Statistical models for planning the selective breeding against scrapie in sheep

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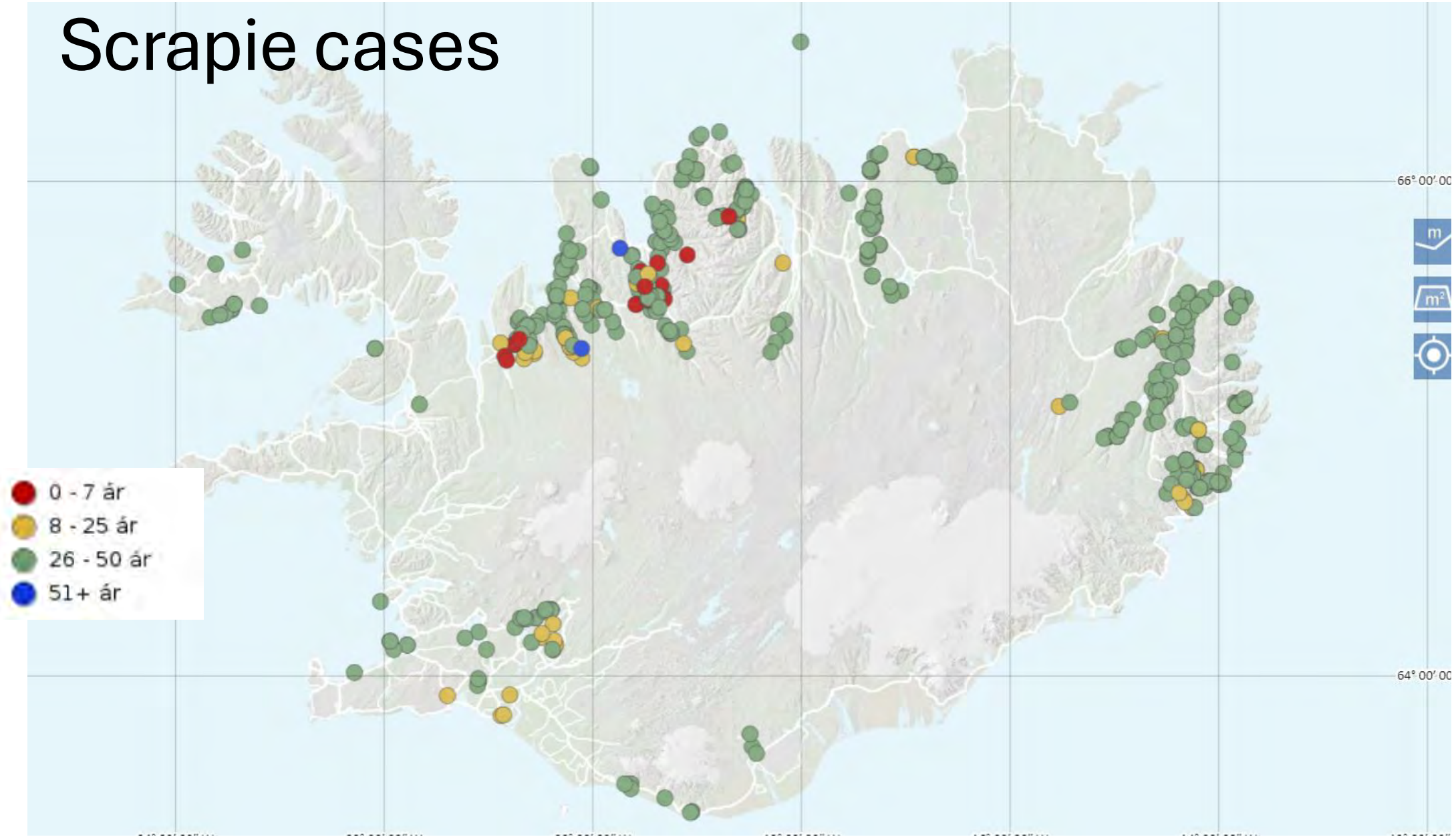
Scrapie

One of the transmissible spongiform encephalopathies (TSEs), prion diseases

BSE “mad cow” is also a TSE

- Transmissible
- Fatal
- No cure known
- The pathogen is an abnormal form of the prion protein

Scrapie cases

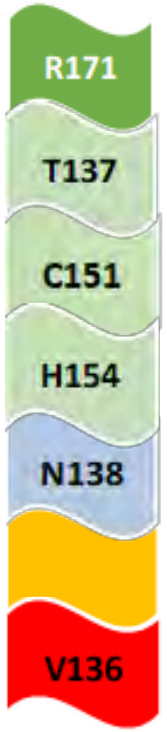


Mynd: Matvælastofnun

Genotype of the *PRNP* affects susceptibility

Each animal's *PRNP* genotype consists of two alleles

7 different alleles of *PRNP* known in Iceland



0.01%

0.1%

0.5%

7.8%

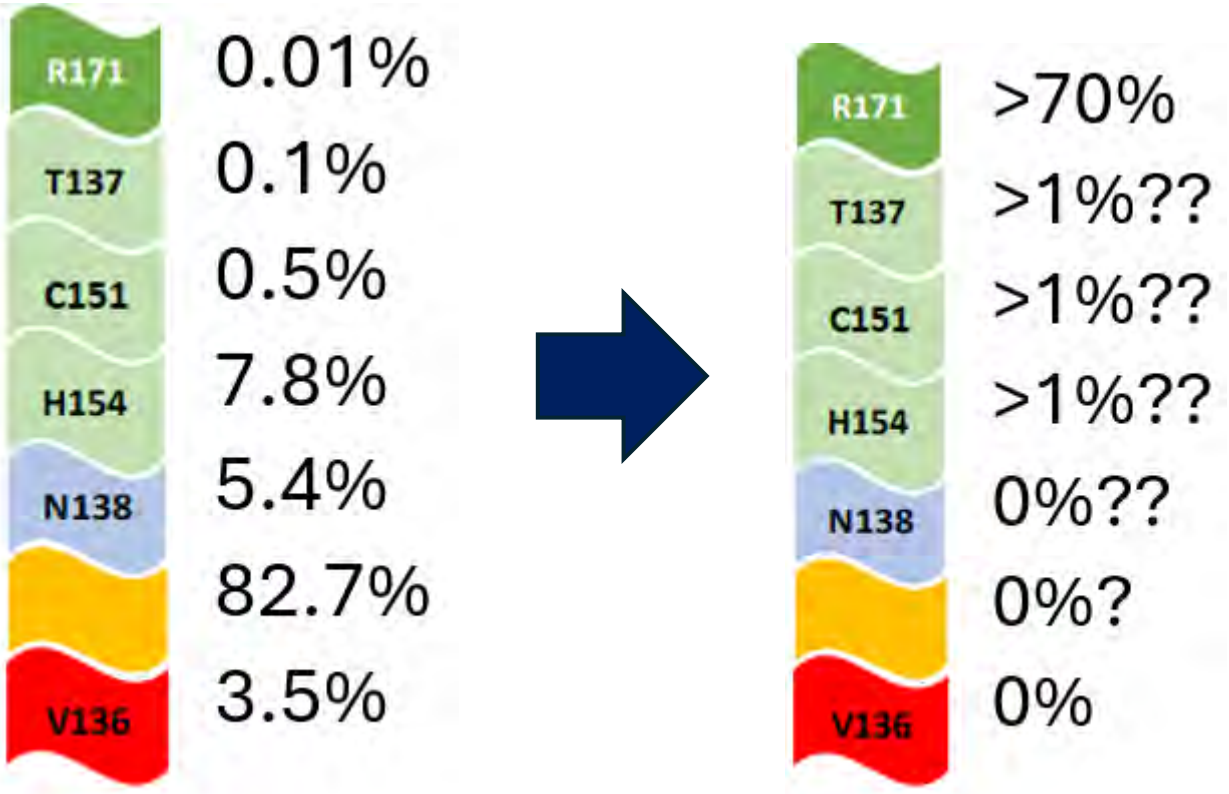
5.4%

82.7%

3.5%

How can we make the population resistant?

- Cost
- Time
- Production traits
- Inbreeding
- Genetic diversity



Breeding against scrapie

Effect of different strategies for introducing resistant genotypes estimated with stochastic simulations

Þórdís Þórarinsdóttir

Jón Hjalti Eiríksson

Background

- Can we make the population resistant to scrapie by selecting for the R171 allele?
- Few carriers raises worries:
  - Costly and takes long time
  - Selection for R171 slows genetic improvement in other traits
  - Inbreeding
  - Loss of genetic diversity

Methods

Stochastic simulation

Population size 130,000 breeding ewes

30,000 ewes on high-risk areas – 100,000 in low-risk

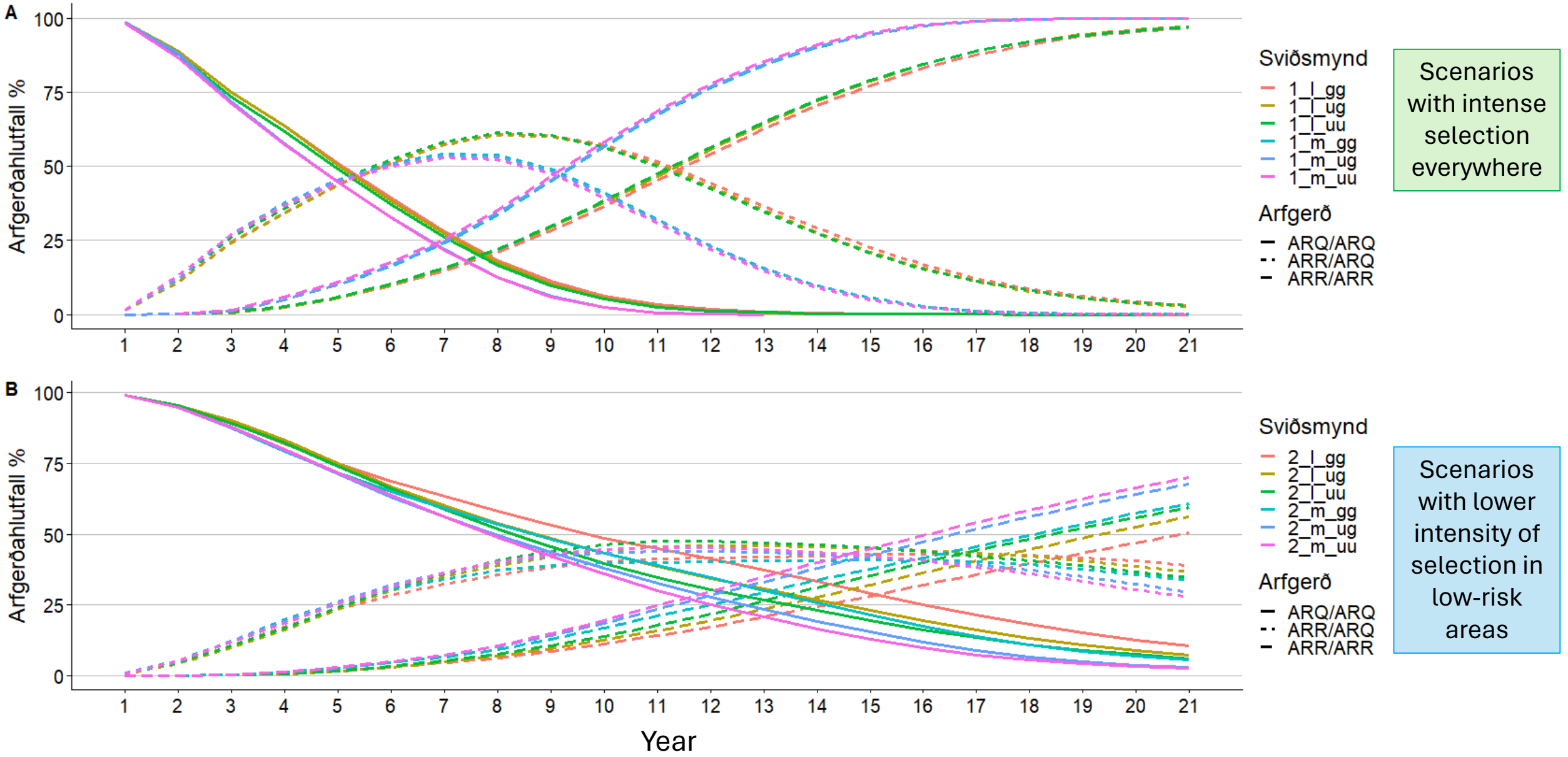
Population structure mimicking the Icelandic sheep population

“planted” in a few animals in one flock

The rest assumed wild-type

13 different scenarios

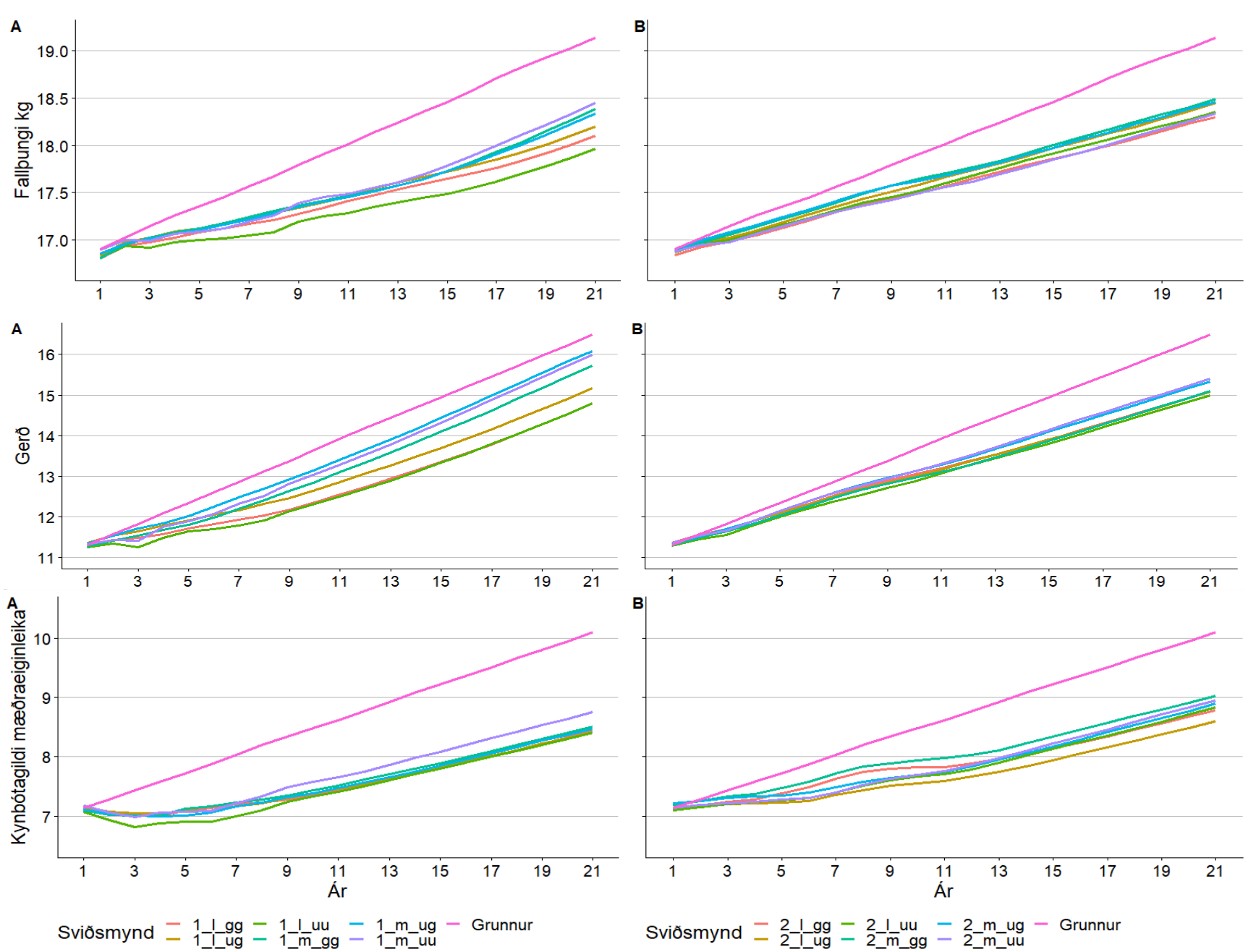
Genotype % in the population by years



Scenarios with intense selection everywhere

Scenarios with lower intensity of selection in low-risk areas

Genetic trend in production traits

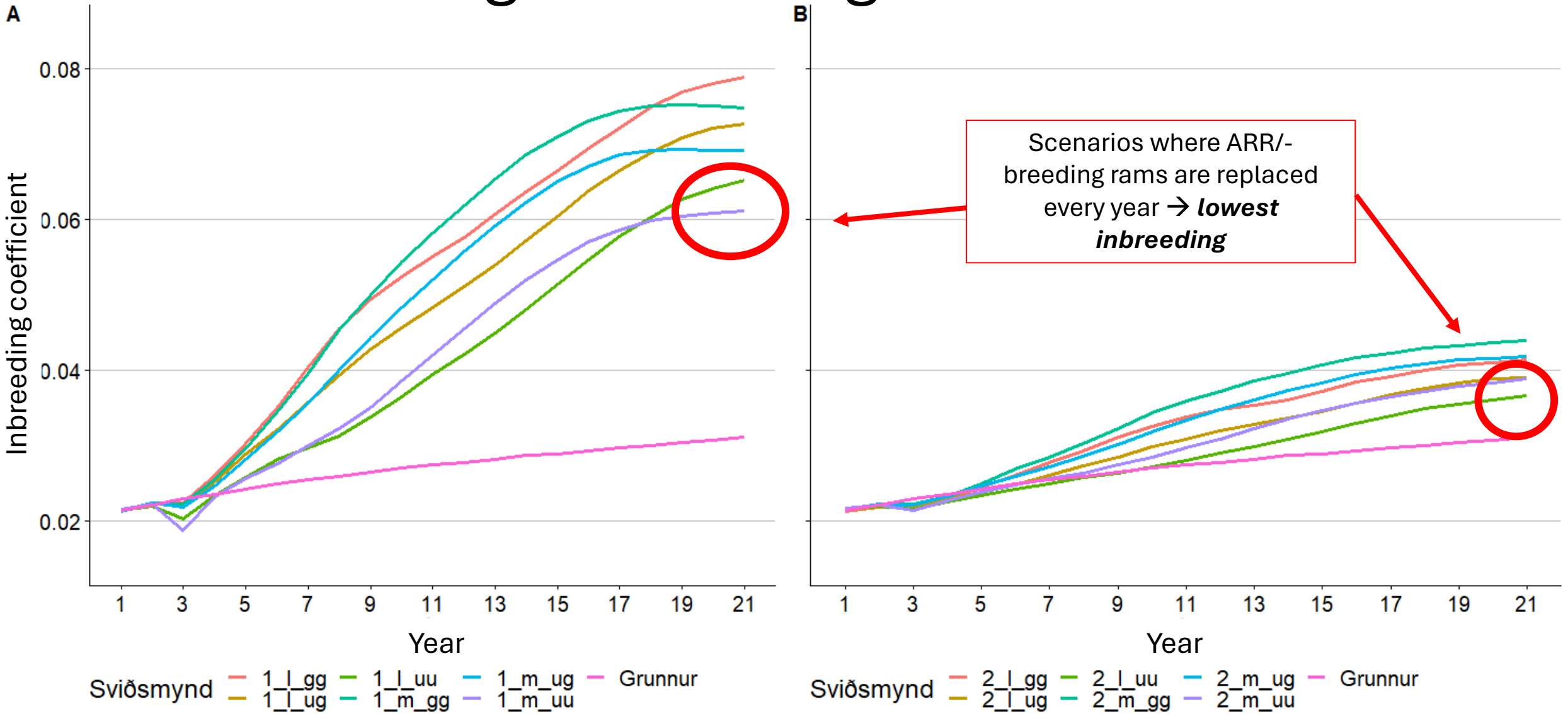


The pink line is the Base scenario

Scenarios with intense selection everywhere

Scenarios with lower intensity of selection in low-risk areas

Average inbreeding coefficient



Scenarios with intense selection everywhere

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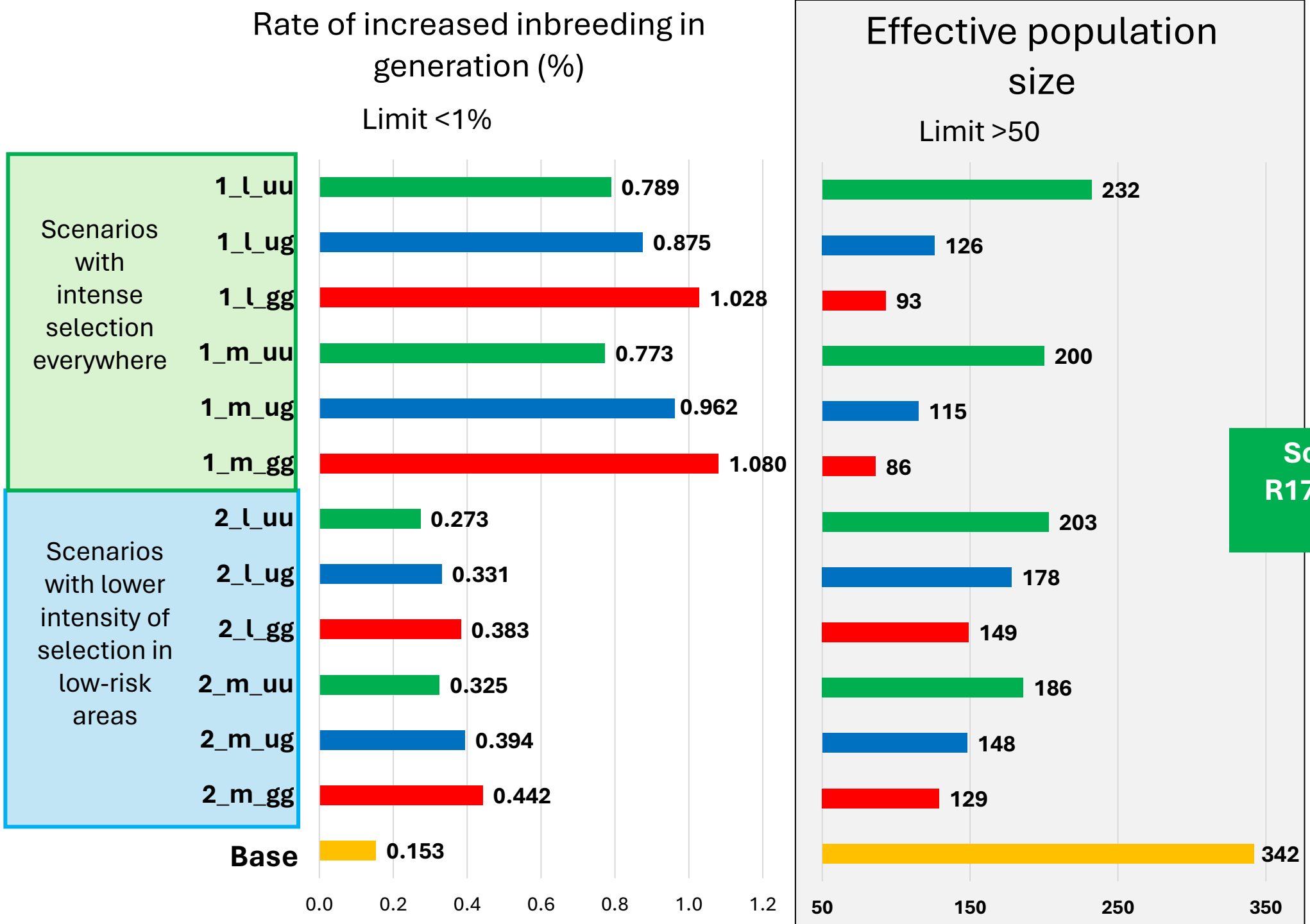

Scenarios with use of R171/- rams limited to 1 year

~ Conclusions ~

Despite few ARR carriers in the beginning:

- Making the population resistant to scrapie in less than 20 years is possible
- Negative impact on genetic improvement and inbreeding
- Limiting the use of the same ARR/- breeding rams to 1 year in the beginning is an effective way to reduce risk

Estimated breeding value (EBV) for relative scrapie susceptibility

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Objectives

We cannot genotype all sheep – and we don't have to!

1. Predict *PRNP* genotypes in ungenotyped sheep based on pedigree

2. Compile existing estimates of the relative scrapie susceptibility (RSS) associated with different *PRNP* genotypes

3. Calculate estimated breeding value (EBV) of RSS based on the predicted genotype + genotypic RSS

EBV for RSS - methods

(Estimate of) number of alleles $\hat{\gamma}_{i,j}$

Multi-trait linear model based on pedigree

Estimate of susceptibility of the genotypes $\hat{g}_{k,l}$

Meta-analyses of published odds-ratio (as far as they are available)

10 papers found on PubMed

RSS from meta-analysis. The numbers are ln() of odds ratio relative to ARQ/ARQ in affected flocks

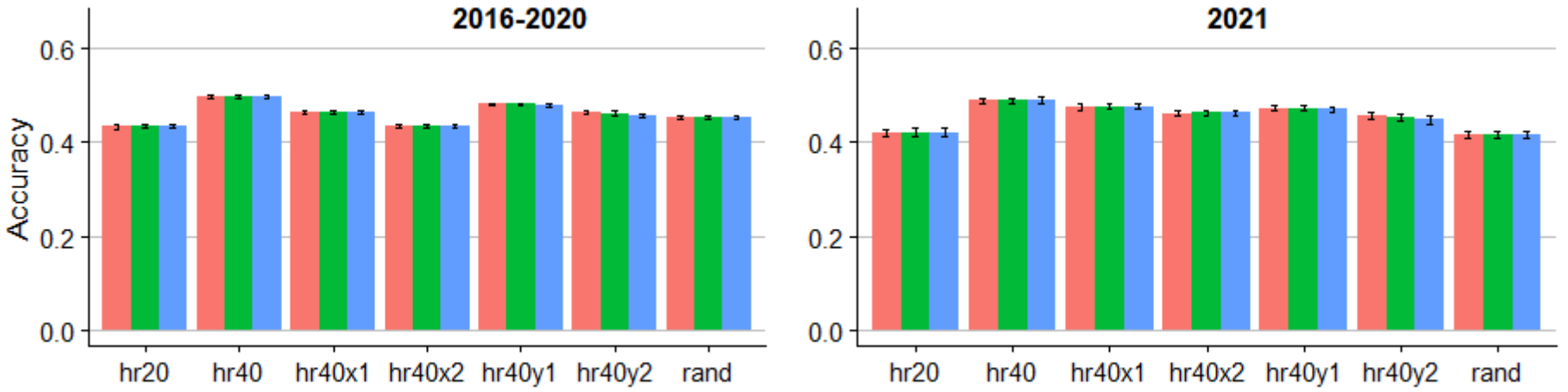
Coloured is based on data

Extrapolated, assuming T137 is dominant, N138=ARQ and C151=AHQ

	V136		N138	H154	C151	T137	R171
V136	2.45						
	1.81	0					
N138	1.81	0	0				
H154	-2.4	-1.48	-1.48	-1.94			
C151	-2.4	-1.48	-1.48	-1.94	-1.94		
T137	1.81	-3.01	-3.01	-3.01	-3.01	-3.01	
R171	-0.26	-3.53	-3.53	-3.65	-3.65	-3.01	**-4.74**

Accuracy of predicted breeding value of scrapie susceptibility for in ungenotyped sheep

Correlation between true BV and EBV



Scenario	Description
rand	5% genotyped at random
hr20	20% of rams genotyped at random
hr40	40% of rams genotyped at random
hr40x1	40% of rams genotyped at random, 5% pedigree errors
hr40x2	40% of rams genotyped at random, 10% pedigree errors
hr40y1	40% of rams genotyped at random, 1% genotyping errors
hr40y2	40% of rams genotyped at random, 2% genotyping errors

Accuracy – real data

Assumed heritability	Female 2021 to 2022		2022		2023	
	Accuracy	Dispersion	Accuracy	Dispersion	Accuracy	Dispersion
0.90	**0.64(0.01)**	1.09(0.02)	**0.65(0.01)**	1.06(0.02)	**0.46(0.01)**	1.01(0.02)
0.95	**0.64(0.01)**	1.06(0.02)	**0.65(0.01)**	1.03(0.02)	**0.46(0.01)**	0.99(0.02)
0.99	**0.63(0.01)**	1.03(0.02)	**0.65(0.01)**	1.00(0.02)	**0.46(0.01)**	0.97(0.02)

Conclusions in scrapie EBV

Useful tool for, e.g. selecting replacement ewes or prioritizing sheep for genotyping

Genotyping still important for ram selection and for tracing rare alleles

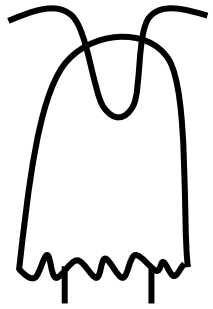
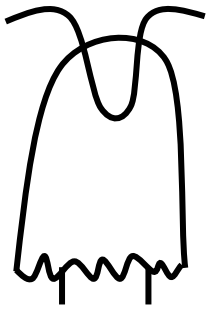
Final points

This work has impact

- The scrapie eradication plan is partly based on the simulation results
- The scrapie EBV will be published next fall

Future perspectives

- More results on the T137, C151 alleles may change strategies
- Monitoring the progress – effect on genetic variation in particular



Thank you