Natural Genetic Resistance to Infection

The Discovery of Natural Determinants of Susceptibility to Infection in Cattle, especially Tarentaise



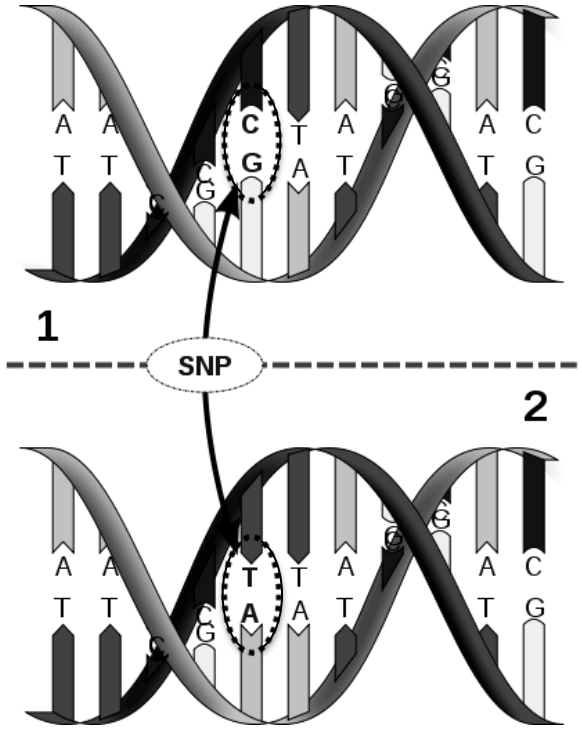
Steve A Carlson, DVM PhD
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Scott City, KS

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Goal of Our Approach

To identify single nucleotide polymorphisms (SNPs) that produce alternate proteins conferring genetic resistance

What are SNPs?

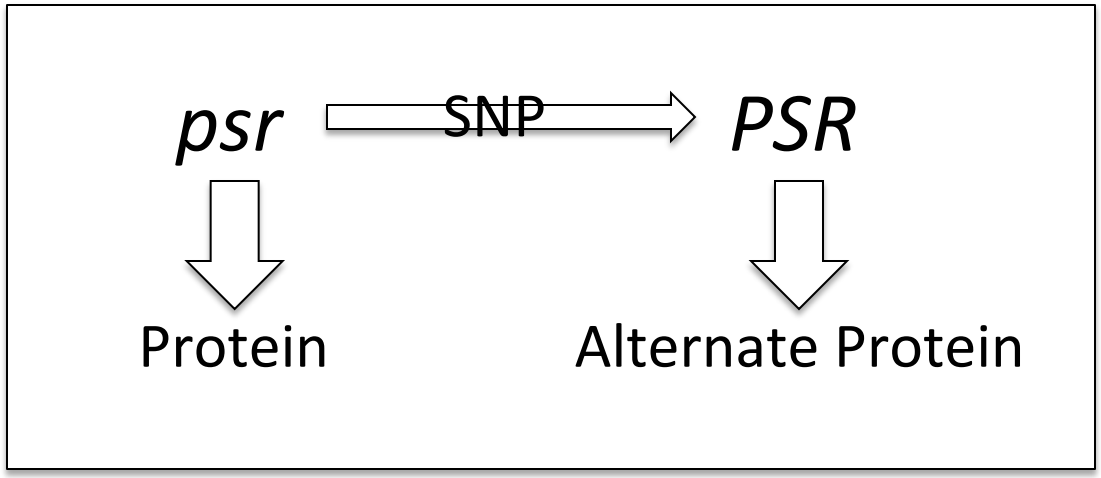


Silent Polymorphism: no change in protein

Replacement Polymorphism: alternate protein

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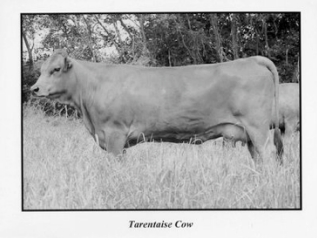
Results of Our Approach



PSR Genetics

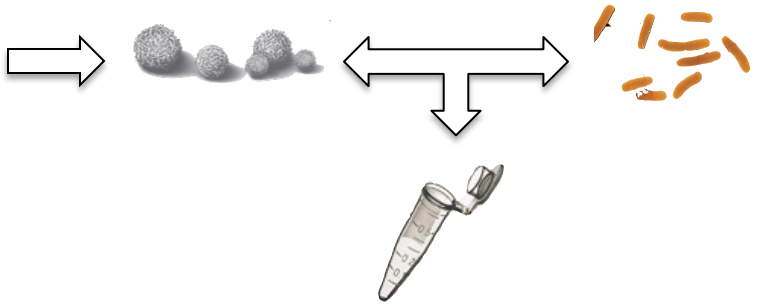
Salmonella Infectivity of Bovine Cells

Does the presence of the *PSR* gene confer natural resistance to *Salmonella* infection of cattle cells *in vitro*?



White Blood Cells

Salmonella

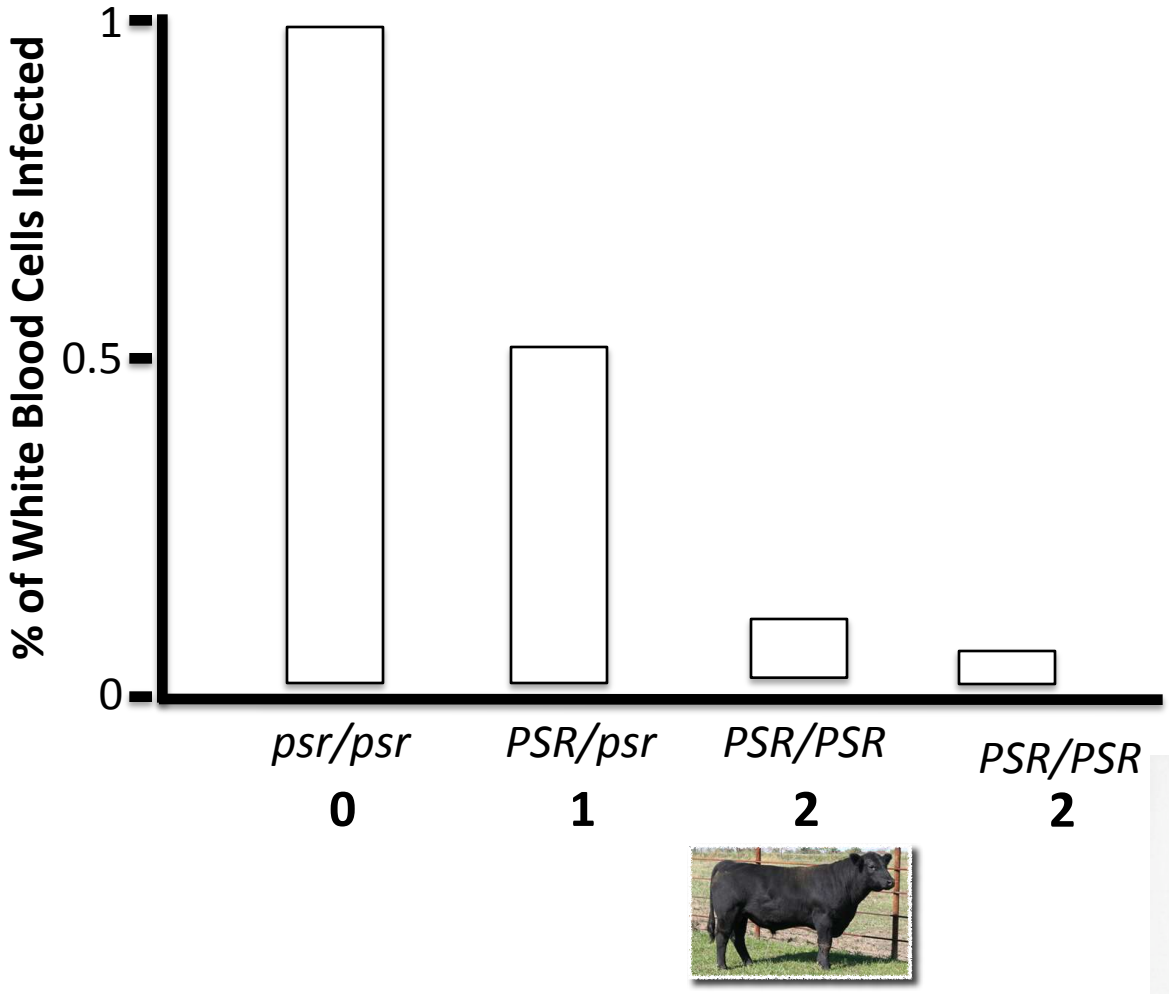


Incubate and
Count Infected
White Blood Cells

PSR Genetics

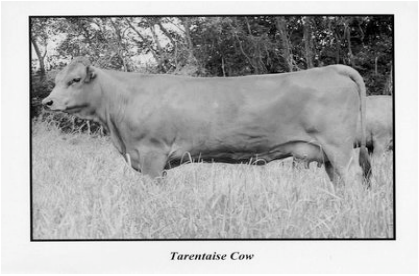
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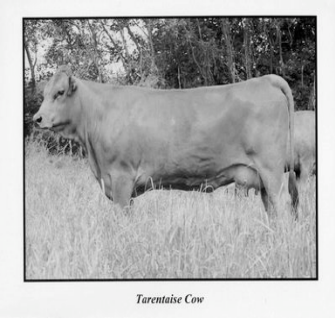
This *PSR* SNP appears to lead to *Salmonella* resistance especially in non-black cattle.

Non-Black, *PSR/PSR* cattle have even greater natural resistance.

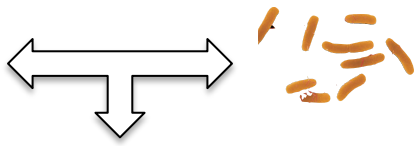


Salmonella Infectivity of Live Cattle

Does the presence of the *PSR* gene confer natural resistance to *Salmonella* infection for live cattle?



Salmonella



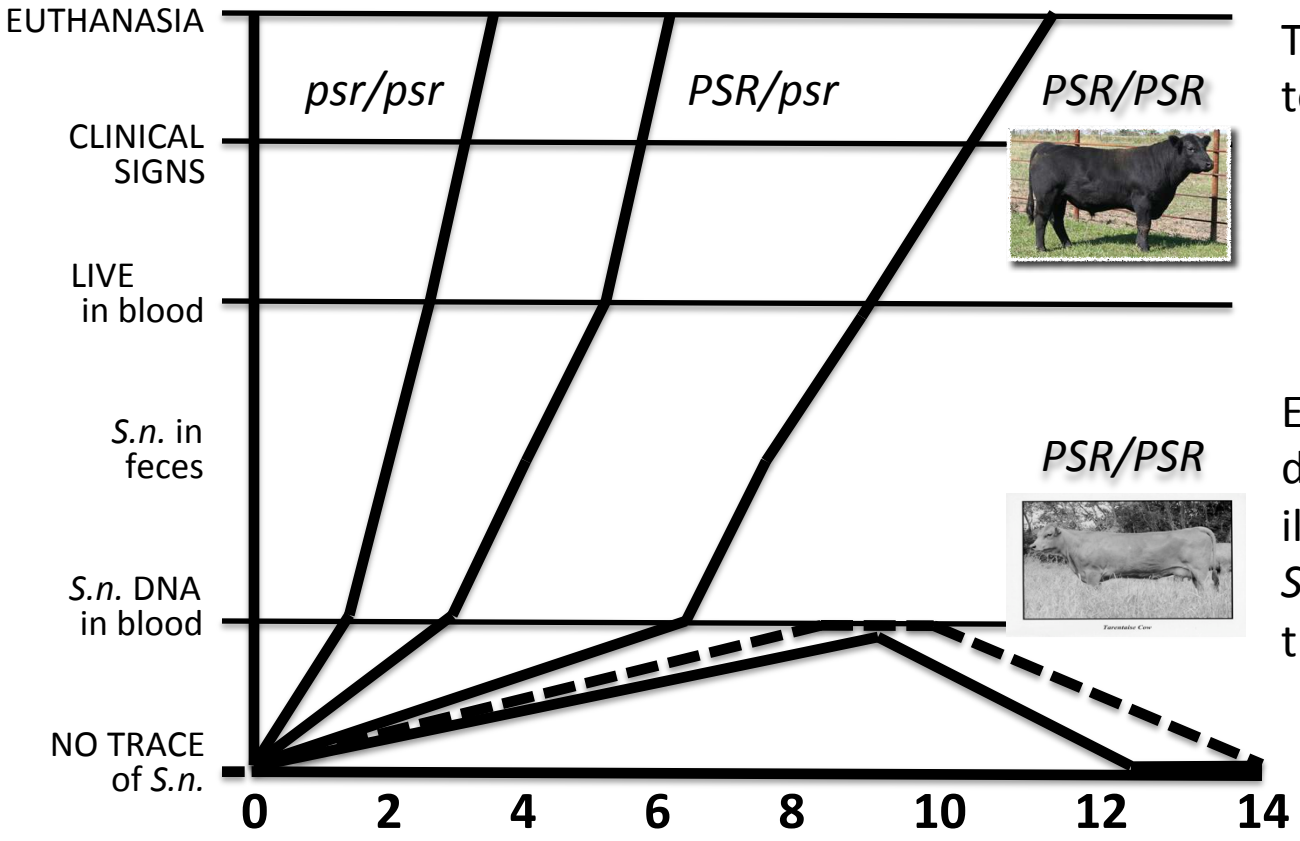
Monitor Progression of Infection

1. Look for *Salmonella* DNA in blood
2. Look for *Salmonella* in feces
3. Look for live *Salmonella* in blood
4. Monitor illness
5. Euthanasia required

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Salmonella Infectivity of Live Cattle

Does the presence of the *PSR* gene confer natural resistance to *Salmonella* infection for live cattle?

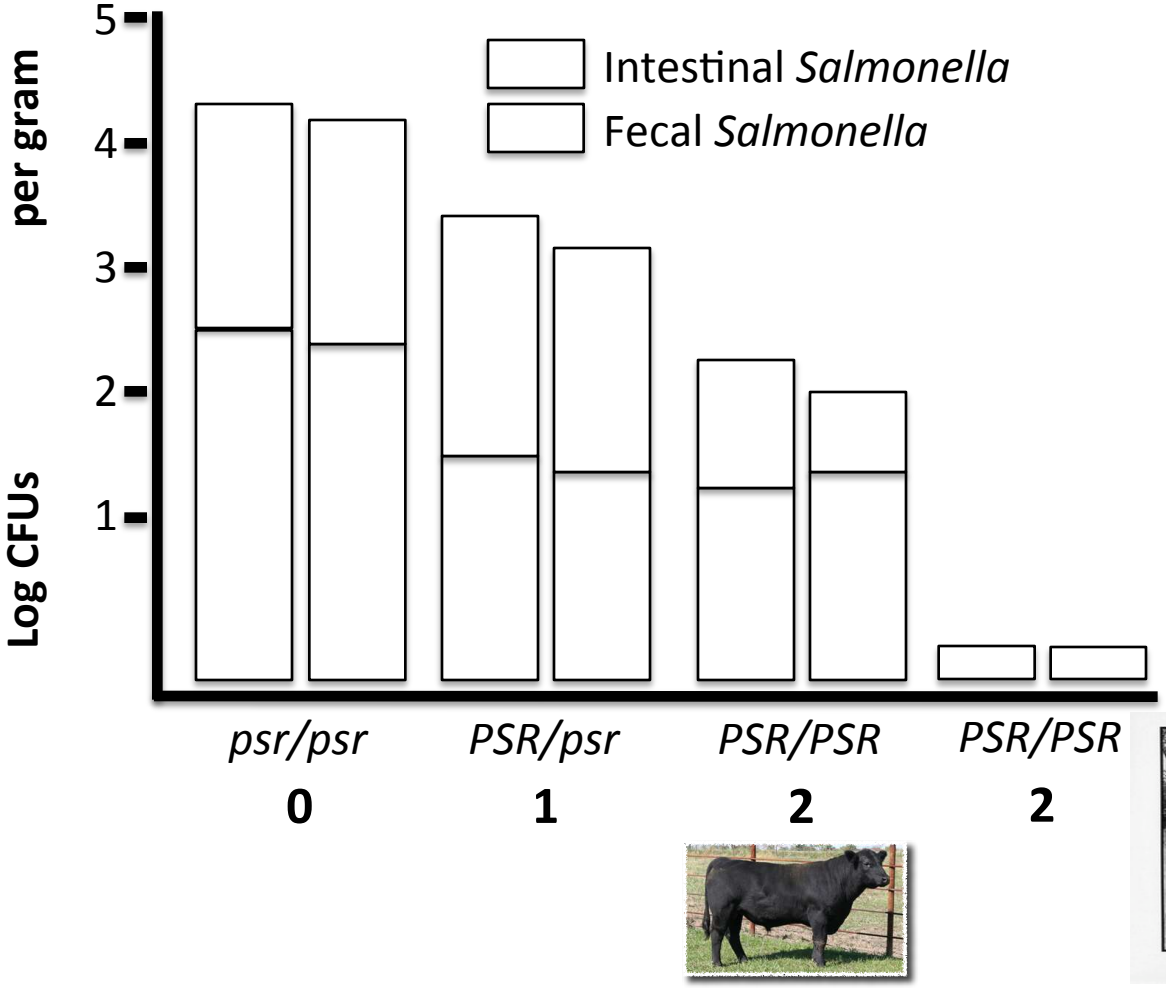


The *PSR* SNP does lead to *Salmonella* resistance.

Even 10X the challenge dose could not produce illness or any shedding of *Salmonella* in the feces in these cattle.

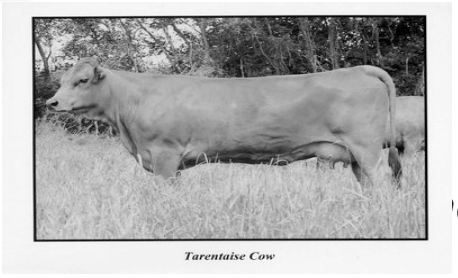
Salmonella Infectivity of Live Cattle

Does the presence of the *PSR* gene confer natural resistance to colonization and shedding for more typical *Salmonella* exposures in live cattle?



Salmonella is unlikely to be harbored by non-black cattle with two copies of the *PSR* SNP.

There is no sign of fecal *Salmonella* in the Non-Black, *PSR/PSR* cattle.



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Conclusions from the Initial Studies

- ✓ **Non-black *PSR/PSR* cattle demonstrate significant and remarkable natural resistance to *Salmonella*.**
  - They resist clinical disease after exposure to lethal challenges of *Salmonella*
  - They harbor very few *Salmonella* after massive challenges
  - They shed no *Salmonella*

- ✓ **The natural resistance is dependent upon having <u>two</u> copies of the *PSR (PSR/PSR)* gene *<u>and</u>* the non-black coat color genotype *(mcr/mcr)*.**

Genetics of the Non-Black Coat Color

- ✓ **Black coat color is determined by a gene (*MCR1*) encoding the melanocortin-1 receptor**
- ✓ **MCR1 is needed for black pigmentation and it also has other functions**
- ✓ **SNPs in *MCR1* produce inactive receptors that are needed for black pigmentation**
- ✓ ***MCR/MCR* and *MCR/mcr* are black, while *mcr/mcr* are non-black**
- ✓ **Most Tarentaise are *mcr/mcr* (desirable)**

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Other Characteristics of *mcr/mcr* Cattle

- ✓ **They metabolize antibiotics faster than other genotypes**

  Shorter antibiotic withdrawal times

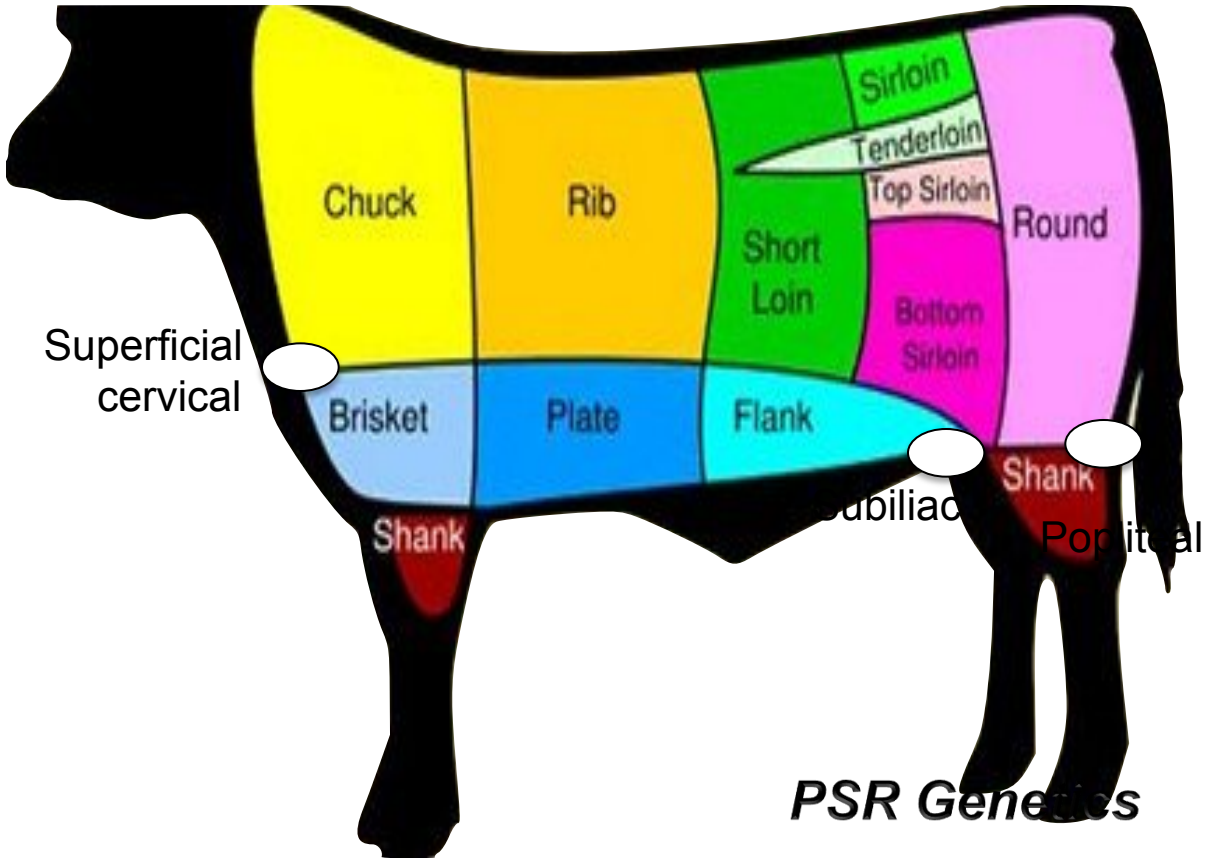
- ✓ **They have elevated an pain threshold**

  Less likely to go off feed

Food Safety Implications for the *PSR/PSR::mcr/mcr* Genotype

- ✓ **Recent studies indicate that up to 30% of peripheral cattle lymph nodes contain *Salmonella***
- ✓ **These lymph nodes are not excised and are incorporated into the grind**

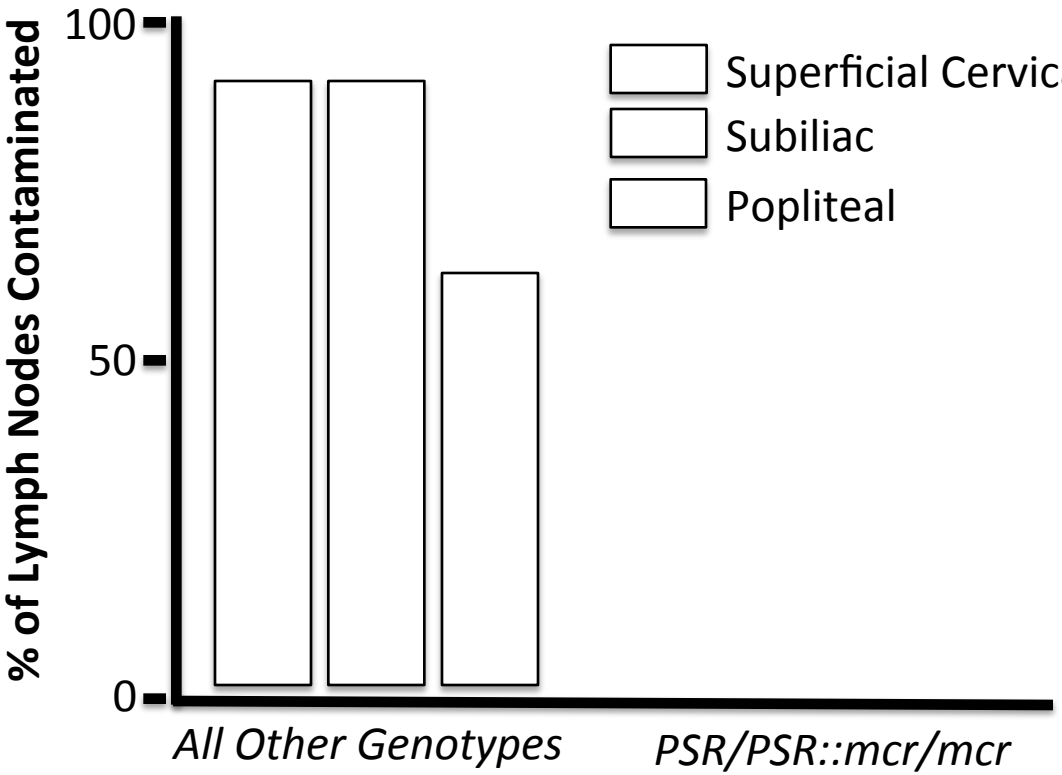




Food Safety Implications for the *PSR/PSR::mcr/mcr* Genotype

Do *PSR/PSR::mcr/mcr* cattle harbor *Salmonella* in peripheral lymph nodes?

Experimental challenges with *S. anatum* and *S. montevideo*





Hamburger from *PSR/PSR::mcr/mcr* cattle is unlikely to be contamination by the *Salmonella* strains implicated in this emerging problem.

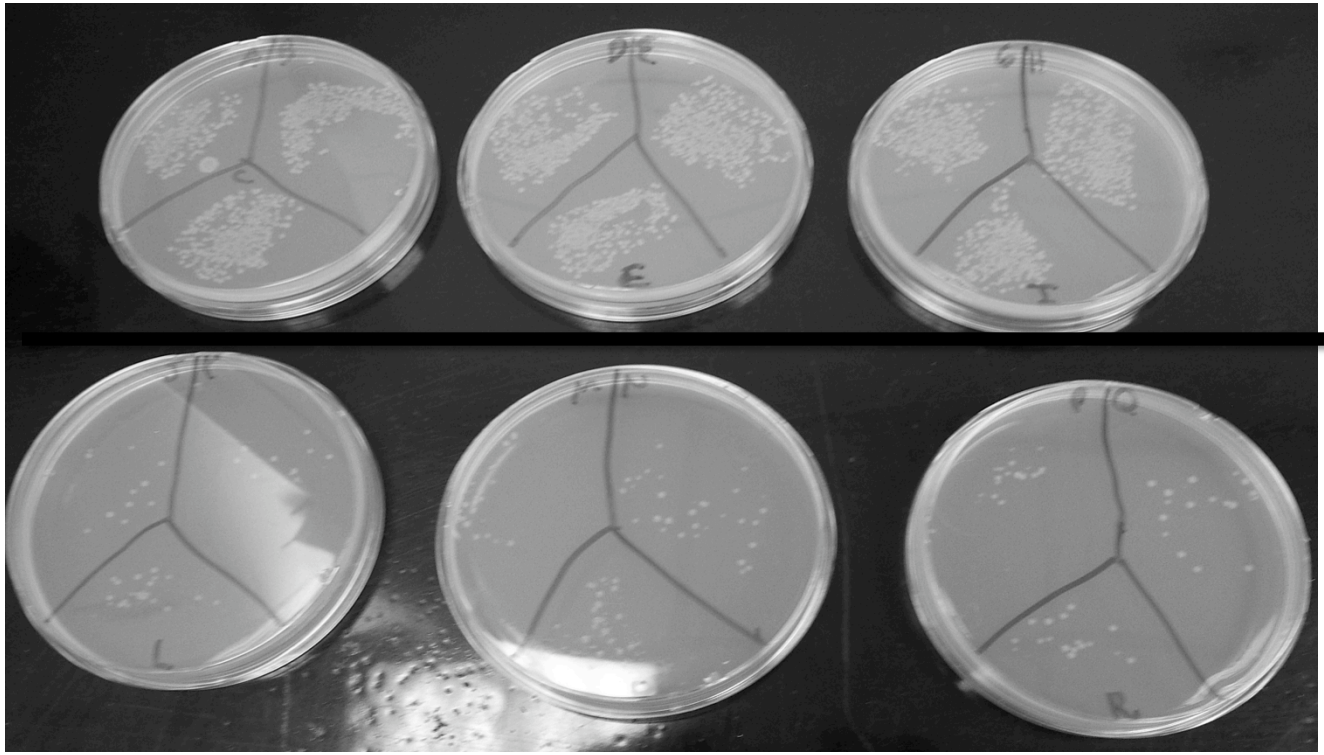
After experimental infection, *Salmonella* could not be found in any peripheral lymph nodes of *PSR/PSR::mcr/mcr* cattle.

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Other Bacterial Pathogens

Does the natural resistance of *PSR/PSR::mcr/mcr* cattle extend to related bacterial pathogens?

E. coli O157:H7 colonization of the intestines of cattle experimentally infected with the microbe



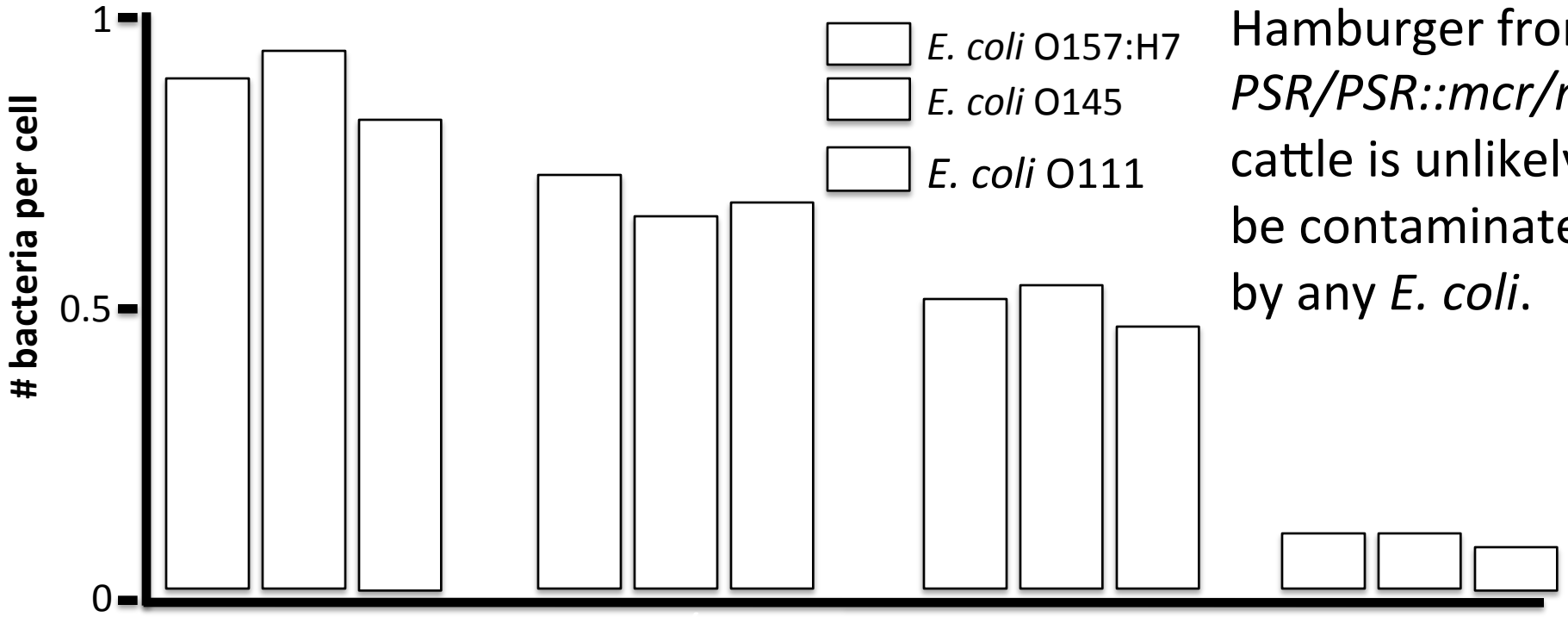
All Other Genotypes

PSR/PSR::mcr/mcr



STEC Adherence to Cattle Cells

Does the presence of the *PSR* gene confer natural resistance to *E. coli* adherence of cattle cells *in vitro*?



Hamburger from *PSR/PSR::mcr/mcr* cattle is unlikely to be contaminated by any *E. coli*.





Advantages of Natural Genetic Resistance

- ✓ **Unlike immunity, natural genetic resistance is 100% heritable.**
- ✓ **Unlike immunity, natural genetic resistance does not require exposure or immunization.**
- ✓ **Unlike immunity, natural genetic resistance is not compromised under stress or other infections.**

Advantages of *PSR/PSR::mcr/mcr* Genotype

- ✓ **They have significant and remarkable natural resistance to *Salmonella* infection.**

  They naturally resist lethal doses

  They naturally resist clinical infections

  They naturally resist colonization and shedding

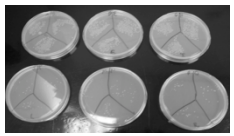
  They naturally resist colonization of lymph nodes

- ✓ **They naturally show significantly less *E. coli* O157:H7 colonization.**

Relevance to ATA

- The *mcr/mcr* genotype produces a visible phenotype.
- We can readily detect the *PSR/PSR* genotype.
- **Tarentaise have one of the highest prevalences of *PSR/PSR***







Overall Advantages of *PSR/PSR* Tarentaise Cattle

- ✓ **Derived hamburger is infinitely less likely to be contaminated with lymph nodes infiltrated by *Salmonella*.**

- ✓ **These cattle are significantly less likely to harbor *E. coli* O157:H7 and related pathogens.**

Tarentaise Beef
Tender.Leaner.Safer®

PSR Genetics

Call to Action for ATA

- ✓ **PSR Genetics is nearing an agreement with either Pfizer or Neogen (GeneSeek) regarding licensure of a genetic test for the *PSR/PSR* genotype.**

- ✓ **Please inform your members about this test and please recommend testing as a means of improving the profile of your breed.**