates at the origin**



Resilience

- A Dynamic (possibly multidimentionnal) approcah of resilience
- Can be applied to health/immune/ traits but also to “classic” production traits
- Need high density records

Application in Smarter : feed efficiency data (Garcia-Baccino et al.,2021), cytokine response to LPS challenge (Pelayo et al., sub.), milk metabolite response to feed restriction (Ithurbide et al., sub.), …

These aspects will be developed in more detail in session 2 and 3 of the course

4. From discovery to application

The main questions to keep adressing

The correct traits ?

(true) resistance
Healthy carriers ?

Universality

Resistance to various species and strains ?
Risk for resistance ?

Selection for Genetic resistance

Effect on other traits ?

Loss of production ?
Other diseases ?

Correlated responses and relationships between traits

Results from divergent selection experiments

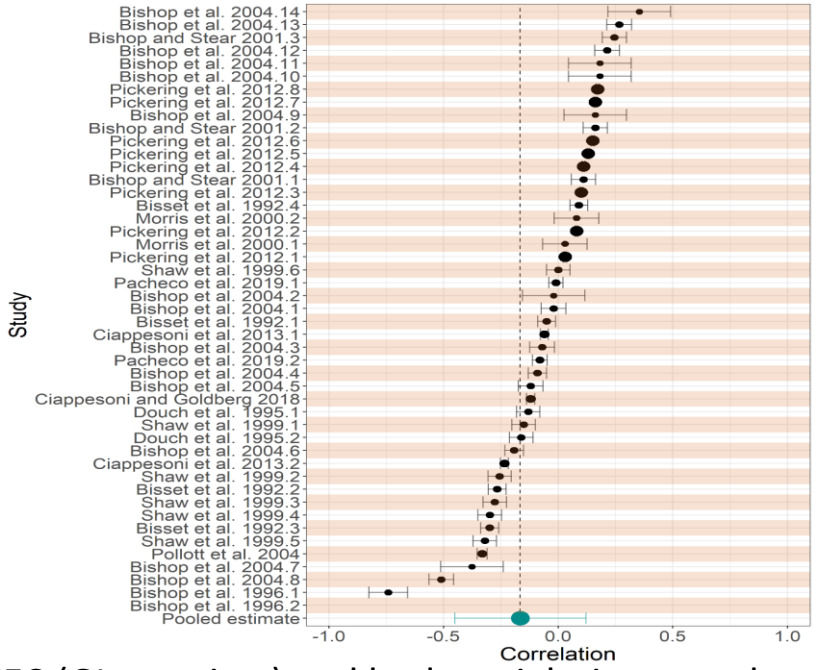
Selection criteria	Species	Results	Reference
SCC (mastitis)	Dairy sheep	✓ Favorable response on bacteria in milk (decreasing) and chronic mastitis ✓ Confirmed in experimental infection design	Rupp et al., 2009 Bonnefont et al., 2011
SCC (mastitis)	Dairy goat	✓ Favorable response on bacteria in milk ✓ No adverse effet on GI parasites	Rupp et al., 2019
Functional longevity	Dairy goat	✓ Favorable impact on length of life ✓ Positive link with mastitis and metablism	Ithurbide et al. 2022
Fecal egg counts (GI parasitism)	Meat sheep	✓ Fav. ✓ No impact on residual feed intake (RFI), feed conversion ratio (FCR), dry matter intake (DMI), average daily gain (ADG) or body weight (BW)	Feirreira et al., 2021
Fecal egg counts (GI parasitism)	Meat sheep	✓ No impact on body condition traits ✓ a cost of resistance on body weight detected	Douhard et al., 2022

Presentation on Tuesday

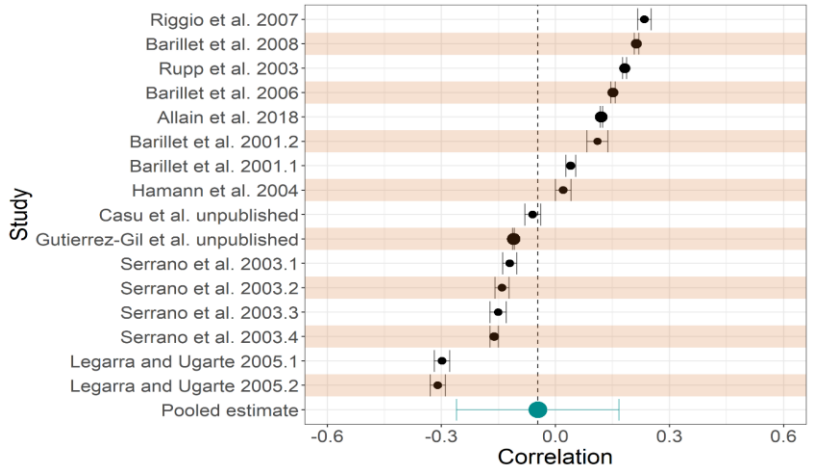
In green: studies in SMARTER project

Correlated responses and relationships between traits

Results from a meta analysis of genetic correlations in sheep and goat (Mucha et al., 2022)



FEC (GI parasites) and body weight in meat sheep



SCS (mastitis) and Milk yield and in dairy sheep

Forest plots showing genetic correlation estimates between:

Limited evidence of genetic antagonisms between resilience and efficiency for mastitis (dairy goats & sheep), and not for parasitism (meat sheep)=> Selection for both R&E feasible. Even though the pooled estimates were non significant, antagonisms may exist but only in specific populations and environments

Conclusions

- Many opportunities to select for disease resistance or resilience (**RR**) in small ruminants
- **Disease resistance** : pay attention to the meaning of the measures and their link with the pathogen and the expression of the disease
- **Resilience** : opportunity to re use existing high throughput data via relevant modelling
- **Heritability for RR** is in general lower than production trait
- **Genomic data** identified some major genes and may provide more tools in the future
- Globally, almost no **trade off** between RR traits, and rather few with production traits

  Trade off may exist but only in specific populations and environments


Thanks for your attention
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