***Where does description of NASM AMR go (relative to limitations and summary of studies?***

***Where does description of NASM risk factors go (relative to limitations and summary of studies)?***

***Where does paragraph about herd-level clonal effect go?***

***Abstract***

***Introduction***

Effective antimicrobial therapy is a cornerstone of livestock veterinary medicine, maintaining the health of animals producing food and fiber to support the global population and alleviating suffering due to infectious disease. However, it is generally accepted that any use of antimicrobial agents is a “powerful selective force that promotes the emergence of resistant strains,” and that the cumulative effect of antibiotic use in general has “clearly been to increase the prevalence of resistance in the population [of bacteria] as a whole” (Lipsitch and Samore, 2002). Resistance to antimicrobials can be acquired by bacteria in multiple ways. Spontaneously occurring genetic mutations (passed vertically to daughter cells) can confer antimicrobial resistance, but more commonly it is acquired by the horizontal transfer of mobile DNA elements from a donor cell, which is often another species of bacteria (Chambers, 2001; Sefton, 2002). In the case of horizontal transfer, antimicrobial resistance genes can become rapidly and widely disseminated throughout a bacterial population either by further genetic exchanges between the newly-resistant strain and other susceptible strains, or by clonal spread of the newly-resistant strain itself (Chambers, 2001).Although the interplay between bacterial susceptibility, antimicrobial use, and resistance is complex and multifactorial, it is generally accepted that antimicrobial resistance (AMR) is potentially amplified in both human healthcare environments and on farms, where frequent exposure to antimicrobial compounds can select for resistant populations of bacteria (Parker et al., 2024). A direct temporal relationship between antimicrobial use and resistance has been described, both in human healthcare settings over the long-term (López-Lozano et al., 2000) and transient increases in resistant fecal bacteria in cattle (Stabler et al., 1982; Langford et al., 2003; Berge et al., 2005; Lowrance et al., 2007). It has been suggested that antimicrobial usage in food animals could negatively affect human health by influencing the selection of drug-resistant foodborne pathogens (Yan and Gilbert, 2004). However, the risk of resistant bacteria from farm systems to humans is not fully understood, as selection for resistant bacteria and transfer of AMR genes occurs through a variety of mechanisms and is not always linked to use of a specific antibiotic (Mathew et al., 2007).

According to Call et al. (2008), the most “obvious selection pressure for AMR” on cattle farms is the use of antimicrobials for treating sick animals, which can promote AMR by two potential mechanisms: 1) treatment with antimicrobials provides a competitive advantage for strains that carry resistance to that particular drug, allowing resistant bacterial populations to increase; and 2) if resistance genes are harbored on horizontally transmissible elements (plasmids, conjugative transposons), strains carrying these elements can then successfully disseminate them to new, previously-susceptible bacteria. The primary reason for antimicrobial drug usage in adult dairy cows in the US is for treatment of mastitis (Pol and Ruegg, 2007b). Bacteria belonging to the genus *Staphylococcus*, which broadly includes the major mastitis pathogen *Staphylococcus aureus* and a heterogeneous group of bacteria known as the non-aureus staphylococci and mammaliicocci (NASM), are the predominant pathogens causing IMI in dairy animals globally (as summarized in De Buck et al., 2021). A limited number of antimicrobials are approved for treatment of mastitis in lactating dairy cattle in the US, including various β-lactams (penicillin, cephapirin, ceftiofur, amoxicillin, hetacillin, and cloxacillin) and one lincosamide (pirlimycin) (FARM, 2020). At this time, *S. aureus,* NASM, and other mastitis pathogens are generally susceptible to antibiotics currently used to treat IMI (Kolar et al., 2024; Pol and Ruegg, 2007b; with the notable exception of *S. aureus* and NASM exhibiting resistance against penicillin). However, continued surveillance of AMR patterns for these ubiquitous mastitis pathogens is warranted, as the importance of *S. aureus* as a human pathogen is well-established (Tong et al., 2015), and virulence genes known to cause disease in both humans and animals have been demonstrated in NASM isolates from bovine IMI (Park et al., 2011; Unal and Cinar, 2012). Additionally, transmission of resistance genes between different staphylococcal species have led to the idea that NASM may act as a “reservoir” of AMR for more pathogenic staphylococcal species such as *S. aureus* (Cuny et al., 2017; Feßler et al., 2018; Khazandi et al., 2018).

A unique opportunity in which to assess the effect of antimicrobial use on AMR of these important mastitis pathogens is to compare dairy farm systems which are managed “conventionally” to those that are managed “organically.” Although the definition differs between countries in the EU and the US (see below), antimicrobial usage on “organic” dairies generally is usually less or non-existent when compared to “conventional’” dairy farms. When comparing bacterial isolates of bovine origin from these two types of systems, the general hypothesis is that AMR likely diminishes in prevalence when antimicrobial use is decreased or discontinued. When the selective pressure of antimicrobial usage is removed (as on organic dairies), bacterial strains that containing resistance genes are gradually replaced by susceptible strains, as selective advantage is no longer conferred by AMR carriage. The goal of this narrative review is to summarize studies which compared the relationship between antimicrobial usage at the farm level (organic vs. conventional) and antimicrobial susceptibility of bovine staphylococcal mastitis isolates.

***Limitations and caveats for comparisons between studies***

An important caveat when considering the body of work comparing resistance patterns of mastitis pathogens between management systems is that “organic” dairies differ between the US and Europe, where the majority of these studies have been carried out. Organic regulations in 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 be permanently 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 systems difficult. Specific 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 what is meant by “organic” dairy production in a retrospective analysis. An additional layer of complexity is that the specific antimicrobials approved for usage in livestock varies by country, as well as which compounds are most commonly-used (e.g., for mastitis: penicillin in Finland, Taponen 2023; cephalosporins in the US, de Campos 2021). Even within the US, the amount and type of antimicrobials used in dairy cows changes over time as new products are developed or regulations around usage shift (USDA, 2009). Consequently, geographic and temporal differences affect the type and amount of antimicrobial selective pressure experienced by mastitis pathogens.

Direct comparison of results across studies reporting antimicrobial sensitivity of mastitis pathogens on organic and conventional farms is problematic for a number of reasons. Importantly, methodology used to determine MIC or categorization of an isolate as susceptible, intermediate, or resistant varies between studies (Table XX). Further, discrepancies exist between phenotypic and genotypic test results, due either to detection of phenotypic resistance in the absence of expected genotypic determinants, or phenotypic susceptibility despite the presence of genotypic determinants. For isolates of *S. aureus* associated with bovine mastitis, both of these types of discrepancies have been reported for penicillin resistance (Sampimon, 2009; Taponen et al., 2023). This also holds true for the other staphylococci: “agreement between phenotypic and genotypic test results for assessment of resistance of CNS of bovine origin to penicillin, oxacillin, and ML [macrolide] antibiotics depended on the antimicrobial compound of interest and on methods used to analyse and interpret test results, but was rarely perfect” (Sampimon, 2009). In a study by Taponen et al. (2023) comparing methods of testing for β-lactamase mediated resistance in staphylococci from cases of bovine mastitis, overall agreement between phenotypic and genotypic resistance tests was moderate to substantial. However, there were some inconsistencies between phenotypic susceptibility by disk diffusion method, the nitrocefin test to assess β-lactamase production, and PCR to detect the presence of the *blaZ, mecA*, and *mecC* genes encoding the β-lactamase gene. Discrepancies also exist between different methods of phenotypic determination of resistance for mastitis isolates. A study comparing agreement between broth microdilution (Sensititre Custom Plates) and agar disk diffusion for determining antimicrobial susceptibility of isolates from bovine mastitis found fair agreement overall (80.7%) between the two methods, but this varied based on the particular bacterial-antimicrobial combination tested (Palladini et al., 2023). No NASM species were tested, but there was satisfactory agreement (89 to 100%) for *S. aureus* and all antimicrobial agents tested. In a study comparing Sensititre (broth microdilution) and disk diffusion for determining AMR in clinical mastitis pathogens, agreement was good between the two methods for most isolate-antimicrobial MIC combinations (Saini et al., 2011). An important caveat in this study was that diagnostic accuracy was low when *S. aureus* was tested against both ceftiofur and oxacillin with either method. Low correlation between the two methods was also found when *S. aureus* was tested against erythromycin and neomycin in another study comparing dilution methods to determine MIC and disk diffusion diameters for mastitis bacterial isolates (Klement et al., 2005). Further complicating comparison of AMR profiles between studies is shifting criteria for classifying an isolate as susceptible or resistant. Breakpoints for antimicrobial susceptibility testing are updated every few years, and there are multiple conflicting standards for categorization of resistant or susceptible bacteria which are dependent on geographical location (Clinical & Laboratory Standards Institute, CLSI; European Committee on Antimicrobial Susceptibility Testing, EUCAST).

Difference in sampling scheme for studies collecting milk from individual cows will affect observed resistance profiles in bacteria isolated from samples. Within the studies summarized in Table XX, sampling strategies for quartermilk and criteria for cow inclusion vary widely. Some studies included sampled cows in a herd at random or without using any specific criteria (Tikofsky et al., 2003; Bombyk et al., 2008; Garmo et al., 2010), while others used CMT to selectively sample cows with evidence of extant mastitis (Busato et al., 2000; Roesch et al., 2006). Bennedsgard et al. (2006) used a specific set of criteria in order to maximize their chances of sampling cows with *S. aureus* IMI specifically, while others sampled only multiparous cows in the herd (Pol and Ruegg, 2007a; McDougall et al., 2021). Sampling multiparous cows exclusively increases the likelihood samples collected will have an IMI, as increasing parity is a risk factor for mastitis generally (Barkema et al., 1998; Busato et al., 2000) and IMI with *S. aureus* specifically (Zadoks et al., 2001; Tenhagen et al., 2006). Additionally, the prevalence and distribution of NASM species causing IMI varies by parity (see above/below XX), so sampling multiparous cows exclusively will bias which species are included and thereby the resistance profiles of mastitis pathogens described (as resistance patterns are species-specific for NASM).

An additional consideration for studies describing AMR of isolates from bovine mastitis is whether the bacteria were associated with cases of subclinical mastitis, clinical mastitis, or both (or not specified; Table XX). AMR is more prevalent in NASM isolates associated with clinical vs. subclinical mastitis, so inclusion criteria around sample type will affect the observed AMR prevalence. Oxacillin resistance was found to be more frequent in clinical mastitis isolates (56.5%) than in subclinical mastitis isolates (43.9%; Frey et al., 2013), and β-lactamase production was more common in subclinical vs. clinical cases (Persson Waller et al., 2011). Wuytack et al. (2020) found that carriage of the resistance gene *mecA* was proportionately higher in NASM isolates causing clinical vs. subclinical infection. However, as certain NASM species are more likely to be associated with cases of clinical mastitis vs. subclinical mastitis and vice versa (Persson Waller et al., 2011; although, see Condas et al., 2017b) and resistance patterns of NASM are species-specific, the difference in AMR prevalence between samples from clinical vs. subclinical may ultimately result from species differences between the 2 categories. In Persson Waller et al. (2011), *S. epidermidis* and *S. saprophyticus* were more prevalent in subclinical vs. clinical mastitis, while *S. hyicus* was more common in clinical mastitis. The authors attribute the higher proportion of penicillin resistance in subclinical vs. clinical isolates to the high prevalence of *S. epidermidis* and *S. saprophyticus* in subclinical mastitis samples, as these species demonstrated significantly more penicillin resistance compared with other NASM species. Further support that differences in AMR for NASM isolates associated with clinical vs. subclinical mastitis is primarily a result of species differences is found in Naushad et al. (2018). In their analyses of 328 NASM isolates from subclinical mastitis and 57 isolates from clinical mastitis, they found that within the same species, no significant differences existed in the prevalence of drug-specific AMR or resistance determinants when contrasting the two sample types.

***Other factors explaining differences in antimicrobial susceptibility of staphylococci***

* ***Most (all) studies didn’t speciate CNS***
* ***Different NASM species vary in AB susceptibility***

Table XX summarizes work describing the species-specific antimicrobial susceptibility of staphylococci isolates from bovine IMI. The 10 observational studies included describe phenotypic resistance profiles and are limited to work where isolates were speciated using genotypic techniques or MALDI-TOF. Overall, resistance to β-lactam antibiotics is the predominant type of AMR present in NASM as a group. The reported proportion of NASM isolates with β-lactamase resistance can be fairly high, with 51.6% phenotypically resistant to penicillin in Argentina (Raspanti et al., 2016), 63% phenotypically resistant to penicillin in South Africa (Phophi et al., 2019), and 80% of CNS isolates positive for the *blaZ* gene (encoding the production of a β-lactamase enzyme) in a study from the Netherlands (Sampimon, 2009). Proportion of phenotypically penicillin-resistant NASM seems to vary geographically, with Nordic countries reporting 34% (Nyman et al., 2018), 23% (Fergestad et al., 2021), and 29% (Persson Waller et al., 2011), while a Korean study found 14% of NASM isolates were resistant to penicillin (Kim et al., 2019) and Nobrega et al. (2018) report a prevalence of 10% in Canada. β-lactam antibiotics are among the few choices for treating mastitis in the US, with first- and third-generation cephalosporins being the most commonly-used mastitis treatment (USDA, 2016; de Campos et al., 2021). Moderate resistance has been observed in NASM against tetracycline, another highly important antimicrobial frequently used in dairy herds, with 30.1%, 20.9%, and 10% of isolates reported to be resistant in Argentina, India, and Canada, respectively (Raspanti et al., 2016; Mahato et al., 2017; Nobrega et al. 2018). This marked geographic variation in resistance patterns may likely be due to differing selective pressure in dairy farm systems around the world. Which specific antimicrobials are most typically used to treat mastitis and in what amount, as well as the various regulation around their usage, varies from country to country.

Another factor contributing to differences in AMR among staphylococci as a group is that distribution and prevalence of NASM species varies geographically (SEE above/below; XX). Studies comparing resistance profiles of NASM by species consistently show that AMR profile varies between species (Sampimon, 2009; Persson Waller et al., 2011; Taponen et al., 2016; Nobrega et al., 2018; Fergestad et al., 2021; Taponen et al., 2023). Overall, both phenotypic resistance and resistance genes are relatively rare in the most common species, *S. chromogenes,* in comparison to other NASM (Sampimon, 2009; Persson Waller et al., 2011). A notable exception is the presence of *blaZ* gene, which was found in 80% of all 170 CNS isolates and 87% of *S. chromogenes* in a Flemish study (Sampimon, 2009). β-lactamase production was significantly lower for *S. chromogenes* vs. *S. epidermidis* and *S. haemolyticus* in Sweden (Persson Waller et al., 2011). Although a smaller-scale study in Argentina found a relatively high proportion of *S. chromogenes* were resistant to penicillin (45.1%), both *S. haemolyticus* and *S. xylosus* had an even higher proportion of penicillin-resistant isolates (58.6% and 92.9%, respectively; Raspanti et al., 2016). Across a number of studies, authors report some less-commonly isolated NASM species carried the most concerning AMR profiles. Sampimon et al. (2011) found a high prevalence of genotypic resistance (particularly *mecA*) or presence of multiple resistance genes in species with relatively a low prevalence (*S. cohnii, S. equorum, S. fleurettii, S. sciuri*). In Nobrega et al. (2018), resistance to quinupristin/dalfopristin (a combination of 2 drugs used to treat serious nosocomial infections in humans) was common in *S. gallinarum* (98% prevalence of resistance among isolates), and *S. cohnii* and *S. arlettae* were frequently resistant to erythromycin (prevalence of 63 and 100%, respectively). The authors specifically highlight *S. arlettae* as particularly concerning in its AMR profile; it had the highest prevalence of AMR against penicillin (61%), ampicillin (23%), erythromycin (100%), pirlimycin (18%) and clindamycin (99.9%), as well as the highest prevalence of multidrug resistance. A number of studies also call attention to concerning AMR patterns for *S. epidermidis,* which is moderately common in the US and Canada but one of the predominant species found in Nordic countries. In Sampimon et al. (2009), *S. epidermidis* was the second most commonly-found species, it carried multiple resistance genes in ~50% of isolates, and phenotypic penicillin resistance was more common compared to other CNS. The proportion of penicillin-resistant isolates was highest for *S. epidermidis* in a Finnish study compared to other NASM, with *S. epidermidis* accounting for 6/8 NASM isolates carrying the *mecA* gene (Taponen et al., 2023). Similarly, β-lactamase production was higher for *S. epidermidis* compared to other species (Persson Waller et al., 2011), and itwas one of a few species where AMR (including resistance to trimethoprim-sulfonamide) was most frequently observed in Fergestad et al. (2021). Lastly, Taponen et al. (2016) found that *S. epidermidis* was the most resistant among the four major species studied, several isolates were multidrug resistant, and 19% of isolates were *mecA*-positive (encoding methicillin resistance).

Even within a given species, AMR carriage has been linked to certain strain types. For *S. aureus*, carriage of methicillin resistance has been linked to particular clonal complexes both in human medicine (Smith et al., 2021; Garrine et al., 2023) and certain clusters of *spa* ­type for bovine clinical mastitis isolates (Freu et al., 2022). The linkage between strain type and AMR is not as well studied for NASM, but Persson Waller et al. (2023) found that *blaZ* was significantly more common among *S. chromogenes* strains belonging to 2 specific clusters of strain types vs. strains belonging to other clusters.

***Not sure where this goes:***

A related factor explaining some variation in AMR carriage of mastitis isolates is clonal dissemination within a particular herd. Consistent with the behavior of a contagious mastitis pathogen, a particular strain or strains of *S. aureus* will predominant for any given herd (Lange et al., 1999; Zadoks et al., 2000; Freu et al., 2022). If the dominant strain of *S. aureus* causing IMI in a dairy herd happens to carry a certain AMR determinant, a high proportion of isolates from that herd will likely be phenotypically resistant to that particular antimicrobial: not as a result of environmental pressures and selection, but strictly as a consequence of phylogeny and the behavior of the pathogen itself. As Call et al. (2008) point out, this effect of a dominant strain type within a herd can lead to issues of non-independence between isolates from a particular farm. This would especially be a problem for studies enrolling a relatively small number of herds. Pol and Ruegg (2007a) directly address this issue in their study of 40 herds. They state that in order to avoid statistical dependence, only 1 isolate per cow and no more than 20 isolates per herd were included in the analysis; additionally, they report the range of isolates used per herd for the different categories of mastitis pathogens.

* ***Different animal factors and mgmt. factors influence what NASM species predominate for a farm, animal***

Numerous regional and herd-level factors risk-factors have been identified explaining some of the diversity and prevalence of different NASM species associated with mastitis and bulk tank milk. Different times of year were associated with higher likelihood of IMI for *S. chromogenes, S. haemolyticus, S. xylosus,* and *S. warneri* in Dolder et al. (2017), and *S. cohnii, S. simulans, S. sciuri* in BTM in De Visscher et al. (2017). Geographical differences in NASM species diversity among quartermilk samples have been documented, between 4 regions in Canada (Condas et al., 2017a) and 4 states in the US (Jenkins et al., 2019). Although *S. chromogenes* is the dominant species causing IMI in many countries (as summarized in De Buck et al., 2021), *S. epidermidis* (closely followed by *S. simulans*) was the most commonly-found species in both a Finnish (Taponen et al., 2022) and a Swedish study (Nyman et al., 2018). It is difficult to discern whether or not these differences in species diversity are truly a function of geographical variation, or are a result of farms in the same region sharing certain management practices resulting in similar NASM species prevalence and diversity. At the herd level, facility type has been shown to explain some of the diversity of NASM species: for herds using a tiestall barn, prevalence of IMI due to *S. simulans*, *S. xylosus, S. cohnii, S. saprophyticus, S. capitis,* and *S. arlettae* was higher, and prevalence for *S. epidermidis* was lower(Condas et al., 2017a)*.* Herds in Canada using a bedded pack system were at higher relative risk for IMI due to *S. chromogenes* and *S. sciuri* (Condas et al., 2017a), while Adkins et al. (2022) found *S. cohnii*, *S. hyicus*, and *S. pseudintermedius* in BTM from sand-bedded freestalls (but not bedded packs), and *S. pasteuri* *and S. piscifermentan*s were unique to BTM from bedded packs. In a study by Piessens et al. (2011), sawdust bedding material was associated with IMI due to *S. xylosus* and *S. succinus* for Belgian dairy herds. De Visscher et al. (2017) identified a number of management practices around milking protocol and hygiene associated with the presence of different NASM species in BTM. These include a decreased risk for *S. xylosus, S. simulans,* and *S. chromogenes* in BTM from herds that clip udders, a decreased risk of *S. devriesei* in herds with consistent glove use during milking, an increased likelihood of *S. cohnii* in herds sharing towels between cows when drying udders, and a decreased likelihood of *S. haemolyticus, S. cohnii,* and *S. simulans* in herds that flushed or steamed milking units after use. Hogan et al. (1987) found more IMI due to *S. epidermidis* in herds using no teat dip compared to herds that did, that that *S. hyicus* constituted a greater proportion of staphylococci IMI in herds that used teat dip vs. herds that did not. However, it should be noted that speciation of staphylococci in this study was performed using a biochemical test, which may have had limited typeability and accuracy for identification of bovine staphylococci isolates (Vanderhaeghen et al., 2015). Lastly, some herd-level management factors associated with NASM diversity were related to feed and water provided to dairy cows: De Visscher et al. (2017) found an increased likelihood of *S. simulans* in BTM if drinking water for cows was from a public supply (vs. well), and Petzer et al. (2022) reported proportionally more IMI due to *S. chromogenes* from herds that were pasture-based compared to those that fed TMR, while *S. haemolyticus* was more prevalent among the TMR herds.

In addition to herd and regional differences, cow-level factors determining NASM diversity and prevalence have also been identified. Both Thorberg et al. (2009) and Mork et al. (2012) found that *S. chromogenes* was more likely to be isolated from first-lactation animals, while *S. epidermidis* was found more often in third-lactation and older cows. These findings are consistent with three other studies reporting *S. chromogenes, S. xylosus,* and *S. simulans* were more commonly found in heifers vs. third-lactation and older cows (De Visscher et al., 2016; Condas et al., 2017a; Nyman et al., 2018). Various NASM species causing IMI are predominant at different stages within a lactation: Dolder et al. (2017) found that *S. xylosus* was more commonly found in early lactation, and *S. warneri* was isolated from mid- to late-lactation animals, while Condas et al. (2017a) report the prevalence of *S. chromogenes, S. gallinarum, S. cohnii,* and *S. capitis* to be highest at freshening, and the prevalence of *S. chromogenes, S. haemolyticus, S. xylosus,* and *S. cohnii* increased throughout lactation. In Belgian herds, *S. chromogenes* was the predominant species causing IMI both at parturition and throughout lactation; the next most commonly seen species at freshening were *S. sciuri* and *S. cohnii* (De Visscher et al., 2016), while *S. simulans, S. xylosus, S. epidermidis,* and *S. haemolyticus* were the next most common causes for NASM IMI during lactation (Piessens et al., 2011; Supré et al., 2011). Dirty teats have been associated with an increased likelihood of IMI due to *S. cohnii, S. equorum, S. saprophyticus,* and *S. sciuri,* which the authors point out is consistent with a likely environmental origin for these species (De Visscher et al., 2016). Even physical features of the udder and teats have been associated with different NASM species (De Visscher et al., 2016: quarters with an inverted teat end had higher odds of being infected with *S. chromogenes, S. simulans,* or *S. xylosus*; Dolder et al., 2017: udder edema was a risk factor for IMI with *S. chromogenes*).

* ***Therefore, without speciation, can’t fully attribute differences to organic vs. conventional mgmt.; good deal of difference could likely due to species diversity/prevalence***
* ***Unmeasured animal or herd-level mgmt. factors could be confounding results***

***Summary of studies describing AMR of staphylococci from conventional vs. organic dairies***

The nomenclature for the group of staphylococci causing IMI excluding *S. aureus* has shifted over the past few decades, as both phylogeny and speciation techniques have evolved. Some species which had been previously identified as staphylococci were recognized more recently as belonging instead to a closely related genus (*Mammaliicoccus*), and identification methods beyond the coagulase test have become more widely used. Although NASM is the preferred term used throughout the rest of the review, the terminology used when referring to the results of a specific study is consistent with authors’ language and groupings of organisms (e.g., “coagulase-negative staphylococci,” or “CNS;” “non-*aureus* staphylococci,” or “NAS”), in an attempt to be consistent with the contemporary understanding of phylogeny and methodology.

Overall, studies comparing AMR of mastitis-associated staphylococci between herds under organic management and herds managed conventionally find either no difference or more susceptibility for isolates originating from organic farms (Table XX). However, these studies vary widely in their approach to exploring this question, primarily in 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 susceptibility 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 AMR 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 AMR 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 NAS isolates between systems was very similar (ORG: 9/19, 47%; CON: 10/19, 53%).

Contrastingly, Bombyk et al. (2008) found that overall, staphylococci causing mastitis on organic dairies were associated with more overall antimicrobial susceptibility than those from conventional farms. For this study, researchers differentiated mastitis-associated staphylococci 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 mastitis-associated bacteria between conventional and organic dairy systems have 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 was evaluated by management category, and numeric differences in mean zone diameter was compared 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 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 with the goal of surveilling dairy-associated methicillin-resistant *S. aureus* (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 geographical region and herd size, both of which were also significant 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 a 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 the 12 methicillin-resistant CNS) compared with previous work, and also suggest that a potential methicillin-resistant *Staphylococcus* reservoir in the dairy herd population of the US may be independent of the type of production system. 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 *S. 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 highlight that this finding demonstrates cows on organic farms may harbor multidrug-resistant staphylococci despite the limited use of antimicrobials 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 or presented. As the basis for this work is to evaluate if level of usage of antimicrobials in food animals selects 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 on intramammary pathogens. Although all antimicrobial usage is prohibited on US organic 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 report a standardized level of exposure to 10 different antimicrobials by calculating of the number of defined daily doses used per cow on each enrolled farm, and then categorize the 40 enrolled herds based on their respective antimicrobial usage. Herds are categorized into 3 groups: organic (no antimicrobial usage), conventional–low usage (conventional farms not using or using ≤ the first quartile of use of each drug; CON-LO), and conventional–high usage (conventional farms using > the first quartile of a particular drug; CON-HI). The 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 of “time to event,” antimicrobial concentration in wells of the susceptibility test was considered “time,” and the “event” was inhibition of any 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 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 comparing 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 dry cow therapy (CON-AC), and 8 conventional herds using cephalonium dry cow therapy (CON-CE) in New Zealand (McDougall et al., 2021). Although the study was carried out in NZ, 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 dry cow therapy (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.Results from this multilevel model showed that 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 breakpoints were made for each compound.When comparing the proportion of *S. aureus* isolates falling into the 3 different breakpoint groups for ceftiofur resistance, the only significant difference was that there were fewer organic isolates in the middle breakpoint category (1 μg/mL); otherwise, there were no differences in the proportion of isolates falling into the different breakpoint groups from each of the 3 herd types.When comparing the proportion of *S. aureus* isolates falling into 3 different breakpoint 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 differences in the proportion of isolates falling into the different breakpoint groups 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 breakpoint groups for erythromycin resistance. For CNS isolates, 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, the proportion of penicillin-resistant CNS isolates was 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 made to compare penicillin resistance of CNS with herd type as the main explanatory variable. Results from this multilevel model showed that the 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 the proportion of CNS isolates falling into 3 different breakpoint 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 differences in the proportion of isolates falling into the different breakpoint groups 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 breakpoint groups for sulfadimethoxine resistance.When comparing the proportion of CNS isolates falling into 3 different breakpoint 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 differences in the proportion of isolates falling into the different breakpoints 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, 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, suggesting 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.

Dairy farms in the process of transitioning from conventional management to organic certification provide a unique opportunity to study patterns resistance over time after a change in the level of antimicrobial exposure. In addition to comparing conventional and organic farms, Bennedsgaard et al. (2006) followed 19 Danish herds in the process of transitioning to certified organic dairies. These herds were sampled at year 0, 1, and 2 of transition, where quartermilk samples were collected from 30 cows at each farm at high risk of infection with *S. aureus* (as determined by a score based on a history of high SCC, breed, and lactation). Herds in the “old organic” category were certified for ≥ 5 years. Antimicrobial exposure for each herd was approximated by calculating the amount of mastitis treatments used, in % cows treated/cow-year. The amount of mastitis treatment used by the conventional group was significantly higher than the “old organic” herds, but no other significant differences existed between “old organic” herds or the conventional herds in comparison to any of the transition groups (transition year 1, transition year 2, transition year 3) with respect to usage of antimicrobial mastitis treatment. As previously mentioned, the prevalence of penicillin resistance in *S. aureus* and the proportion of penicillin-resistant isolates was similar between “old organic” and conventional herds. Furthermore, no differences were seen in these measures of penicillin resistance between “old organic,” conventional, or any of the transition groups. As the same 19 herds were sampled repeatedly over 3 years, the amount of penicillin resistance among *S. aureus* on these farms did not decrease year after year as they transitioned to organic status; this finding is somewhat unsurprising in light of the fact that antimicrobial usage also was not significantly different. In contrast, Park et al. (2012) found that β-lactam resistance rates of CNS decreased with discontinuation of β-lactam antibiotics in a study following 2 dairies through the process of converting from conventional to organic management over a 3-year period. Composite milk samples were collected from cows at the end of lactation, at freshening, and from cases of clinical mastitis during the last year of conventional dairy production, the transition year, and during the first year of organic production. While still conventional, cows with clinical mastitis were treated with an intramammary product with pirlimycin, and a product with cephapirin, streptomycin and penicillin, or novobiocin and penicillin was given to all cows at dry-off. There was a significant increase in zone diameter for mastitis-associated CNS isolates against cephalothin, cloxacillin, and penicillin when comparing the conventional vs. organic phase. There was no significant change in the zone diameter of the other 8 antimicrobials tested. Interestingly, no changes in resistance patterns were seen for mastitis-associated *S. aureus* isolates for the 12 antimicrobials tested. Of importance to note is that the 2 farms in Park et al. were in the US, and therefore antimicrobial usage was completely discontinued at the beginning of the transition to organic status. A similar small-scale case report from Thailand compared AMR of mastitis pathogens before and after the experimental farm’s transition from conventional to organic status for 7 antimicrobial drugs used to treat mastitis (Suriyasathaporn, 2010). All cows in the herd were sampled before beginning the transition, and after 6 months of operating as an organic dairy. The frequency of antimicrobial treatment on the farm decreased from <3 cases/month to > 1 case/month during the study period. Although isolate numbers were small (7 CNS isolates from before transition, 6 from after), a significant decrease was seen in the percent of CNS isolates resistant to gentamycin. Although numeric decreases in percent of resistant CNS isolates were seen for the other 6 antimicrobials, no changes were statistically significant. Data on susceptibility was not reported for *S. aureus* isolates.

***Why is AMR maintained in organic systems?***

In almost all studies summarized in this review, some degree of AMR was found in isolates despite decreased (EU) or absence (US) of selective pressure of antimicrobial use; organic farms in McDougall et al. (2021) had no antimicrobial usage for a range of 7-19 years, with a median of 12 years of organic certification. Assuming there is a fitness cost to bacteria for maintaining AMR genes (Vanacker et al., 2023), this certainly begs the question of why resistance genes have been maintained to any degree in the absence of selective antimicrobial pressures. Although researchers were specifically looking at commensal *E. coli* in dairy calves and not mastitis pathogens A rather extreme example of AMR persistence in cattle farms is a study comparing bacteria isolated from retail ground beef raised in conventional and “raised without antibiotics” operations. LeJeune and Christie (2004) identified resistance against chloramphenicol in isolates from both systems, an antimicrobial that had been banned from use in US food animals since 1986. Resistant bacteria remaining on organic farms long after the selective pressure of antimicrobial use is gone suggests that other factors play an important role in this long-term persistence. In a study where feedlot steers were fed subtherapeutic levels of antibiotics, Alexander et al. (2008) found that ampicillin-resistant *E. coli* in the control group (no antibiotics) increased due to an evident clonal expansion of an environmental strain (detected by PFGE) during the latter part of this longitudinal study. This environmental strain outcompeted other strains of *E. coli* present in the intestinal tract of the steers in the control group, suggesting that fitness traits beyond carriage of AMR genes play an important role in the prevalence of AMR bacteria. Specifically, the authors suggest that one environmental factor related to the level of AMR was diet, as the prevalence of steers shedding tetracycline-resistant *E. coli* was higher in animals fed grain-based vs. silage-based diets in both treatment and control groups. Although specifically looking at commensal *E. coli* in dairy calves and not mastitis pathogens, one group of researchers set out to explore which factors beyond antimicrobial usage may explain the persistence of an *E. coli* strain (SSuT) in the GI tract which was resistant to streptomycin, sulfonamide and tetracycline (Khachatryan et al., 2004, 2006a, 2006b, 2008; as summarized in Call et al., 2008). Their first study asked if direct antimicrobial selection pressure was maintaining a high prevalence of SSuT *E. coli* strains in calves, and they found that it was not; a clinical trial showed that addition or removal of oxytetracycline from the diet had no effect on the prevalence of SSuT strains in fecal samples over a period of 3 months. Their next step was to ascertain if SSuT traits themselves provide a secondary but unrecognized fitness advantage to these particular strains of *E. coli,* by generating null mutants for the SSuT traits. On average, they found that the null mutant strains retained a competitive advantage over susceptible strains, and concluded that the specific genes conferring the SSuT phenotype were not responsible for providing any secondary fitness advantages. At some point between studies, the farm stopped feeding a medicated milk replacer. The researchers observed that after only a short time frame, the SSuT strain had suddenly declined in prevalence. This was unexpected, given that previous work demonstrated these strains had an obvious advantage compared to the susceptible strains. This unexplained decline prompted an additional study, which hypothesized that the milk supplement itself (dried milk powder, vitamin A and D) was somehow providing an advantage to the SSuT strains. When the milk supplement was reintroduced (both with and without tetracycline), the prevalence of SSuT *E. coli* strains nearly doubled for both groups of animals receiving the milk supplement vs. those that received none. This work highlights an example of a positive selective force (a dietary supplement) in a dairy farm system either directly or indirectly favoring strains of resistant *E. coli,* which was completely unrelated to antimicrobial exposure.

Call et. al (2008) summarize the 3 possible outcomes in a population of bacteria after exposure to antimicrobials in an individual animal produces a transient increase in AMR prevalence, as has been documented to occur in fecal bacteria. Once the negative selective pressure of antimicrobial usage is removed, the first possible outcome is subsidence of AMR in the population, assuming there is a fitness cost to maintaining the AMR traits. Alternatively, if there is no additional fitness cost to maintaining AMR, we would expect to see “eventual displacement in the face of natural turnover of clonal types at the level of individual animals.” A third possibility, as seen in the work from Khachatryan et al., is that there is no (or limited) change in the level of AMR prevalence after selective pressure from antimicrobials is removed. This would occur if AMR traits have been coupled with other some other locally beneficial traits which provide them an advantage in their specific environmental niche. Call et al. (2008) illustrate this with a hypothetical model illustrating the effect of AM exposure in an individual animal (Figure XX). First, a transient increase occurs in the relative number of resistant bacteria within a population after exposure to an antimicrobial. During this time of increased replication, there is an increased probability for a genetic event to occur which links AMR carriage to some other trait providing increased fitness in that specific environment. Organisms with the linked AMR carriage and locally advantageous trait survive better in the population, but in the absence of antimicrobial exposure, there is nothing to actively suppress the susceptible strains in the population. Although the relative proportion of bacteria with AMR may decline gradually over time, linkage of AMR to some other advantageous trait could also lead to a gradual increase or maintenance of a baseline prevalence of AMR, even in systems devoid of antimicrobial exposure. So far, work exploring this question has been limited to studying the effect of antimicrobials on resistant bacteria present in the GI tract of cattle. The potential exists for research focused on exploring why maintenance of AMR genes occurs in mastitis pathogens from organic dairies, years after the selective pressure of antimicrobial use has been removed.

***Conclusions***

Organic dairy systems provide a novel opportunity in which to identify the antimicrobial resistance patterns of mastitis pathogens experiencing decreased or no selective pressure from antimicrobial usage. This narrative review aimed to summarize studies comparing antimicrobial susceptibility of bovine staphylococcal mastitis isolates on organic vs. conventional dairy farms. Numerous factors make generalizing results of AMR difficult between studies, including: use of various methods for antimicrobial susceptibility testing and continuously evolving or conflicting schemes for breakpoints; variation in sampling scheme between studies (random vs. targeted sampling of cows, bulk tank milk vs. quartermilk samples, inclusion of isolates associated with clinical vs. subclinical mastitis); differing definitions of “organic” between herds in the EU (where antimicrobial usage is still allowed, but is more tightly regulated and limited) and the US (any animal treated with antimicrobials must leave the herd). Furthermore, studies including a limited number of herds may suffer from a lack of independence between observations. Overall, studies comparing the resistance profiles of staphylococci associated with bovine milk samples show that isolates from organic farms are similar or slightly more susceptible to antimicrobials than those associated with mastitis on conventional farms. Although some level of resistance was observed against a number of antimicrobials important for veterinary medicine (cephalosporins, penicillin, tetracycline), overall resistance of mastitis-associated staphylococci is generally low and the most commonly-used mastitis treatments are still effective. A considerable resistance of resistance for both NASM and *S. aureus* against penicillin has been described, but the majority of isolates in European and US studies remain susceptible. Other factors influencing AMR of staphylococci causing mastitis are the prevalence and diversity of NASM present in a particular herd, as resistance profiles are species-specific. Furthermore, as there is evidence that strain types within species can differ in likelihood of AMR carriage, the predominate strain types present in a given herd are also likely to affect prevalence of AMR in staphylococci at the farm level. A number of different management factors (unrelated to antimicrobial usage) affect the prevalence and species diversity of NASM causing IMI on particular dairy farms, thereby also affecting the prevalence of observed AMR in isolates from a given herd (as resistance profiles vary by species). A consistent finding between all studies described was the persistence of resistant mastitis-associated staphylococci on dairy farms which had not used antimicrobials for many years. Some insight on this phenomenon may be gleaned from a theory put forth to explain the observed maintenance of AMR in fecal bacteria in cattle despite the absence of antimicrobial use. In the transient expansion of a population of resistant isolates following antimicrobial treatment in an individual animal, the likelihood increases that an AMR gene can become linked with some other locally-advantageous trait during replication. The selective advantage bestowed on the resistant bacteria could then lead to an increase in their relative abundance and maintenance of the AMR genes over the long term, as long as the trait linked to AMR continues to provide a selective advantage.

The biggest limitation of most studies comparing resistance profiles is lack of speciation of staphylococci. Organisms were primarily identified as either *S. aureus* or “coagulase-negative staphylococci.” Before MALDI-TOF became more widely available, accurate speciation of mastitis-associated staphylococci on a relatively large scale was prohibitively expensive and time-consuming. As resistance profile varies by species, additional work comparing resistance of a large number of isolates from various NASM may give further insight as to whether resistance profiles differ between management systems at the species level. Further, comparison of predominant strain types within a given species causing IMI between organic and conventional farms may prove interesting, as well as exploring if AMR varies by strain type for each type of system. The interplay between phylogeny and selection pressures from management factors on AMR profiles of mastitis pathogens is likely complex. A study of fecal *E. coli* found that on average, phylogenetic groupings were different between organic and conventional dairies, suggesting there may be differences between lineages of *E. coli* in their ability or likelihood of acquiring resistance genes (Walk et al., 2007). Based on their findings, the authors conclude that “organic farming practices not only change the frequency of resistant strains but also impact the overall population genetic composition of the resident *E. coli*flora.” Studying AMR differences at this level would further our understanding of factors affecting the resistance of mastitis-associated staphylococci. Few studies have described resistance patterns of mastitis pathogens before and after transitioning to organic status, and they were limited in both the number of herds enrolled and the amount of time farms were followed. Although it would likely be logistically difficult and expensive, a long-term, larger study of farms transitioning from conventional to organic status would be incredibly valuable in understanding what types of AMR are maintained in organic dairy herds and for how long. Fortunately, AMR in general remains relatively low in mastitis pathogens from dairy farm. Nevertheless, continued surveillance and further understanding of factors affecting resistance profiles of staphylococci is warranted. Staphylococci are not only important pathogens in human health, they are the predominant group of bacteria responsible for mastitis in dairy animals globally. The prevalence of AMR bacterial populations on dairy farms is influenced by a complicated interplay of factors, and continued efforts to further understanding of AMR is vital to making science-based decisions around regulations dictating antimicrobial usage. It is in the best interest of the dairy industry to keep effective antimicrobial treatments which keep cows healthy by curing infections, decrease animal suffering, minimize production expenses for livestock producers, and allow dairy cows to produce a high-quality product.

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