* **Intro material (set up the premise)**
  + Resistance to antibiotics may be acquired by spontaneously occurring genetic mutations, and be passed vertically by selection to daughter cells. More commonly, resistance is acquired by the horizontal transfer of mobile DNA elements from a donor cell, often from another bacterial species (Chambers, 2001; Sefton, 2002). The two main factors involved in the development of antibiotic resistance in bacteria are the selective pressure by the use of antibiotics and the presence of resistance genes (Levy, 1997; Witte, 2000).
  + There is growing evidence and little doubt that resistance genes can be spread and exchanged between different bacterial populations (McDermott et al., 2002; O’Brien, 2002; Teale, 2002). Resistance that is acquired by horizontal transfer of resistance genes can become rapidly and widely disseminated either by clonal spread of the resistant strain itself or by further genetic exchanges between the resistant strain and other susceptible strains (Chambers, 2001)
* **Literature showing/suggesting AB usage = selection pressure**
  + - *“Antibiotic resistance is equally likely to diminish in prevalence when antibiotic use is decreased or discontinued. Although individual bacterial strains may retain resistance genes, they are often (gradually) replaced by susceptible strains when the selective pressure is removed”*
      * Phillips I, Casewell M, Cox T, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. J Antimicrob Chemother 2004;53:28 –52.
    - *“Generally, percentages of antimicrobial resistance before (conventional) were significantly higher than after (organic) the transition. Overall, percentages of antimicrobial resistant mastitis pathogens decreased after 6 months operating as an organic farm system. An 8-month study was conducted in Thailand to investigate the effects of antimicrobial-resistant patterns of mastitis pathogens during an experimental farm’s 6-month transition from conventional to organic farming. Antimicrobial resistance of mastitis pathogens in the before (conventional) and after (organic) transition periods were compared for 7 antimicrobial drugs used to treat mastitis.”*
      * Suriyasathaporn W. Milk quality and antimicrobial resistance against mastitis pathogens after changing from a conventional to an experimentally organic dairy farm. Asian Austral J Anim Sci May 1, 2010
    - Erskine RJ, Walker RD, Bolin CA, et al. Trends in antibacterial susceptibility of mastitis pathogens during a seven-year period. J Dairy Sci 2002;85:1111– 8
      * Not much evidence that ***AMR increasing over time,*** which is a different question
      * 7-year study of Michigan dairy herds; the proportion of bacterial isolates susceptible to antibiotics did not change for the majority of tests
      * Overall, the prevalence of AMR over a 7-year period did not change (1994–2000). The prevalence of S. aureus isolates resistant to ampicillin, penicillin and erythromycin declined during this period. Streptococcus uberis isolates became more susceptible to oxacillin, sulfa-trimethoprim gentamicin, and pirlimycin while becoming more resistant to penicillin. Linear declines in AMR were also reported for Streptococcus dysgalactiae, Streptococcus agalactiae, E. coli and Klebsiella pneumoniae. Overall, the authors concluded that there was no indication of increased resistance among mastitis clinical isolates for antimicrobials used commonly to treat mastitis
    - Nam HM, Lim SK, Kang HM, et al. Prevalence and antimicrobial susceptibility of gram-negative bacteria isolated from bovine mastitis between 2003 and 2008 in Korea. J Dairy Sci 2009;92:2020 – 6. 31.
    - Nam HM, Lim SK, Kang HM, et al. Antimicrobial resistance of streptococci isolated from mastitic bovine milk samples in Korea. J Vet Diagn Invest 2009;21:698 –701.
* **BUT support for using AB**
  + Call 2008: decreasing animal health could increase the probability of a higher pathogen load in these animals with commensurate increased risk of exposing humans to genuine pathogens (Cox and Popken, 2006) (also see Claycamp (2006)).
  + It reduces the suffering of animals and prevents pathogenesis in humans via consumption of milkborne/foodborne mastitis pathogens that are potential human pathogens
  + Danger of consumption of raw milk
    - Oliver SP, Boor KJ, Murphy SC, et al. Food safety hazards associated with consumption of raw milk. Foodborne Pathog Dis 2009;7:793– 806.
  + Find papers about pain/inflammation associated with mastitis
    - An Update on the Effect of Clinical Mastitis on the Welfare of Dairy Cows and Potential Therapies
    - Christina S Petersson-Wolfe 1, Kenneth E Leslie 2, Turner H Swartz 3
    - Assessment and Management of Pain in Dairy Cows with Clinical Mastitis Kenneth E. Leslie, DVM, MSca,\*, Christina S. Petersson-Wolfe
    - Ginger L, Ledoux D, Bouchon M, Rautenbach I, Bagnard C, Lurier T, Foucras G, Germon P, Durand D, de Boyer des Roches A. Using behavioral observations in freestalls and at milking to improve pain detection in dairy cows after lipopolysaccharide-induced clinical mastitis.
* **Summarize studies**
  + Start out with weaker, smaller ones
  + Describe results of largest, most rigorous analysis ones
    - Ruegg
    - Mcdougall
  + Other short communications that aren’t in the table
    - Studies on transitioning
      * Park 2012
      * Can compare to Erskine one which was long term
    - Walther 2007, org farm with MRSA epi – maybe this goes with point in cicconi hogan about org status doesn’t matter in regards to being source for MRSA
    - Rajala-schultz
      * Not organic, but cows exposed to dry terat and not
        + Age has so many other affects on animals though
        + Type of NAS, immune function, SCC
    - Fecal papers
      * Whole other body of work, different system
        + Different exposures, different pathogen behavior, different pathogen community interactions

***Things to keep in mind when comparing studies:***

Additionally, organic regulations for European countries still allow for some antimicrobial use (albeit with extended withdrawal periods and stricter veterinary oversight), while organic regulations in the US mandate that any animal treated with antimicrobials is removed from the herd. The level of on-farm antimicrobial usage (and therefore selective pressure for resistance) therefore differs between European (EU Commission, 2024) and US dairies (USDA, 2024), making comparisons between studies carried out under these varying regulations difficult. Regulations for both organic dairy production certifications have evolved over time (Dimitri and Nehring, 2022; Grodkowski et al., 2023), further adding to the nuance of how organic dairy production is defined in both entities. Consequently, these geographic and temporal differences must be kept in mind when reviewing studies comparing organic and conventional dairy systems between the EU and US.

**Which AB’s chosen** – relevance to human medicine or most common drugs used for mastitis therapy

**Methodology for antimicrobial susceptibility**

**Sampling scheme –** random, targeting cows likely to have aureus or any infection, some studies specify clinical mastitis samples were discluded, others don’t and likely included both subclinical and clinical isolates – paper looking at AB susceptibility for clinical vs. subclinical mastitis isolates… and is it different?

Bennedsgard, TRYING to find cows with SA

Using CMT to find mastitis: Busato, Roesch

Open sampling: Tikofsky, Bombyk, garmo

Mulitparous: pol and ruegg, multiparous plus other criteria mcdougall

**Purely descriptive studies**

Busato (EU) – no AM quant – CNS and SA

Garmo (EU) – no AM quant – CNS and SA

**CNS and SA**

Roesch (EU) – no AM quant

Bombyk (EU) – novobiocin CNS – no AM quant

**Purely SA?**

Tikofsky (US) -- no AM quant

Sato (US and EU) -- no AM quant

Bennesgaard (EU) – dup -- SOME AM quant

**BTM studies**

Cicconi-Hogan (US) -- no AM quant – both CNS and SA

Tenhagen (EU) -- no AM quant – only MRSA

**Large, statistically robust studies (both SA and CNS) for quartermilk**

Pol and Ruegg (US) – very detailed AM quant

McDougall (US/NZ) – very detailed AM quant

Overall, studies comparing antibiotic resistance of staphylococci between herds under organic management and herds managed conventionally find either no difference or more susceptibility for isolates originating on organic farms (Table XX). However, these studies vary widely in their approach to exploring this question, primarily in the number of isolates included and herds sampled, as well as approach to statistical analysis. In a descriptive study from Switzerland, Busato et al. (2000) found that the proportion of *S. aureus* isolates from organic herds resistant to different antimicrobials was similar to those from conventional herds. Similarly, the proportion of resistant isolates of CNS was comparable between the two systems, with the exception of a numerically higher proportion of isolates resistant to rifamyin from organic herds. A limitation of this study is that the data describing the proportion of staphylococci from conventional herds was from a previously unpublished survey by the authors, and not contemporaneous with analysis of the organic isolates. In another descriptive study, researchers in Norway (Garmo et al., 2010) found similar proportions of *S. aureus* and CNS isolates resistant to penicillin between the two herd types (*S. aureus:* 6/68 or 8.8% from CON, vs. 9/64 or 14.0% from ORG; CNS: 81/167 or 48.5% for CON, vs. 93/200 or 46.5% from ORG). The authors note that penicillin resistance was proportionately higher in CNS vs. *S. aureus* isolates, consistent with more recent work looking at the resistance of staphylococci from bovine milk samples (as summarized in Taponen, 2023). In a Swiss study comparing the resistance profiles of NAS and *S. aureus* from quartermilk samples, Roesch et al. (2006) also found that NAS isolates had a higher percentage of antibiotic resistance than *S. aureus* isolates. For 12 antimicrobials representing either drugs used to treat mastitis in dairy herds or drugs important in human medicine, they found that percentage of antibiotic resistance did not differ significantly between *S. aureus* and NAS isolates from cows kept on organic and conventional herds. Although the proportion of resistant *S. aureus* isolates was numerically higher from organic cows (16/46, 35%) vs. conventional cows (6/33, 18%), this difference was not statistically significant. The proportion of resistant CNS isolates between systems was very similar (ORG: 9/19, 47%; CON: 10/19, 53%).

Contrastingly, Bombyk et al. (2008) found that overall, staphylococci isolates causing mastitis on organic dairies were associated with more overall antimicrobial susceptibility than those from conventional farms. For this study, researchers differentiated staphylococci isolates from mastitis into 3 categories: coagulase-positive *Staph.* (CPS), novobiocin-sensitive CNS (NSCNS), and novobiocin-resistant CNS (NRCNS). In an analysis combining all 3 groupings of staphylococci, a larger proportion of isolates from organic herds were susceptible to pirlimycin and tetracycline compared with those from conventional herds. Susceptibility to erythromycin and penicillin did not differ significantly by herd type when all staphylococci were combined (CON vs. ORG). No significant differences between organic and conventional systems were found for *S. aureus*, although the numbers of isolates found was fairly small compared to both categories of CNS (36 *S. aureus* vs. 210 NSCNS and 159 NRCNS). When each category of CNS (novobiocin-susceptible or resistant) was analyzed separately, isolates within both groups from organic herds were more likely to be susceptible to pirlimycin than CNS from conventional dairies. No difference in tetracycline, erythromycin or penicillin susceptibility was seen between herd types (CON vs. ORG) within either CNS category. A larger proportion of NSCNS vs. NRCNS (when analyzed separately for conventional and organic herds) were susceptible to tetracycline, leading the authors to suggest that management practices unrelated to antimicrobial use may contribute to the observed differences in susceptibility patterns of CNS on dairy herds.

A number of studies comparing resistance patterns of bacteria isolates between conventional and organic dairy systems focused specifically on *S. aureus.* Researchers in New York and Vermont (US) found that *S. aureus* isolates from both types of herds showed good susceptibility to most mastitis antimicrobials, but isolates from organic herds were significantly more susceptible (Tikofsky et al., 2003). In this study, researchers took two different approaches to analyzing the data; the strength of association between the proportion of susceptible and resistant isolates and management category was evaluated, as well as numeric differences in mean zone diameter for isolates from organic vs. conventional herds. When results were combined over both analyses, *S. aureus* isolates from organic herds were more susceptible than those from conventional herds for 7 of the 9 antimicrobials studied. Contrary to these findings, researchers comparing resistance of isolates from bulk tank milk of organic and conventional systems in both the US and Denmark found that overall, antimicrobial susceptibility was very similar for *S. aureus* in both countries (Sato et al., 2004). Bulk tank isolates from conventional herds in Wisconsin (US) had significantly reduced susceptibility to ciprofloxacin (vs. isolates from organic herds), and isolates from organic herds in Denmark had reduced susceptibility to avilamycin (vs. isolates from conventional herds). In a finding highlighting the importance of geography in epidemiological studies, authors point out that differences in the antimicrobial susceptibility of *S. aureus* isolates between organic and conventional herds were small relative to differences in isolates observed between countries. In agreement with Sato et. al, Bennedsgaard et al. (2006) observed no statistically significant differences in the prevalence of cows with penicillin-resistant *S. aureus* mastitis or the proportion of *S. aureus* isolates from quartermilk resistant to penicillin between herd conventional and organic dairies in Denmark.

Two studies looking at bulk tank milk focused on detection of staphylococci carrying genetic determinants conferring penicillin resistance (*mecA* and *mecC* genes), an important consideration for public health globally. In a large study surveilling dairy-associated MRSA in Germany, researchers collected bulk tank milk samples from 372 conventional and 303 organic herds (Tenhagen et al., 2018). Using a binary logistic regression to describe association of MRSA-positive samples with herd type (conventional vs. organic), they found that the prevalence of MRSA was significantly higher in BTM samples from conventional herds (9.7%) compared with organic herds (1.7%). The model-based approach allowed researchers to control for the effects of both geographical region and herd size, both significant of which were also predictors of MRSA herd status. When comparing the proportion of MRSA isolates resistant to 12 different antimicrobials between conventional and organic herds, MRSA isolates from conventional farms tended to be more resistant. However, as there were limited number of isolates from organic herds (n = 5) compared to conventional herds (n = 36), no statistical analyses were performed. A large, multistate study in the US, sampled bulk tank milk from 192 organic herds and 100 conventional herds matched for geographical location and herd size (Cicconi-Hogan et al., 2014). They identified 13 isolates from bulk tank milk as methicillin resistant (*mecA* positive): 7 isolates from conventional herds and 6 from organic. Using 16S rRNA and rpoB genes for speciation, these 13 isolates were identified as *S. aureus* (n = 1), *S. sciuri* (n = 5), *S. chromogenes* (n = 2), *S. saprophyticus* (n = 3), *S. agnetis* (n = 1), and *Macrococcus caseolyticus* (a genus closely related to staphylococci; n = 1). Surprisingly, the single methicillin-resistant *S. aureus* isolate was from an organic herd, for an observed 0.3% prevalence of MRSA at the herd level. Methicillin-resistant CNS were found at a prevalence of 2% in the organic population and 5% in the conventional population. The authors highlight the high number of methicillin-resistant *S. sciuri* identified (6 out of 12 methicillin-resistant CNS) compared to previous work, and also suggest that a potential methicillin-resistant *Staphylococcus* reservoir in the dairy herd population of the United States may be independent of production system type. To this point, Walther and Perreten (2007) report the occurrence of a dairy cow on an organic farm in Switzerland that was diagnosed twice within 2 months with subclinical mastitis caused by methicillin-resistant *Staphylococcus epidermidis*. The two strains had identical PFGE patterns of chromosomal DNA, exhibited resistance to chloramphenicol, and contained streptomycin- and trimethoprim-resistance genes but did not display phenotypic resistance against these drugs *in vitro*. Furthermore, the second *S. epidermidis* isolate contained an additional aminoglycoside-resistance gene, indicating the potential acquisition of resistance by horizontal gene transfer since isolation of the first bacterium. Similar to Cicconi-Hogan et al., the authors point out that this finding demonstrates that cows on organic farms may harbor multidrug-resistant staphylococci despite the limited use of antibiotics under EU organic regulations.

Perhaps a limitation of the above studies comparing the resistance of staphylococci from organic and conventional dairy farms is that limited or no quantification of on-farm antimicrobial usage was calculated and presented. As the basis for many of these studies was to explore if the level of usage of antimicrobial drugs in food animals may select for drug-resistant pathogens (Yan and Gilbert, 2004), an important component in a study exploring this question would be a quantification of antimicrobial use at the farm- or cow-level to be able to estimate the amount of selective pressure that may be occurring for intramammary pathogens. Although all antimicrobial usage is prohibited on US dairy farms, the amount and type of antimicrobials used by conventionally-managed farms can vary widely (Pol and Ruegg, 2007b). Two of the largest-scale, statistically robust studies comparing the resistance profiles of staphylococci from quartermilk samples between conventional and organic dairies include a detailed, numeric quantification of antimicrobial usage by enrolled farms. In a 2007 study in the US, Pol and Ruegg standardize exposure to 10 different antimicrobials by calculating of the number of defined daily doses used per cow, and then categorize the 40 enrolled herds based on their respective antimicrobial exposure. Herds are categorized into 3 groups: organic (no antimicrobial usage), conventional–low usage (CON-LO; conventional farms not using or using ≤ to the first quartile of use of each drug), and conventional–high usage (conventional farms using more than the first quartile of a particular drug; CON-HI). Authors took multiple approaches to compare resistance among isolates from the 3 antimicrobial usage groups. First, they compared the proportion for each type of isolate (CNS or *S. aureus*) that was susceptible or resistant in each category (CON vs. ORG) using a categorical test of association, in order to explore if proportion of susceptible isolates was independent of herd type. Secondly, they used a test of association to explore if the MIC for each type of isolate (CNS or *S. aureus*) was independent of herd type (CON vs. ORG). Lastly, they performed survival analysis of each type of isolate (CNS or *S. aureus*) based on the 3 antimicrobial usage categories (ORG, CON-LO, or CON-HI). In this last analysis, antimicrobial concentration in wells of the susceptibility test were used as “time,” and the “event” was inhibition of bacterial growth. In order to avoid correlation between the effects of cow, herd, and exposure category, the authors included only 1 isolate per cow and ≤ 20 isolates per herd in all analyses. Overall, Pol and Ruegg found that isolates from organic herds were more susceptible to antimicrobials than those from conventional herds. Specifically, for *S. aureus,* (1) isolates from conventional herds were more likely to be resistant to ampicillin and penicillin when compared with isolates from organic herds, and herd type was not associated with the proportion of resistant isolates for the other antimicrobial drugs tested; (2) isolates from conventional herds had a higher MIC for pirlimycin and sulfadimethoxine compared with isolates from organic herds, and herd type was not associated with the MIC of the other antimicrobial drugs tested; and (3) in the survival analysis, the MIC that inhibited 90% (MIC90) of *S. aureus* isolates from organic herds for penicillin and pirlimycin was lower than the MIC90 of the isolates from CON-LO and CON-HI herds (MIC50, the MIC that inhibited 50% of isolates, was not different for these drugs). For CNS, (1) isolates from conventional herds were more likely to be resistant to ampicillin, penicillin, pirlimycin, and tetracycline compared with isolates from ORG herds, and herd type was not associated with the proportion of resistant isolates for the other antimicrobial drugs tested; (2) isolates from conventional herds had a higher MIC for ampicillin, pirlimycin, and tetracycline compared with isolates from organic herds, and herd type was not associated with the MIC of the other antimicrobial drugs tested; and (3) in the survival analysis, the MIC that inhibited 90% (MIC90) of CNS isolates from organic herds for ampicillin, penicillin, pirlimycin, and tetracycline was lower than the MIC90 of the isolates from CON-LO and CON-HI herds (ORG and CON-LO herds had a lower MIC50 for erythromycin than CON-HI herds, but the MIC90 did not differ by usage group). The authors highlight that although some differences were found between antimicrobial usage groups, most isolates from all farm types were inhibited at the lowest dilution tested of most antimicrobial drugs routinely used on dairy farms.

The other study exploring the difference in resistance of staphylococci between organic and conventional dairies to include a detailed quantification of antimicrobial usage enrolled 7 organic herds, 11 conventional herds using ampicillin-cloxacillin DCT (CON-AC), 8 conventional herds using cephalonium DCT (CON-CE) in New Zealand (McDougall et al., 2021). Although the study was carried out in New Zealand, participating herds were all certified under the USDA National Organic Program. Conventional herds of both categories were selected on the basis that >50% of the cows were treated in each of the 3 previous years with at least 1 DCT product. Similar to Pol and Ruegg (2007a), the authors took a multifaced approach to exploring the resistance patters of *S. aureus* and CNS from organic and conventional systems. Overall, the authors found that the MIC of CNS from ORG herds were lower than isolates from both types of CON herd. For *S. aureus,* they found that the MIC50 for ampicillin and penicillin were greater by more than 1 dilution for isolates from CON-CE herds compared with CON-CA and ORG herds, but this relationship did not hold for the MIC90 of these drugs (MIC for CON-CE and ORG herds was greater than that for CON-CA herds).In a univariate analysis, the proportion of penicillin-resistant *S. aureus* isolates was significantly higher in CON-CE herds (76/111; 68.5%) compared to CON-CA (4/99; 4.0%) or ORG herds (32/110; 29.1%). A multilevel model (accounting for clustering of quarter within cow within herd) was made, where the 3 herd types were the main explanatory variable. Other potential variables offered to this model included age of the cow, breed, DIM at time of sampling, SCC at last test, and antimicrobial treatment history for that cow.In this multilevel model, the proportions of penicillin-resistant *S. aureus* isolates did not differ between the 3 herd types. For analysis of resistance to ceftiofur, sulfadimethoxine, and erythromycin, 3 different groupings of cut-points were made for each compound.When comparing proportion of *S. aureus* isolates falling into the 3 different cut-point groups for ceftiofur resistance, the only significant difference was that there were fewer organic isolates in the middle cut-point category (1 μg/mL); otherwise, there were no significant differences in the proportion of isolates falling into the different cut-point groups from each of the 3 herd types.When comparing proportion of *S. aureus* isolates falling into 3 different cut-point groups for sulfadimethoxine resistance, the only significant difference was that there were more organic isolates in the lowest category (32 μg/mL); otherwise, there were no significant differences in the proportion of isolates falling into the different cut-points from each of the 3 herd types.There were no significant differences between the 3 herd types when comparing the proportion of *S. aureus* isolates falling into 3 different cut-point groups for erythromycin resistance. For CNS isolates, they found that the MIC50 and MIC90 for ampicillin and penicillin were lower by more than 1 dilution for CNS isolates from organic herds compared to both types of conventional herds; otherwise, these values did not differ by more than 1 dilution between the 3 herd types for the other antimicrobials tested.In a univariate analysis, proportions of penicillin-resistant CNS isolates were significantly greater in both types of conventional herds (CON-CE, 42/82; 51%; CON-CA, 22/74; 30%) than organic herds (14/84; 17%). Similar to the analyses for *S. aureus,* a multilevel model was also made to compare penicillin resistance with herd type as the main explanatory variable. In this multilevel model, proportion of penicillin-resistant CNS isolates was significantly greater for CON-CE herds (0.50 ± 0.07) compared to CON-CA (0.31 ± 0.06) or ORG herds (0.17 ± 0.05).When comparing proportion of CNS isolates falling into 3 different cut-point groups for ceftiofur resistance, the only significant difference was that there were more organic isolates in the lowest (0.5 μg/mL) and highest (2 μg/mL) categories compared to both conventional herd types; otherwise, there were no significant differences in the proportion of isolates falling into the different cut-points from each of the 3 herd types.There were no significant differences between the 3 herd types when comparing the proportion of CNS isolates falling into 3 different cut-point groups for sulfadimethoxine resistance.When comparing proportion of CNS isolates falling into 3 different cut-point groups for erythromycin resistance, the only significant difference was that there were more CON-CA isolates in the highest category (≥1 mg/mL); otherwise, there were no significant differences in the proportion of isolates falling into the different cut-points from each of the 3 herd types.Importantly, the authors point out that any differences in MIC between isolates from different herd types occurred below clinical breakpoints, and so therefore may not affect bacteriological cure rates. Rather unexpectedly, they found bimodal distributions of MIC for ampicillin and penicillin in *S. aureus* isolates from organic herds, and suggest either (1) isolates with a higher MIC are “a natural part of the bacterial population of the bovine mammary gland,” or (2) isolates with higher MIC have persisted within organic herds from a time when antimicrobials were used on the farm.

**Studies about transitioning**

Bennesgaard (EU) – dup -- SOME AM quant

Park

* Other short communications that aren’t in the table
  + Studies on transitioning
    - Park 2012
    - Can compare to Erskine one which was long term
  + Rajala-schultz
    - Not organic, but cows exposed to dry treat and not
      * Age has so many other effects on animals though
      * Type of NAS, immune function, SCC
  + Fecal papers
    - Whole other body of work, different system
      * Different exposures, different pathogen behavior, different pathogen community interactions
* **Limitations of some of the studies**
  + Enumeration/standardization of drug usage
  + Europe vs. US
  + Complicated to compare between
    - Sampling strategies
    - Methodology of determination of antibiograms
      * agar diffusion, broth microdilution
      * the interpretive criteria used for categorizing isolates as susceptible or resistant are based on human data for the majority of compounds tested (Watts and Yancey, 1994; Thornsberry et al., 1997). They cannot be used to predict clinical efficacy and they may not accurately reflect the efficacy of the drug in treatment of bovine mastitis
  + Summarized in Call 2008
    - post-hoc analysis of individual studies is highly problematic due to differences in methods used (e.g. disc diffusion versus serial broth dilution and changing criteria) (Klement et al., 2005); failure to speciate the organisms under study when there can be considerable variation between species and strains (Rossitto et al., 2002); changes in management practices; differences in sample collection and culture methods can bias recovery of organisms; differences in sampling frame (independence between isolates; random, opportunistic, or clinical sampling) can also introduce bias; stochastic events (e.g. heterogeneous clonal dissemination) could easily bias interpretation of smaller studies; even well-organized, large-scale, and centralized studies encounter deviations in study protocols and unequal reporting efforts that make comparisons between countries tenuous (Hendriksen et al., 2008).
      * Clinical cases: analyses of clinical isolates, it is important to acknowledge that resistant isolates may be amplified by therapeutic treatments that are administered to sick animals prior to isolation of resistant organisms; this may bias prevalence estimates for AMR pathogens compared with a random sampling design
    - as with all correlation studies readers should be cautious about inferring causation when there are limited controls for confounding variables or when conclusions are drawn from a limited number of independent observations
  + *“variation among herds in MIC may in part be due to introduction of resistant isolates, rather than selection for, or perpetuation of, such isolates within a herd. Additionally, other mastitis management practices may affect the probability that resistant isolates remain in the herd. For example, selection criteria for culling of cows may remove cows infected with resistant isolates”* McDougall 2021
* **Overall significance of this work?**
  + Many MIC below clinical breakpoints – so, technically still susceptible – so, what is clinical significance? Not really sure. BUT keeping an eye on it; and reporting MIC numbers, not just lumping in as SIR bc those cut points change over time
    - bacteriological cure rates may not differ between isolates of differing MIC
* **What else explains degree of AMR carriage? Herd effect** – clonality, esp. of contagious organisms
  + Dominant strain aureus may have resistance
  + Different strains associated with carrying resistance?
    - Find literature
  + So, dominant strain in one herd may carry resistance
  + Strain associated with resistance – phylogeny and not just env. pressures
    - From Call 2008: Walk et al. (2007) found that on average organic and conventional dairies have different representation of phylogenetic groupings of E. coli, suggesting there are differences between lineages of E. coli in their ability or probability of assimilating resistance genes
* **What else explains degree of AMR carriage? Species effect** – carriage of AMR likely associated with species of CNS
  + Older studies not differentiating
  + Literature showing AMR difference by species of NASM?
    - Strep: Rossitto PV, Ruiz L, Kikuchi Y, Glenn K, Luiz K, Watts JL and Cullor JS (2002). Antibiotic susceptibility patterns for environmental streptococci isolated from bovine mastitis in central California dairies. Journal of Dairy Science 85: 132–138.
* **Why is AMR maintained in organic systems at all?**
  + When is “long enough” not to be have selective pressure still on bacteria? Amount of time a dairy has been organic/no antimicrobial usage at all
  + Call 2008: “*transient expansion of resistant populations can lead to genetic linkage with other selective traits that permit long-term persistence of AMR subpopulations in production environments”*
    - Example of persistence, chloramphenicol banned but still finding resistance 20 years later:
      * One study found that bacteria from retail ground beef from conventional operations had a higher prevalence of chloramphenicol and ceftiofur resistant bacteria, but there were no differences for nine other antimicrobials (LeJeune and Christie, 2004). It should be noted that chloramphenicol has been banned from use in US food animals since 1986 because of the risk of aplastic anemia and elevated risk of lymphoma in humans (Settepani, 1984), and thus the mechanism allowing persistence of chloramphenicol resistance in fecal bacteria is unclear for US cattle populations
  + Lots of other notes about this in Call above
    - Heuristic model they propose

*Original outline (not deleting parts from here)*

* **Intro material (set up the premise)**
  + Resistance to antibiotics may be acquired by spontaneously occurring genetic mutations, and be passed vertically by selection to daughter cells. More commonly, resistance is acquired by the horizontal transfer of mobile DNA elements from a donor cell, often from another bacterial species (Chambers, 2001; Sefton, 2002). The two main factors involved in the development of antibiotic resistance in bacteria are the selective pressure by the use of antibiotics and the presence of resistance genes (Levy, 1997; Witte, 2000).
  + There is growing evidence and little doubt that resistance genes can be spread and exchanged between different bacterial populations (McDermott et al., 2002; O’Brien, 2002; Teale, 2002). Resistance that is acquired by horizontal transfer of resistance genes can become rapidly and widely disseminated either by clonal spread of the resistant strain itself or by further genetic exchanges between the resistant strain and other susceptible strains (Chambers, 2001)
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      * Phillips I, Casewell M, Cox T, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. J Antimicrob Chemother 2004;53:28 –52.
    - *“Generally, percentages of antimicrobial resistance before (conventional) were significantly higher than after (organic) the transition. Overall, percentages of antimicrobial resistant mastitis pathogens decreased after 6 months operating as an organic farm system. An 8-month study was conducted in Thailand to investigate the effects of antimicrobial-resistant patterns of mastitis pathogens during an experimental farm’s 6-month transition from conventional to organic farming. Antimicrobial resistance of mastitis pathogens in the before (conventional) and after (organic) transition periods were compared for 7 antimicrobial drugs used to treat mastitis.”*
      * Suriyasathaporn W. Milk quality and antimicrobial resistance against mastitis pathogens after changing from a conventional to an experimentally organic dairy farm. Asian Austral J Anim Sci May 1, 2010
    - Erskine RJ, Walker RD, Bolin CA, et al. Trends in antibacterial susceptibility of mastitis pathogens during a seven-year period. J Dairy Sci 2002;85:1111– 8
      * Not much evidence that ***AMR increasing over time,*** which is a different question
      * 7-year study of Michigan dairy herds; the proportion of bacterial isolates susceptible to antibiotics did not change for the majority of tests
      * Overall, the prevalence of AMR over a 7-year period did not change (1994–2000). The prevalence of S. aureus isolates resistant to ampicillin, penicillin and erythromycin declined during this period. Streptococcus uberis isolates became more susceptible to oxacillin, sulfa-trimethoprim gentamicin, and pirlimycin while becoming more resistant to penicillin. Linear declines in AMR were also reported for Streptococcus dysgalactiae, Streptococcus agalactiae, E. coli and Klebsiella pneumoniae. Overall, the authors concluded that there was no indication of increased resistance among mastitis clinical isolates for antimicrobials used commonly to treat mastitis
    - Nam HM, Lim SK, Kang HM, et al. Prevalence and antimicrobial susceptibility of gram-negative bacteria isolated from bovine mastitis between 2003 and 2008 in Korea. J Dairy Sci 2009;92:2020 – 6. 31.
    - Nam HM, Lim SK, Kang HM, et al. Antimicrobial resistance of streptococci isolated from mastitic bovine milk samples in Korea. J Vet Diagn Invest 2009;21:698 –701.
* **BUT support for using AB**
  + Call 2008: decreasing animal health could increase the probability of a higher pathogen load in these animals with commensurate increased risk of exposing humans to genuine pathogens (Cox and Popken, 2006) (also see Claycamp (2006)).
  + It reduces the suffering of animals and prevents pathogenesis in humans via consumption of milkborne/foodborne mastitis pathogens that are potential human pathogens
  + Danger of consumption of raw milk
    - Oliver SP, Boor KJ, Murphy SC, et al. Food safety hazards associated with consumption of raw milk. Foodborne Pathog Dis 2009;7:793– 806.
  + Find papers about pain/inflammation associated with mastitis
    - An Update on the Effect of Clinical Mastitis on the Welfare of Dairy Cows and Potential Therapies
    - Christina S Petersson-Wolfe 1, Kenneth E Leslie 2, Turner H Swartz 3
    - Assessment and Management of Pain in Dairy Cows with Clinical Mastitis Kenneth E. Leslie, DVM, MSca,\*, Christina S. Petersson-Wolfe
    - Ginger L, Ledoux D, Bouchon M, Rautenbach I, Bagnard C, Lurier T, Foucras G, Germon P, Durand D, de Boyer des Roches A. Using behavioral observations in freestalls and at milking to improve pain detection in dairy cows after lipopolysaccharide-induced clinical mastitis.
* **Summarize studies**
  + Start out with weaker, smaller ones
  + Describe results of largest, most rigorous analysis ones
    - Ruegg
    - Mcdougall
  + Other short communications that aren’t in the table
    - Studies on transitioning
      * Park 2012
      * Can compare to Erskine one which was long term
    - Walther 2007, org farm with MRSA epi – maybe this goes with point in cicconi hogan about org status doesn’t matter in regards to being source for MRSA
    - Rajala-schultz
      * Not organic, but cows exposed to dry treat and not
        + Age has so many other effects on animals though
        + Type of NAS, immune function, SCC
    - Fecal papers
      * Whole other body of work, different system
        + Different exposures, different pathogen behavior, different pathogen community interactions
* **Limitations of some of the studies**
  + Enumeration/standardization of drug usage
  + Europe vs. US
  + Complicated to compare between
    - Sampling strategies
    - Methodology of determination of antibiograms
      * agar diffusion, broth microdilution
      * the interpretive criteria used for categorizing isolates as susceptible or resistant are based on human data for the majority of compounds tested (Watts and Yancey, 1994; Thornsberry et al., 1997). They cannot be used to predict clinical efficacy and they may not accurately reflect the efficacy of the drug in treatment of bovine mastitis
  + Summarized in Call 2008
    - post-hoc analysis of individual studies is highly problematic due to differences in methods used (e.g. disc diffusion versus serial broth dilution and changing criteria) (Klement et al., 2005); failure to speciate the organisms under study when there can be considerable variation between species and strains (Rossitto et al., 2002); changes in management practices; differences in sample collection and culture methods can bias recovery of organisms; differences in sampling frame (independence between isolates; random, opportunistic, or clinical sampling) can also introduce bias; stochastic events (e.g. heterogeneous clonal dissemination) could easily bias interpretation of smaller studies; even well-organized, large-scale, and centralized studies encounter deviations in study protocols and unequal reporting efforts that make comparisons between countries tenuous (Hendriksen et al., 2008).
      * Clinical cases: analyses of clinical isolates, it is important to acknowledge that resistant isolates may be amplified by therapeutic treatments that are administered to sick animals prior to isolation of resistant organisms; this may bias prevalence estimates for AMR pathogens compared with a random sampling design
    - as with all correlation studies readers should be cautious about inferring causation when there are limited controls for confounding variables or when conclusions are drawn from a limited number of independent observations
  + *“variation among herds in MIC may in part be due to introduction of resistant isolates, rather than selection for, or perpetuation of, such isolates within a herd. Additionally, other mastitis management practices may affect the probability that resistant isolates remain in the herd. For example, selection criteria for culling of cows may remove cows infected with resistant isolates”* McDougall 2021
* **Overall significance of this work?**
  + Many MIC below clinical breakpoints – so, technically still susceptible – so, what is clinical significance? Not really sure. BUT keeping an eye on it; and reporting MIC numbers, not just lumping in as SIR bc those cut points change over time
    - bacteriological cure rates may not differ between isolates of differing MIC
* **What else explains degree of AMR carriage? Herd effect** – clonality, esp. of contagious organisms
  + Dominant strain aureus may have resistance
  + Different strains associated with carrying resistance?
    - Find literature
  + So, dominant strain in one herd may carry resistance
  + Strain associated with resistance – phylogeny and not just env. pressures
    - From Call 2008: Walk et al. (2007) found that on average organic and conventional dairies have different representation of phylogenetic groupings of E. coli, suggesting there are differences between lineages of E. coli in their ability or probability of assimilating resistance genes
* **What else explains degree of AMR carriage? Species effect** – carriage of AMR likely associated with species of CNS
  + Older studies not differentiating
  + Literature showing AMR difference by species of NASM?
    - Strep: Rossitto PV, Ruiz L, Kikuchi Y, Glenn K, Luiz K, Watts JL and Cullor JS (2002). Antibiotic susceptibility patterns for environmental streptococci isolated from bovine mastitis in central California dairies. Journal of Dairy Science 85: 132–138.
* **Why is AMR maintained in organic systems at all?**
  + Call 2008: “*transient expansion of resistant populations can lead to genetic linkage with other selective traits that permit long-term persistence of AMR subpopulations in production environments”*
    - Example of persistence, chloramphenicol banned but still finding resistance 20 years later:
      * One study found that bacteria from retail ground beef from conventional operations had a higher prevalence of chloramphenicol and ceftiofur resistant bacteria, but there were no differences for nine other antimicrobials (LeJeune and Christie, 2004). It should be noted that chloramphenicol has been banned from use in US food animals since 1986 because of the risk of aplastic anemia and elevated risk of lymphoma in humans (Settepani, 1984), and thus the mechanism allowing persistence of chloramphenicol resistance in fecal bacteria is unclear for US cattle populations
  + Lots of other notes about this in Call above
    - Heuristic model they propose

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