$E_{coli}$ pre-harvest cattle interventions update: Cattle vaccines and direct-fed microbials – How good are these interventions?

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How do we know if an intervention works?
Overview method of systematic reviews
What do we mean by “treatment works” – What is the appropriate outcome to measure this?
Systematic review results for Vaccines and Probiotics to reduce *E. coli* O157
Limitations of the method
Limitations of the data
Summary of findings
How do we determine whether an intervention works?

Building evidence for efficacy under “real-world” conditions

Randomized Controlled Trials (RCTs) (commercial herds, research herds)
Deliberate disease challenge trials

Cohort (hypothesis testing under real-world conditions)
Case-control (hypothesis testing under real-world conditions)

Cross-sectional observational (hypothesis generating)

Laboratory models (proof of concept)
How do we summarize the results of intervention research?

- Systematic review / meta-analysis of RCTs
- Randomized Controlled Trials (RCTs) (commercial herds, research herds)
- Deliberate disease challenge trials
- Cohort (hypothesis testing under real-world conditions)
- Case-control (hypothesis testing under real-world conditions)
- Cross-sectional observational (hypothesis generating)
- Laboratory models (proof of concept)
Systematic review and meta-analysis

- A review of a clearly formulated question that uses systematic and explicit methods to identify, select, critically appraise, and summarize relevant research

- Defined steps that are structured and documented, multiple reviewers at each stage

- Quality assessment is performed to identify studies with potential methodological flaws to aid in interpretation

- Meta-analysis is used to pool data from multiple studies to calculate a summary measure of effect (outcome)
Systematic Review methods for vaccines and probiotics to reduce *E. coli* O157

- Search terms entered into multiple electronic databases to identify English language studies published after 1980
- Abstracts / titles screened for relevance
- Full publications obtained for relevant citations reporting field trials (natural exposure to *E. coli* O157)
- Quality assessment performed (random allocation, allocation concealment, blinding, reporting of losses to follow-up)
- Data extraction: population, details of intervention, details on outcomes
What outcomes are appropriate / available?

- Presence / absence of *E. coli* O157
  - In feces throughout the trial, at end of trial
    - Fecal grab, fecal pat, RAMs (by swab, TRM at slaughter)
  - In saliva (ROPES)
  - “high shedding” cattle
  - On hides, carcasses at slaughter

- Concentration (level) of *E. coli* O157
  - In feces throughout the trial, at end of trial
  - “high shedding” cattle
  - In saliva (ROPES), hides, carcasses at slaughter

- Vaccine Efficacy
What outcomes are appropriate / available?

- Presence / absence of *E. coli* O157
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- Concentration (level) of *E. coli* O157
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- Vaccine Efficacy
Vaccines to reduce fecal shedding of *E. coli* O157

**Epitopix (Pfizer)**
Siderophore receptors and porin (SRP) proteins
Inhibits iron uptake by bacteria

**Econiche™ (Bioniche Life Sciences)**
Type III secretion system
Inhibits bacterial attachment
15 field trials (natural exposure) identified
  ◦ 33 treatment comparisons
  ◦ Commercial and research herd studies, feedlot and cow–calf
  ◦ 2 or 3 doses used

Vaccine types included a bacterin vaccine, Type III (Econiche™ by Bioniche Life Sciences), and SRP (Epitopix / Pfizer O157:H7 SRP®)

Meta–analysis for prevalence (presence / absence measured in feces, saliva, or TRM)
  ◦ Not all trials provided information on this outcome
**Vaccines - E. coli 0157 - beef cattle**

Outcome as measured at the end of the trial

Overall summary estimate = 0.61 (0.39 – 0.96)

Cattle receiving vaccine are 1.7 times LESS LIKELY to shed *E. coli* O157

High amount variability between trials
Overall summary estimate = 0.40 (0.32 – 0.50)

Cattle receiving vaccine are 2.5 times LESS LIKELY to shed *E. coli* O157

Moderate variability between trials
Probiotics to reduce fecal shedding of *E. coli* O157

- "Live microorganisms which when administered in adequate amounts confer a health benefit on the host"

- **Bovamine®** direct fed microbial
  - "Probiotic" effects – *Lactobacillus acidophilus (NP51)* & *Propionibacterium freudenreichii*
  - No label claim for reducing *E. coli* O157
**Probiotics results**

- 15 field trials (natural exposure)
  - 37 comparisons
  - Research feedlots (not described in 2 trials)
  - Variable doses and duration of feeding
- Variety of different probiotic products were evaluated
- Meta-analysis for prevalence (presence / absence measured in feces)
  - Not all trials provided information on this outcome
  - Results shown are for Bovamine bacteria combinations
Overall summary estimate = 0.44 (0.33 - 0.58)

Cattle receiving probiotics are 2.3 times LESS LIKELY to shed *E. coli* O157

2.5 for high dose
2 for low dose

Moderate variability between trials

“high” = $10^9$ CFU
Overall summary estimate = 0.45 (0.33 – 0.62)

Cattle receiving probiotics are 2.3 times LESS LIKELY to shed *E. coli* O157

Moderate variability between trials
Limitations of the method

- Time consuming and resource intensive
- Potential for publication bias
  - Results showing no effect of an intervention are less likely to be published, particularly for smaller trials (some evidence that this was true for both vaccines and probiotics)
  - Summary results are therefore likely a “best case scenario”
- Research is still continuing – like all synthesis research, need a “best before” date?
Systematic reviews need periodic updating as new work becomes available

- **Vaccine SRs**
  - Sargeant et al., 2007
  - Snedeker et al., 2012
  - Wisener (submitted: compares results from challenge trials and field trials)

- **Probiotics SRs**
  - Sargeant et al., 2007
  - Wisener (ongoing)

Cull et al., 2012: Large study in a commercial herd
Vaccine efficacy of 53% (77% in high shedders) using *E. coli* SRP® vaccine
No significant reduction with Bovamine at $10^6$ CFU/animal/day of *L. acidophilus*
Limitations of the results

- Inconsistency in outcomes reported between studies means that not all studies could be included.
- Prevalence outcomes does not evaluate decreases in concentration, which may have implications to control at slaughter.
- Limited information on non-O157 outcomes:
  - other VTECs, other pathogens, impact (positive or negative) on production / health, cost–benefit....
  - Limited information on impact on carcasses, no information on human health.
Despite differences in results between studies, both type III and SRP vaccines appear to reduce the proportion of cattle shedding (although they do not eliminate shedding).

In research herds, probiotics appear to reduce the proportion of cattle shedding by approximately the same amount.

- Single commercial herd study showed no effect
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