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Review

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Influence of Socioeconomic and Environmental Determinants of Health on Human Infection and Colonization with Antibiotic-Resistant and Antibiotic-Associated Pathogens: A Scoping Review

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Abstract

Background: Antibiotic-resistant and antibiotic-associated pathogens are commonly encountered by surgeons. Pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides difficile* infection (CDI), and carbapenem-resistant *Enterobacteriaceae* (CRE) result in considerable human morbidity, mortality, and excess healthcare expenditure. Human colonization or infection can result from exposure to these pathogens across a range of domains both inside and outside of the built healthcare environment, exposure that may be influenced by socioeconomic and environmental determinants of health, the importance of which has not been investigated fully.

Methods: We performed a scoping review of published literature describing potential socioeconomic and environmental variables that may increase the likelihood of human infection or colonization with common antibiotic-resistant or antibiotic-associated pathogens, using MRSA, CDI, and CRE as examples.

Results: We identified 7,916 articles meeting initial search criteria. Of these, 101 provided supportive evidence of socioeconomic and environmental determinants of human infection or colonization and were included in the scoping review after abstract and full-text screening. Sixty-seven evaluated MRSA, nine evaluated CRE, and 29 evaluated CDI. Twenty-nine articles evaluated exposure to livestock or companion animals; 28, exposure to antibiotics; 20, impact of socioeconomic factors, education level, or race; 14, the influence of temperature, humidity, or season; 13, the effect of travel or human population migration; 11, exposure to built healthcare environments; and eight assessed impact of population density or urbanization.

Conclusions: Although articles outlining socioeconomic and environmental drivers of antibiotic-resistant and antibiotic-associated infection are still disconcertedly few, evidence of such associations are overwhelming for MRSA and CDI and supportive for CRE. Additional research is needed to investigate the role and importance of different potential socioeconomic and environmental drivers of antibiotic-resistant and antibiotic-associated infections and colonization in humans.

Keywords: antibiotic resistance*; Clostridioides difficile*; *Enterobacteriaceae*; methicillin-resistant *Staphylococcus aureus;* MRSA; One Health

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Antibiotic-resistant and antibiotic-associated pathogens result in considerable human morbidity, mortality, and excess healthcare expenditure. Each year in the United States, an estimated 3,092,600 infections, 48,700 deaths, and $7.2 to $14.9 billion are attributed to antibiotic-resistant or antibiotic-associated infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), or *Clostridioides difficile* infection (CDI) [1,2]. The burden of these pathogens worldwide is likely orders of magnitude greater [3]. Existing surgical literature has appropriately focused on modifiable risk factors in the perioperative period for colonization and infection by these pathogens [4–7]. However, additional risk factors for infection and colonization of these pathogens, outside of traditional modifiable risk factors in the peri-operative period, may also contribute to disease burden. Importantly, some socioeconomic and environmental risk factors may be modifiable at the population level.

One Health is a theoretical framework for evaluating disease that recognizes human health and disease should be studied within the context of the ecosystem that humans share with microbes, non-human hosts, and the remainder of the natural world [8]. Using the One Health framework, human colonization or infection with antibiotic-resistant or antibiotic-associated pathogens can result from exposure to these pathogens across a range of domains both inside and outside of the built healthcare environment, exposure that may be influenced by socioeconomic and environmental determinants of health [9–11].

We conducted a scoping review of socioeconomic and environmental variables to synthesize and summarize existing data supporting positive association between these socioeconomic and environmental determinants of health on human infection or colonization with three representative antibiotic-resistant and antibiotic-associated pathogens commonly encountered by surgeons: MRSA, CRE, and CDI.

Methods

Methodology for this scoping review was based on the conceptual framework described by Arksey and O'Malley in 2005 [12]. A research team with expertise in surgery, infectious disease epidemiology, ecology, and scoping reviews was established to determine the broad research question and the overall study protocol. Our review included five phases: establishment of the research question, identification of relevant studies, study selection, data charting, and collation and summary of results [13]. The guiding question was: ''Can socioeconomic or environmental variables influence the risk (or odds) of colonization or infection by MRSA, CRE, and CDI?'' Methicillin-resistant *Staphylococcus aureus*, CRE, and CDI were chosen as representative antibiotic-resistant or antibiotic-associated pathogens because they are commonly encountered by surgeons, are ubiquitous, morbid, and exact a high health system cost in the United States and globally [1–3]. Socioeconomic and environmental determinants of health were interpreted broadly to include any climate, ecologic, socioeconomic, or human population-level demographic variables that could influence colonization or infection by MRSA, CRE, or CDI in accordance with Environmental Change and Infectious Disease (EnvID) framework (Fig. 1) [14].

A research librarian (C.W.) designed and performed searches of four bibliographic databases: PubMed (including Medline), EMBASE, Web of Science, and the Cochrane Library (Supplementary Appendix SA1). Eligible studies included epidemiologic and environmental studies published in English from database inception to December 4, 2020. Studies were excluded if they: (1) did not involve MRSA, CRE, or CDI; (2) had a primary focus on risk factors or exposures experienced during hospitalization; (3) were a literature review, case study, conference abstract or opinion piece without new primary research; or (4) had no association, linkage, or causal inference made between a

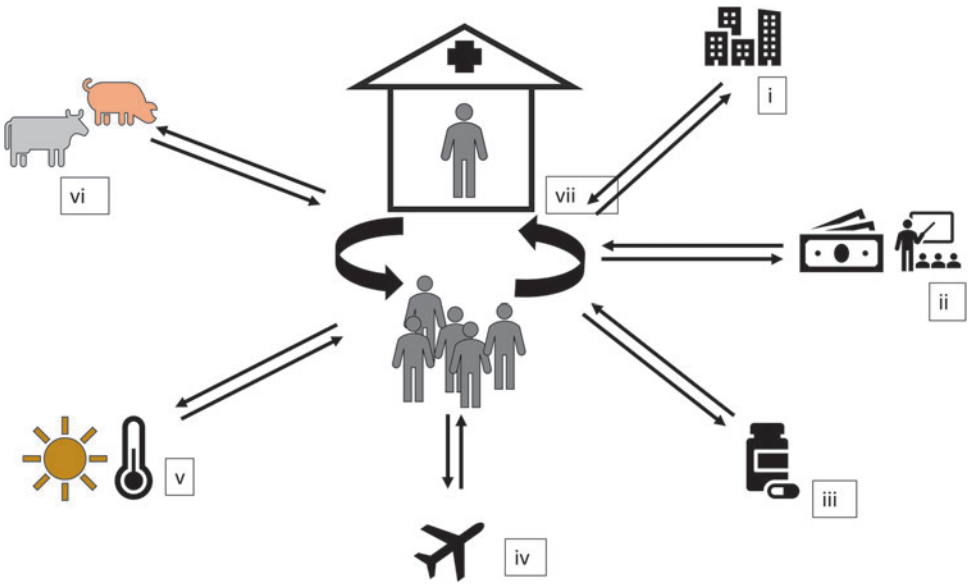

FIG. 1. Socioeconomic and environmental determinants of health that could influence colonization or infection by methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), or *Clostridioides difficile* infection (CDI).

socioeconomic or environmental determinant of human infection or colonization. A study could also be excluded for criteria 4 if either the study did not investigate for a possible association or if the study investigated whether a relationship existed, but results did not support the hypothesis. Criteria 4 was applied to focus this review on potential positive associations for hypothesis generation, rather than provide definitive evidence on presence or absence of a given association.

We did not differentiate between human colonization (presence of bacteria without disease) and infection (presence of bacteria with disease) in excluding studies because these pathologic states exist along a spectrum and colonization for all three pathogens may also increase risk of infection. Health-care-associated (HA)–, community-associated (CA), or livestock-associated (LA)– terminology was used in the review when used by authors of studies but were not independently defined. Studies evaluating veterinarian- or livestock-worker–specific risk factors were not included because several systematic review and meta-analyses address this risk specifically [15–17]. The term strain was used preferentially but not exclusively when describing bacterial clones, types, and lineages to standardize language throughout the text. Studies not written in English were included during the initial search phase to err on the side of sensitivity for the initial search. However, when the number of full-text articles not in English was found to be exceedingly low, we excluded them at the next stage.

Database search results were uploaded to Covidence, a Cochrane-sanctioned Web-based application. Using standardized forms, three reviewers (S.C., R.L., D.S.) independently screened eligible studies and extracted data. A third reviewer (J.D.F.) resolved disagreements. A snowball technique was applied to search citations within articles [13].

For each study we report study design, population size, effect sizes, infection or colonization, and environmental determinant(s) of health evaluated. Studies with multivariable analyses were preferentially reported when available and some measure of association had to be present for studies to be described. Odds ratios (OR) and confidence intervals (CI) or equivalent measures of relation significant on multivariable or adjusted analysis were reported unless otherwise stated. A $p < 0.05$ was generally considered significant unless a study's authors reported a lower threshold. Because this was a review of publicly available articles, this study was exempt from Stanford University Institutional Review Board approval.

Results

There were 7,916 articles identified meeting search criteria, of which 101 (1%) were selected after application of exclusion criteria (Fig. 2). Sixty-seven evaluated MRSA, nine evaluated CRE, and 29 evaluated CDI. Although most articles (n = 32; 32%) were from the United States, 22 countries were individually represented, including seven low- or middle-income countries. Median year of publication was 2015 (range, 1990–2020). Twenty-nine of the included articles evaluated exposure to livestock or companion animals; 28, exposure to antibiotic agents; 19, impact of socioeconomic factors, education level, or race; 14, the influence of temperature, humidity, or season; 13, the effect of travel or human population migration; 11, exposure to built healthcare environments; and eight evaluated the impact of population density or urbanization. Below we present synopses of these seven categories of socioeconomic and environmental determinants on each of the three pathogens of interest (Table 1). Breakout descriptions of each article included in review are listed chronologically by publication year.

Livestock and non-livestock animals

Synopsis: Transmission of MRSA or *Clostridioides difficile* between humans, livestock, and non-livestock animals is documented. Little published data support transmission of CRE between humans, livestock, or companion animals, although presence of CRE in humans and among livestock and non-livestock animals is documented.

Methicillin-resistant *Staphylococcus aureus*. Twenty-three articles documented positive association between livestock (18 studies) or non-livestock animals (5 studies) and human infection or colonization with MRSA. Livestock and non-livestock articles are described in subsections because of the volume of available literature.

Methicillin-resistant *Staphylococcus aureus* and livestock. Eighteen studies assessed proximity to livestock on

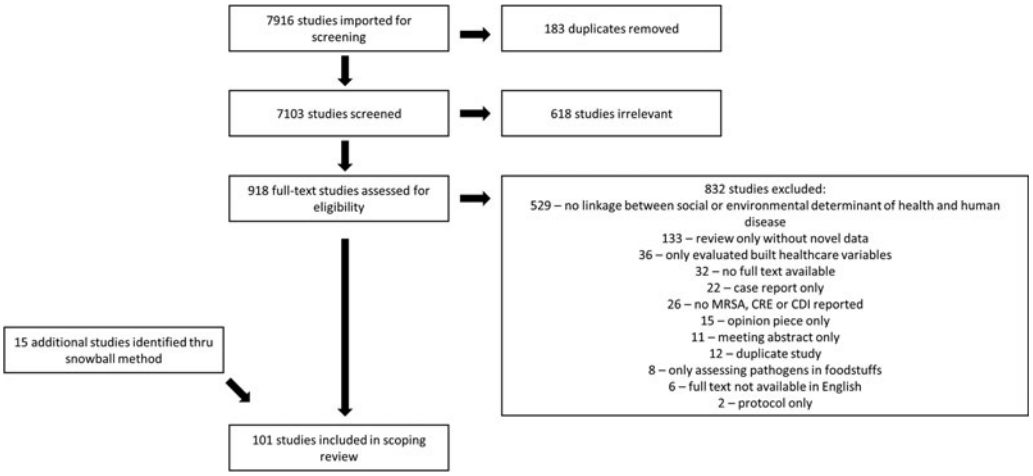

FIG. 2. Selection process for articles included in scoping review.

Table 1. Summary Statements of Data Supporting Association between Socioeconomic and Environmental Determinants of Health and Human Colonization or Infection with MRSA, CRE, and *Clostridium difficile*

Socioeconomic or environmental determinant of health	*Summary statement*
Livestock and non-livestock animals	Transmission of MRSA or *Clostridium difficile* between humans, livestock, and non-livestock animals is documented. Little published data support transmission of CRE between humans, livestock or companion animals, although presence of CRE in humans and among livestock and non-livestock animals is documented.
Antibiotic exposure outside of the built healthcare environment	Antibiotic exposure, including exposure outside of the built healthcare environment, has been documented to increase infection or colonization with MRSA, CRE, or *Clostridium difficile*. More data supporting this association exist for MRSA and *Clostridium difficile* compared with CRE.
Socioeconomic status, race, and education	Greater colonization or infection by MRSA has been documented to be associated with lower socioeconomic status or education level. Race may be associated with greater colonization or infection by MRSA but more commonly when race is associated a lower socioeconomic status. It is unclear how *Clostridium difficile* or CRE infection or colonization may be impacted by socioeconomic status, race or education as existing literature is discrepant and sparse for each pathogen respectively.
Temperature, humidity, season	Higher temperatures and humidity have been documented to increase colonization and infection with MRSA. Seasonality has been reported to affect colonization or infection with *Clostridium difficile* and varies by Southern and Northern hemisphere. Although no data supporting associations for temperature, humidity or seasonality were found for CRE, it is plausible associations exists given relationships between these variables and MRSA and *Clostridiumdifficile*.
Human population migration and travel	Increased human population migration and travel has been documented to be associated with colonization or infection by MRSA and CRE. Given these associations, similar associations may be present with *Clostridium difficile* although additional data is currently lacking.
Exposure to the built healthcare environment	Exposure to built healthcare environments has been documented to be associated with colonization and infection with MRSA and *Clostridium difficile*. No studies were identified associating prior exposure to the built healthcare environment to CRE colonization or infection, although this risk factor is plausible based on associations for MRSA and *Clostridium difficile*.
Human population density and urbanization	Living in a rural setting compared to an urban setting may increase infection or colonization with MRSA and *Clostridium difficile*. The number of studies supporting this association is low and those studies that also assessed livestock exposure found that livestock exposure many have caused the difference in association rather than the rural setting itself. No data were found documenting association between colonization or infection with CRE and population density or rural-urban status although this association is plausible given data on MRSA and *Clostridium difficile*.

MRSA = methicillin-resistant Staphylococcus aureus; CRE = carbapenem-resistant *Enterobacteriaceae.*

human infection or colonization with MRSA. In 2011, van Cleef et al. [18] surveyed 24 laboratories from 17 European countries to identify risk factors for incidence of livestock-associated MRSA (LA-MRSA) at the population level. Proportion of MRSA ST398 among human MRSA isolates at country-level correlated with country swine density (Spearman $\rho = 0.79$; $p = 0.001$) and with an index combining swine density with human population density (Spearman $\rho = 0.76$; $p = 0.002$) [18]. A slightly weaker and marginally significant correlation was observed between LA-MRSA and density of cattle less than one year of age (Spearman $\rho = 0.61$; $p = 0.05$), but the LA-MRSA association with an index combining cattle less than one year of age with human population density was strong and significant (Spearman $\rho = 0.74$; $p = 0.01$) [18]. This article was followed by Feingold et al. [19] in 2012 who performed a retrospective analysis of persons carrying LA-MRSA in The Netherlands to controls carrying other strains of MRSA. Doubling swine, cattle, and veal calf densities per municipality increased odds of LA-MRSA carriage by 25% (95% CI, 1%-54%), 77% (95% CI, 11%–81%), and 24% (95% CI, 6%–46%), respectively [19]. In 2013, Casey et al. [20] performed a population-based, nested case-control study of outpatients with MRSA infection from a single-health system in Pennsylvania. Higher use of swine manure for crop fields was associated with increased community-associated MRSA (CA-MRSA; OR, 1.38; 95% CI, 1.13–1.68) and health-care–associated MRSA (HA-MRSA; OR, 1.30; 95% CI, 1.05–1.61), and heavy dairy/veal exposure was associated with increased CA-MRSA (OR, 1.24; 95% CI, 1.01–1.52) [20].

In 2013, Spoor et al. [21] sequenced 220 *Staphylococcus aureus* isolates between 1956 and 2012 from 18 countries on four continents. Using whole genome sequencing and phylogenetic analysis, the authors identified repeated cattle-to-human host jumps of the human ST97 *Staphylococcus aureus* strain and methicillin-resistance acquisition by human CC97 strains subsequent to host jumps from cattle [21]. In 2014, Benito et al. [22] performed a cross-sectional survey of 98

patients with tetracycline-resistant MRSA isolates and subsequent molecular strain typing at a single center in Spain. Fifty-nine (60%) isolates were identified as the CC398 strain, suggesting an animal lineage [22]. Although CC398 isolates were more common in the 25 patients that reported direct livestock exposure (76% vs. 50%; no p value or 95% CI reported), its presence in all groups suggested possible community spread of LA-MRSA [22].

Also in 2014, Carrel et al. [23] performed a cross-sectional study of 2,996 patients who underwent nasal MRSA screening upon admission to an Iowa Veterans Administration hospital. Authors geocoded patient addresses and compared proximity to swine animal units and found that people living in proximity to high-density swine farms (≥1,000 swine animal units within one mile) had higher odds of MRSA nasal colonization (OR, 2.76; 95% CI, 1.27–5.99) [23]. Similarly, Schinasi et al. [24] performed a case-control study evaluating environmental exposures associated with MRSA carriage in patients admitted to a single U.S. institution in 2014. The authors found an association with nearby swine density: one to 149 swine per square mile was associated with the greater odds of MRSA carriage compared to zero swine per square mile (OR, 4.76; 95% CI, 1.36–16.69) [24]. In 2014, van Rijen et al. [25] performed genotyping of 1,020 MRSA of unknown origin (MUO) (i.e., neither HA- nor LA-) in The Netherlands. In this cohort, 65% of isolates were from symptomatic persons, 64% of isolates were identified as the CC398 strain suggesting livestock origin, and the relative risk of having CC398 in a patient presenting with MUO was higher in hospitals with locally high swine densities compared to those without (risk ratio, 4.25; 95% CI, 1.35–17.21) [25].

In 2015, Deiters et al. [26] performed a case-control study of MRSA isolates from hospitalized German patients, comparing those with MRSA CC398 to those with other MRSA strains. Of 384 patients, 55 (21%) were colonized with MRSA CC398. Twenty-one (38%) had no history of occupational livestock contact suggesting non-occupational–related pathways (i.e., transmission from the environment while living in a livestock-rich region, contact with livestock workers, or recent hospitalization) for acquisition of MRSA CC398 [26]. Similarly, in 2015 Larsen et al. [27] performed a cross-sectional retrospective analysis of 7,429 Danish MRSA isolates from 1999–2011. Risk of MRSA CC398 infection among patients not exposed to livestock included living in an area in which patients with LA-MRSA lived (incidence rate ratio, 2.5; 95% CI, 1.1–5.7) [27]. In 2015, Lekkerkerk et al. [28] compared sequencing of human MRSA CC398 MUO isolates from the Dutch MRSA surveillance network, finding that MRSA CC398 in humans was more similar to animal MRSA CC398 rather than human methicilin-susceptible *Staphylococcus aureus* (MSSA) CC398, suggesting human MRSA CC398 was acquired from animal sources, rather than by acquisition of MRSA-resistance by human MSSA CC398. In 2017, Larsen et al. [29] followed up their 2015 study and explored phylogeny of human cases of MRSA CC398 in blood stream, skin or soft tissue infections from Denmark between 2010 and 2015. Sixteen of 17 blood stream isolates and 59 of 66 skin or soft tissue infection isolates were more closely related to Danish swine isolates than 89 international *Staphylococcus aureus* CC398 isolates from humans and other animals, suggesting local transmission of the swine-associated strain [29].

In 2017, Zomer et al. [30] performed a cross-sectional analysis of 2,492 adults living in a livestock-dense area of The Netherlands assessing for risk factors for MRSA carriage. Even though the number of persons carrying MRSA was low ($n = 14$), a univariable analysis suggested that odds of MRSA carriage was decreased the further a person lived from a livestock farm (OR, 0.13; 95% CI, 0.04-0.43) [30]. A similar study was performed by Anker et al. [31] in 2018 that compared geographic proximity of patients with MUO CC398 to those with LA-MRSA CC398 between 2006 and 2015. Patients with MUO CC398 did not live closer to swine farms than population controls, suggesting human-to-human community spread was likely [31]. In 2018, Reynaga et al. [32] performed a prospective cross-sectional study evaluating risk factors for carriage of MRSA CC398 among patients in six nursing homes in Spain. Among the eight residents (25% of all MRSA-positive residents) with MRSA CC398, having relation to a swine farmer ($p = 0.026$) and having contact with a swine farm in the last 12 months ($p = 0.018$) were associated with infection although no attempt was made to account for confounders [32].

In 2019, Feingold et al. [33] performed a retrospective cross-sectional study to evaluate if MUO MRSA strains in a repetitive sequence-based polymerase chain reaction (PCR) library were geographically associated with exposure to swine-farming in North Carolina. Two clusters of MUO MRSA isolates were highly associated with increased swine density (relative risk [RR] = 15.02; no 95% CI presented; $p = 0.02$ and RR = 54.08; no 95% CI presented; $p < 0.0001$) and were mostly ST-5 or ST-398 strains consistent with livestock origin [33]. Also in 2019, Sieber et al. [34] performed a single nucleotide polymorphism and genome-wide association study of 73 MRSA CC398 isolates obtained from Danish patients with HA-MRSA in Denmark from 2014–2016. In that study, most MRSA CC398 colonizations/infections were determined to be associated with direct livestock-human transmission after phylogenetic analyses, although human–human transmission of the MRSA CC398 strain did occur. Genome-wide single nucleotide polymorphism and association studies demonstrated human-specific virulence genes were acquired as the isolates adapted to selective pressure in different hosts within the healthcare system [34]. Also in 2019, Wu et al. [35] performed a meta-analysis of studies describing risk factors for MRSA colonization in the Chinese population. In their meta-regression, contact with livestock (OR, 6.31; 95% CI, 3.44–11.57) was independently associated with MRSA colonization [35].

Methicillin-resistant *Staphylococcus aureus* and non-livestock animals. Five studies evaluated impact of non-livestock animals on MRSA human infection or colonization. In 2009, Faires et al. [36] performed a cross-sectional survey investigating prevalence of MRSA in patients and domestic animals residing in the same household; clonal similarity was assessed with pulsed-field electrophoresis. Among five of 30 sampled households in which MRSA was isolated concurrently from humans and pets, all MRSA isolates belonged to the same strain, either USA100 (Panton-Valentin leucocidin [PVL]-absent) or USA300 (PVL-carrying). In 2014, Harrison et al. [37] performed a high-resolution genomic study of 46 companion animal (42 dogs and 4 cats) MRSA isolates and 22 human isolates, and found humans, dogs, and cats readily share ST-22 MRSA strains within local geographic populations.

In 2016, Daley et al. [38] performed a cross-sectional survey of humans and animals in a native community in Canada to identify risk factors for MRSA colonization and to identify inter-species transmission through molecular typing. Six factors were found to be associated with higher odds of colonization, of which recreational dog exposure (through hunting, camping, or work) had the greatest odds ratio (OR, 6.35; no 95% CI provided; $p = 0.003$) [38]. In 2019, Hogan et al. [39] performed a prospective cross-sectional survey evaluating factors associated with MRSA pet colonization in households of children with CA-MRSA in Missouri. In a univariable analysis, pets whose caretaker(s) were MRSA-positive were more likely to be MRSA-positive (50% vs. 4%; $p < 0.0001$); no multivariable analysis was performed [39]. Finally, in 2020, Mork et al. [40] performed a prospective longitudinal cohort study evaluating strain-specific MRSA transmission events in households of children with CA-MRSA. Similar to Hogan et al. [39], 19 pets (16 dogs, 3 cats) were associated with 22 transmission events and 35 (33%) pets were reported to have received MRSA from a household member (no statistical comparison provided). There was a trend toward dogs being more likely than cats to serve as a transmission recipient or source (no OR provided; $p = 0.07$) [40].

Carbapenem-resistant *Enterobacteriaceae*. No studies assessed proximity to livestock or companion animals on human infection or colonization with CRE. However, presence of CRE in wildlife, livestock, and the environment has been documented. In 2018, Koch et al. [41] reported a systematic review of 68 studies evaluating CRE among livestock, companion animals, and wild animals. Carbapenem-resistant *Enterobacteriaceae* was absent in 41 studies on livestock and companion animals and present in 27 but at low prevalence: <1% in Europe, 2%–26% in Africa, and 2%–26% in Asia [41]. In reviewed studies, between one-third and two-thirds of exposed humans working on farms carried CRE closely related with, or identical to, animal isolates, suggesting inter-species transmission [41].

Clostridioides difficile. Six studies assessed impact of livestock and companion animals on human infection or colonization with CDI. The study by Norman et al. [42] compared *Clostridioides difficile* isolates from composite wastewater samples of closed populations of swine and swine workers. Twelve percent of human wastewater samples and 9% of swine waste water samples had *Clostridioides difficile,* and among those strains found in humans and swine, similarities between strains suggested a shared environmental source [42]. Subgroup analysis in the previously described Søes et al. [43] study showed contact with animals (both livestock and companion) was associated with increased odds of CDI (OR, 8.1; 95% CI, 1.0–64.0) among children younger than two years of age.

In 2017 Anderson et al. [44] performed a geospatially distinct, population-based retrospective cohort study of patients with CA-CDI (defined by the authors as a positive stool test) and evaluation for environmental variables independently associated with increased risks of CA-CDI. Proximity to livestock farms ($p = 0.01$) and proximity to farming raw materials services ($p = 0.02$) were associated with increased rates of CA-CDI (no OR presented) [44]. Also in 2017, Knight et al. [45] performed whole genome sequencing on 40 Australian *Clostridioides difficile* ribotype 014 isolates. Phylogenies demonstrated clustering of human and swine strains of recent shared ancestry with 42% of human strains showing clonal relation with swine strains [45]. More than one-half of human cases occurred without recent healthcare exposure and were spread out over large geographic areas suggesting presence of a permanent community and/or livestock-based reservoir with potential for long-range dissemination [45].

In 2018, Knetsch et al. [46] performed a whole genome phylogenetic analysis of a diverse set of 247 *Clostridioides difficile* ribotype 078 human and animal strains from 22 countries obtained between 1996 and 2012. There was limited geographic clustering but extensive co-clustering of human and animal strains suggesting linked inter-continental bi-directional transmission between humans and animals [46]. A similar study by Knight et al. [47] published in 2019 performed whole genome analysis on 207 *Clostridioides difficile* isolates (predominately strains ST11 and ST258) from Australia, Asia, Europe, and North America. These authors found widely distributed multiple inter- and intra-species clonal groups again suggesting reciprocal widespread dissemination and transmission between species [47].

Antibiotic exposure

Synopsis: Antibiotic exposure, including exposure outside of the built healthcare environment, has been documented to increase infection or colonization with MRSA, CRE, or *Clostridioides difficile*. More data supporting this association exist for MRSA and *Clostridioides difficile* compared to CRE.

Methicillin-resistant *Staphylococcus aureus*. Fourteen studies assessed impact of antibiotic exposure on human infection or colonization with MRSA. To align with exclusion criteria 2, studies evaluating patients with prior antibiotic exposure, be it inpatient or outpatient, were included, whereas studies evaluating inpatients who developed infection or colonization after antibiotic administration during the same hospitalization were excluded. In 2005, Hidron et al. [48] performed a case-control epidemiologic study with molecular typing evaluating risk factors for MRSA carriage among patients presenting at a single institution in Atlanta, Georgia. Antibiotic use within three months of admission was associated with 2.5 increased odds of MRSA nasal carriage (95% CI, 1.2–5.0) among newly admitted inpatients [48]. In 2010, Lo et al. [49] performed a prospective observational survey of healthy children in Taiwan presenting for a well-child visit to clinic or at school to assess for risk factors for MRSA colonization. Recent antibiotic use, defined as antibiotic use within the last 12 months, was associated with six-fold increased odds of MRSA colonization (OR, 6.0; 95% CI, 3.6–10.0) [49]. In 2012, Sun et al. [50] assessed temporality of antibiotic administration to prevalence of MRSA in the United States. Fluoroquinolone prescriptions were correlated with a one-month lag in prevalence of ciprofloxacin-resistant MRSA (cross-correlation coefficient, 0.23; $p = -0.03$) [50]. Similarly, macrolide-lincosamide prescriptions were correlated with clindamycin-resistant MRSA with correlations that peaked with a one-month lag (coefficients of 0.42 [$p < 0.001$], 0.32 [$p = 0.002$], and 0.43 [$p < 0.001$] for inpatient, outpatient, and all isolates combined, respectively) [50].

In the study by Kirby and Herbert [51] from 2013, effect of outpatient antimicrobial consumption was positively associated with MRSA (pooled correlation r = 0.67; 95% CI, 0.65–0.69). Also in 2013, Schinasi et al. [52] performed a case-control study evaluating for risk factors for MRSA carriage among adult patients presenting at a tertiary medical center in North Carolina. Greatest odds of carriage were seen among patients living with household members who used antibiotic agents within the last four weeks or who were hospitalized in the last 12 months (OR, 3.27; 95% CI, 1.24–8.57) [52]. Likewise, Erami et al. [53] performed a cross-sectional survey of random children presenting to health centers in Kashan City, Iran, to assess for nasal carriage of MRSA. Antibiotic usage in the last three months was the strongest predictor of colonization (OR, 34.29; 95% CI, 0.27–430.2) [53].

In 2015, Dorado-Garcia et al. [54] performed a prospective cross-sectional analysis of swine farms in The Netherlands to assess for dose-response for antibiotics administered to swine and LA-MRSA positivity in swine and humans. Antimicrobial use in swine was associated with increased odds of positivity in humans, particularly among those persons working 20 hours or more per week on the farm (OR, 1.25; 95% CI, 1.01–1.54) [54]. Concerningly, no corresponding decrease in human carriage was observed over time after interventions were implemented to decrease antibiotic administration and improve cleaning practices on the swine farms [54,55]. Also in 2015, Miller et al. [56] performed a prospective longitudinal cross-sectional investigation of persons with *Staphylococcus aureus* skin infection, evaluating risk factors for re-infection of index cases and infection of household members. Although both MSSA and MRSA infections were included, the dominant pathogen was MRSA (64%) [56]. Antibiotic exposure in the 12 months prior to enrollment was associated with increased odds (OR, 1.87; 95% CI, 1.18–2.96) of developing a *Staphylococcus aureus* infection among non-index patient family members [56].

In 2016, Daley et al. [38] performed a cross-sectional survey of humans and animals in a native community in Canada to identify risk factors for MRSA colonization and to identify interspecies transmission via molecular typing of isolates. In their study they found antibiotic use within the last 12 months was associated with a 1.69 increased odds of colonization (p = 0.02; no 95% CI provided) [38]. In 2018 Andreatos et al. [57] compared MRSA blood stream infection rates, extracted from the Medicare Hospital Compare database from 2011 to 2015, with socioeconomic factors and antibiotic prescription rates. At the U.S. county level, antibiotic prescriptions per 100,000 people was strongly associated with development of MRSA blood stream infections (coefficient, 3.44; 95% CI, 3.12–3.76; p < 0.001) [57].

In 2019 Choe et al. [58] performed an ecologic cross-sectional analysis of seasonal variation in detection of MRSA from a single U.S. healthcare system and found peak MRSA detection occurred seven months after peak antibiotic prescriptions (OR, 1.69; 95% CI, 1.21–2.35). Also in 2019, Kubes and Fridkin [59] used data from the U.S. Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Patient Safety Atlas to compare outpatient antibiotic prescriptions per 1,000 population to MRSA prevalence. Outpatient fluoroquinolone prescribing was positively associated with MRSA infection, both in states with large African American populations (coefficient, 0.35; p = 0.03) and small African American populations (coefficient, 0.33; p = 0.04) [59]. Also in 2019, Wu et al. [35] performed a meta-analysis of studies describing risk factors for MRSA colonization in a Chinese population. In meta-regression, antibiotic use within the past year (OR, 2.05; 95% CI, 1.35–3.11) was associated with MRSA colonization.

Finally, in 2020 Kaba et al. [60] performed a 30-country cross-sectional observational study assessing six-year prevalence of MRSA to identify associations between various socioeconomic and environmental variables and MRSA prevalence. Total antibiotic consumption was associated with MRSA prevalence for all countries (standardized regression coefficient [RC], 0.347; no 95% CI provided) and for countries without full gate-keeping roles for general practitioners (standardized RC, 0.43; no 95% CI provided) [60].

Carbapenem-resistant *Enterobacteriaceae*. Two studies assessed impact of antibiotic exposure on human infection or colonization with CRE. In the previously described Kirby and Herbert study [51], effect of antimicrobial consumption was only weakly associated with presence of carbapenem-resistant *Klebsiella pneumonia* (pooled correlation r = 0.67; 95% CI, 0.65–0.69) or carbapenem-resistant *Escherichia coli* isolates (pooled correlation r = 0.34; 95% CI, 0.18–0.49). In the previously described study by Kaba et al. [60], total antibiotic consumption was positively associated with carbapenem-resistant *Klebsiella pneumoniae* prevalence (standardized RC, 0.376; no 95% CI provided).

Clostridioides difficile. Fifteen studies assessed associations of antibiotic prescription practices with *Clostridioides difficile*. In 2005, Palmore et al. [61] performed a single institution matched case-control study to examine risk factors for CDI in ambulatory patients with cancer. Each additional day of either clindamycin or a third-generation cephalosporin was associated with 1.29- and 1.26-fold increase in odds of developing CDI (no 95% CI provided; p < 0.01 and p = 0.04, respectively) [61]. In 2008, Dial et al. [62] performed a nested case-control study to identify risk factors for CDI among persons 65 or more years of age admitted with CA-CDI from two Canadian health databases. Patients who were exposed to any antibiotic within the past 90 days had an increased likelihood of developing CDI (rate ratio, 10.6; 95% CI, 8.9–12.8), and this rate ratio declined to 15.4 (95% CI, 12.2–19.3) from 20 after exposure; this rate ratio further decreased to 3.2 (95% CI, 2.0–5.0) 45 days after exposure [62].

In 2010, Kutty et al. [63] performed a case-control study to determine risk factors for CA-CDI among adult patients treated at six hospitals in North Carolina. Patients were divided into two patient catchment groups; outpatient antibiotic exposure was associated with increased odds of infection among both groups (OR, 17.8; 95% CI, 6.6–48 and OR, 9.1; 95% CI, 2.9–28.9, respectively) [62]. In 2013 Brown et al. [64] performed a meta-analysis of existing studies to examine associations between antibiotic exposure and CA-CDI. Based on seven included studies, exposure to any antibiotic irrespective of class was associated with three-fold increased odds of infection (OR, 3.55; 95% CI, 2.56–4.94), although heterogeneity was high ($I^2 = 90.6\%$) [64]. Heterogeneity decreased when each class of antibiotic was independently

assessed [64]. A similar meta-analysis was published in 2013 by Deshpande et al. [65], who found antibiotic exposure was associated with an increased odds of CDI (OR, 6.91; 95% CI, 4.17–11.44) among eight included studies.

In 2014, Søes et al. [43] performed a matched case-control study of Danish patients presenting with diarrhea to a general practitioner, comparing those with CDI to those without. Prior antibiotic administration was associated with the greatest increase in odds of CDI (OR, 10.0; 95% CI, 4.1–26) when compared with prior hospitalization or consumption of beef [43]. In 2015, Dantes et al. [66] performed cross-sectional analysis of nine geographic locations in the United States to identify associations between antibiotic prescription practices and *Clostridioides difficile*-positive stool specimens from outpatients or patients within three days after hospital admission. There was a 16.8% (95% CI, 6.0%–26.3%) decrease in CA-CDI incidence among adults (≥20 years old) for each 10% reduction in use of antibiotics [66]. Also in 2015, Freedberg et al. [67] performed a population-based, nested case-control study of children younger than 17 years of age to identify risk factors for CDI in a single health care system. Antibiotic exposure was associated with increased odds of infection (OR, 2.18; 95% CI, 1.74–2.73) [66]. In 2016, Wieczorkiewicz et al. [68] performed a case-control study of patients with *Clostridioides difficile* BI/NAP1/027 in a single U.S. hospital to identify risk factors for infection. Fluoroquinolone and macrolide exposure was associated with increased odds of infection with this strain of *Clostridioides difficile* (OR, 3.2; 95% CI, 1.3–7.5 and OR,5.2; 95% CI, 1.1–24.0, respectively) [68].

In 2017, Adams et al. [69] performed a case control study of the U.S. military health system database to evaluate risk factors for CA-CDI among children. Exposure to antibiotic agents was generally associated with increased odds of infection across classes, ranging from OR, 73 (95% CI, 13.85–384.68) for clindamycin to 2.01 (95% CI, 1.04–3.86) for macrolides [68]. Guh et al. [70] reported a matched case-control study of adult patients with a positive *Clostridioides difficile* stool specimen collected as an outpatient or within three days of hospital admission and no exposure to a healthcare facility within the last 12 weeks. Antibiotic exposure increased risk of stool positivity across antibiotic classes, with clindamycin having the greatest odds (OR, 35.31; 95% CI, 4.01–311.14) followed by fluoroquinolones (OR, 30.71; 95% CI, 2.77–340.05) [70]. In 2017, Zomer et al. [71] performed a cross-sectional community-based fecal survey of adults living near, but not working on, livestock farm in The Netherlands. Antibiotic use in the last three and six months was associated with *Clostridioides difficile* (OR, 3.70; 95% CI, 1.25–10.95 and OR, 2.64; 95% CI, 1.05–6.64, respectively) on univariable analysis, although no attempt to account for confounding variables was performed [71]. In the previously described Choe et al. [58] study, peak detection of *Clostridum difficile* occurred three months after the peak in antibiotic prescriptions (OR, 1.24; 95% CI, 1.07–1.43).

Finally, in 2019, Weng et al. [72] performed a nested-case control study of persons one to five years of age from Emerging Infections Program sites in 10 geographically distinct areas of the United States evaluating for risk factors for infections. Only antibiotic exposure in the preceding 12 weeks was associated with increased odds of infection (OR, 6.25; 95% CI, 2.18–17.96) [72].

Socioeconomic status, race, and education

Synopsis: Greater colonization or infection by MRSA has been documented to be associated with lower socioeconomic status or education level. Race may be associated with greater colonization or infection by MRSA but more commonly when race is associated a lower socioeconomic status. It is unclear how *Clostridioides difficile* or CRE infection or colonization may be impacted by socioeconomic status, race, or education as existing literature is discrepant and sparse for each pathogen, respectively.

Methicillin-resistant *Staphylococcus aureus*. Seventeen studies assessed impact of socioeconomic status, race, and education on human infection or colonization with MRSA. In 2004, Bagger et al. [73] evaluated all patients admitted to a single-institution adult cardiothoracic surgery unit over a five-year period starting in 1994. Using the Carstairs score, a score built on overcrowding, unemployment, vehicle ownership, and social class, the authors stratified patients based on degree of social deprivation in addition to other common risk factors for MRSA infection [73]. Increasing Carstairs score (OR, 1.21; 95% CI, 1.06–1.38; $p = 0.004$) was associated with development of MRSA infection. In 2010, Pala et al. [74] reported a prevalence survey of 1,115 food workers evaluated for MRSA colonization. Food workers without health insurance (6% without vs. 2% with; $p = 0.02$) or without periodic medical exams (5% without vs. 2% with; $p = 0.03$) were more likely to have nasal MRSA carriage, although no multivariable analysis was performed [74].

In 2012, Tong et al. [75] calculated population-level MRSA bacteremia incidence rates using the Australian New Zealand Cooperative on Outcomes in Staphylococcal Sepsis and stratified by ethnicity, age, and socioeconomic status. Socioeconomic status was defined using the Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) [75]. Age-standardized incidence risk ratio was 5.9 (95% CI, 5.4–6.4) for indigenous compared with non-indigenous populations [75]. Similarly, persons in the lowest IRSAD quintile had higher incidence rates of MRSA bacteremia than the upper four quintiles ($p < 0.0001$), a trend that held after adjusting for ethnicity [75].

In 2013 Kirby and Herbert [51] compared antimicrobial resistance data and outpatient antimicrobial consumption data to the standardized world income inequality database for all European countries from 2003–2010. These authors identified that the Spearman rank order correlation effect (ρ) between income inequality and MRSA was 0.86 (95% CI, 0.83–0.89) over the eight-year time-period [51]. In 2013, Williamson et al. [76,77] performed a cross-sectional study of adult and pediatric MSSA and MRSA infections within the Auckland District Health Board from 2001 to 2011, using the New Zealand Deprivation Score (NZDepScores) as an aggregate marker of socioeconomic status. Among both adults and children, worse NZDepScore was not associated with increased odds of MRSA infection. However, Maori or Pacific Island ethnicity was associated with increased odds of MRSA infection for both adults (OR, 1.48; 95% CI, 1.26–1.75) and children (Pacific Island OR, 2.8; 95% CI, 1.8–4.6; Maori OR, 2.2; 95% CI, 1.4–23.8) [76,77].

In 2014 Braga et al. [78] performed a cross-sectional study of Brazilian children attending public daycare centers comparing children coming from informal settlements to those

coming from higher socioeconomic conditions. Children from informal settlements had a greater odds of carrying MRSA (OR, 3.27; 95% CI, 1.52–7.0) [78]. In 2014, Ravishankar et al. [79] performed a cross-sectional study of patients presenting with skin or soft tissue infections to a single institution in Delhi, India. Lower monthly family income ($p = 0.02$) and fewer years of education of head of household ($p = 0.02$) were associated with MRSA infection, although no multivariable analysis was performed [79].

In 2016 Popovich et al. [80] published a cross-sectional evaluation of MRSA community colonization transmission networks using whole genome sequencing and epidemiologic data from a single public hospital in Chicago, Illinois. Maximum-likelihood phylogenic analysis demonstrated African American race, human immunodeficiency virus (HIV)-infection, illicit drug use, and living in an area of high-detainee release increased inclusion in a genomic cluster, although only African American race reached statistical significance ($p = 0.004$) [81]. In 2016, Tosas Auguet et al. [81] used geospatial modeling with adjustment for exposure to the healthcare system (inpatient or outpatient) to assess for associations between infection and carriage of HA- or CA-MRSA and socioeconomic status among persons living in southeast London. Household deprivation was associated with increased relative risk for CA-MRSA and HA-MRSA, respectively (RR, 1.72; 95% CI, 1.03–2.94; and RR, 1.57; 95% CI, 1.06–2.33) [81]. Community-acquired MRSA was also associated with a composite index of household overcrowding, low-income, and homelessness ($RR = 1.76$; 95% CI, 1.16–2.70) [81]. In 2016, Vieira et al. [82] performed a case-control study evaluating risk of persistent MRSA carriage among HIV-positive youth from two public hospitals in Brazil and found living in a low-income or slum community was associated with increased odds of persistent carriage (OR, 4.2; 95% CI, 1.1–1.6).

In 2017, See et al. [83] performed a retrospective cohort analysis of the CDC's Emerging Infections Program to explore socioeconomic explanations for observed racial disparities between incidence rates of invasive CA-MRSA among black and white persons. On univariable analysis low-income households (rate ratio, 19.65; 95% CI, 14.78–26.12), persons living below poverty level (rate ratio, 16.78; 95% CI, 11.92–23.62), income inequality index (rate ratio, 12.99; 95% CI, 6.54–25.82), crowding (rate ratio, 437.72; 95% CI, 173.16–1106.48), low education (rate ratio, 47.65; 95% CI, 33.96–66.86), and being in a medically underserved area (rate ratio, 2.40; 95% CI, 2.16–2.68) were associated with higher incidence of invasive CA-MRSA infection [83]. The rate ratio for effect of black race versus white race was 1.68 (95% CI, 1.53–1.84) [83]. On mediation analysis 91% of the effect of race was explained by socioeconomic variables (rate ratio for indirect effect, 1.60; 95% CI, 1.44–1.78), leaving the resulting direct effect of race not significant (rate ratio, 1.05; 95% CI, 0.92–1.20) [83].

In the previously mentioned study by Andreatos et al. [57], MRSA blood stream infection rates were obtained from the Medicare Hospital Compare database and compared to socioeconomic factors and antibiotic prescription rates. At the U.S. county level, increased incidences of MRSA blood stream infections were associated with increased proportion of individuals of black race (RC, 0.41; 95% CI, 0.38–0.45; $p < 0.001$), increase proportion of individuals in poverty (RC, 0.09; 95% CI, 0.03–0.20; $p = 0.002$), decreased proportion of individuals with a college education (RC, –0.04; 95% CI, –0.07 to 0.01; $p < 0.001$) and lower median number of rooms per house (RC, –0.11; 95% CI, –0.13 to 0.08; $p < 0.001$) [57].

In 2019 Gill et al. [84] performed a cross-sectional geospatial analysis of MRSA infections in Calgary, Canada, from 2004–2014 evaluating for socioeconomic predictors of infection. Socioeconomic factors associated with reduced risk of infection included being English-speaking (risk ratio, 0.05; 95% CI, 0.01–0.18), Chinese (risk ratio, 0.09; 95% CI, 0.02–0.42), South Asian (risk ratio, 0.25; 95% CI, 0.08–0.76), and having a median household income higher than $100,000 Canadian dollars (risk ratio, 0.27; 95% CI, 0.19–0.39) [84]. In 2019, Goncalves Neves et al. [85] performed a cross-sectional survey of children attending private and public outpatient pediatric clinics in Rio de Janeiro, Brazil, in the month of April 2014. Children living in households with a monthly income of $971 to $1938, the mid-range income category, had a higher adjusted odds of MRSA colonization (OR, 3.40; 95% CI, 1.45–7.98) [85]. Also, in 2019 Savoldi et al. [86] performed cross-sectional evaluation of surveillance data from 67 countries and compared prevalence rates of MRSA to income. Rate of increase in MRSA prevalence per unit decrease in log gross national income per capita was 9.5% (95% CI, 5.2%–13.7%) although confounder assessment was not performed [86]. Finally, in 2020 Kaba et al. [59] performed an observational study assessing if spatial temperature explains antimicrobial variance in Europe. Although not the primary covariate of interest, study corruption index (standardized RC, –0.542; no 95% CI provided) was associated with increased MRSA prevalence [59].

Carbapenem-resistant *Enterobacteriaceae*. Three studies assessed associations between socioeconomic status, race, and education on human infection or colonization with CRE. In the same 2013 Kirby and Herbert [51] study, income inequality and CRE were positively associated although pooled correlation was only weakly correlated, compared to strong associations with MRSA. Pooled correlation between income inequality and CRE was 0.34 (95% CI, 0.18–0.49) for carbapenem-resistant *Escherichia coli* and 0.33 (95% CI, 0.29–0.37) for *Klebsiella pneumoniae* [51]. In the same 2019 article by Savoldi et al. [86], rate of increase in CRE prevalence per unit decrease in log gross national income per capita was 22.5% (95% CI, 18.2–26.7%) although, as mentioned previously, no assessment of potential confounders was performed. Finally, in the same 2020 Kaba et al. [59] article described under MRSA, corruption index (standardized RC, –0.409; no 95% CI provided) was associated with increased carbapenem-resistant *Klebsiella pneumoniae*.

Clostridioides difficile. Two studies assessed associations between socioeconomic status, race and education on human infection or colonization with *Clostridioides difficile*. In 2016 Mello et al. [87] performed a cross-sectional fecal survey of a convenience sample of children living in Sao Paulo, Brazil, comparing children in slums with those in private schools. One hundred percent of students in private school compared with 43% of children in slums had *Clostridioides difficile* carriage ($p < 0.0001$) although no multivariable analysis was performed and no differentiation was made between infection and colonization [87]. In 2019, Hudspeth et al. [88] used quasi-Poisson regression modelling to evaluate influence of

socioeconomic and racial factors on CA-CDI case rates reported to the New Mexico Emerging Infections program. More than 59% of the variance in *Clostridioides difficile* incidence across census tracts was explained by socioeconomic factors, with percent of persons without health insurance, lower median household income, and percentage of households with higher number of persons per room having higher adjusted incidence rate ratios (all $p < 0.02$) [88].

Temperature, humidity, or season

Synopsis: Higher temperatures and humidity have been documented to increase colonization and infection with MRSA. Seasonality has been reported to affect colonization or infection with *Clostridioides difficile* and varies by Southern and Northern Hemisphere. Although no data supporting associations for temperature, humidity, or seasonality were found for CRE, it is plausible associations exists given relations between these variables and MRSA and *Clostridioides difficile*.

Methicillin-resistant *Staphylococcus aureus*. Nine studies assessed relations between temperature, humidity, or season on human infection or colonization with MRSA. In 2009, Van De Griend et al. [89] performed a cross-sectional survey of MRSA isolates submitted to a single institution laboratory from 1999–2006 as part of a statewide surveillance system. On a subset of patients from 2006, 47% of MRSA infections occurred during summer although seasonality was not explicitly addressed on multivariate analysis [89]. Similarly, in 2011 Mermel et al. [90] performed a retrospective cross-sectional analysis of MRSA isolates submitted to a single-institution microbiology laboratory from 2001–2010. More CA-MSRA isolates were identified during the latter two quarters compared with the first two quarters (OR, 1.85; 95% CI, 1.45–2.36; OR, 1.14; 95% CI, 1.01–1.29, respectively).

In the formerly mentioned 2012 Sun et al. [50] study describing temporality of antibiotic administration to prevalence of MRSA in the United States, antibiotic prescriptions peaked in the winter months, with a corresponding one-month lag in identification of MRSA. In 2013, Wang et al. [91] used time-series and non-linear regression to identify periodicity and seasonality of skin and soft tissue infections among children in a single county in Arizona. Skin and soft tissue infections were seasonal, and independently correlated with increased temperature ($p < 0.05$) and increased humidity (p value not reported) independently correlated with skin and soft tissue infection incidence [91]. Although not specific to MRSA, percentage of skin and soft tissue infections caused by MRSA in the studied area ranged between 42% and 48% over the study period [91]. Also, in 2013, Klein et al. [92] performed a retrospective cross-sectional analysis of MRSA diagnosis in the United States using the National Inpatient Sample. Frequency of CA-MRSA diagnoses peaked in summer months, MRSA-related septicemia had limited seasonal variation, and MRSA-related pneumonia hospitalizations peaked in winter months, although no statistical comparison values were presented [92].

In 2014, Sahoo et al. [93] evaluated relation between temperature and humidity and development of MRSA infection in their single center institution. Number of MRSA cases increased when the weekly average maximum temperature was above 33°C (coefficient, 0.57; $p = 0.04$). In 2017 Blanco et al. [94] performed a prospective cohort analysis of adult patients admitted to 20 geographically dispersed intensive care units across the United States, testing for MRSA on admission. Methicillin-resistant *Staphylococcus aureus* colonization was positively correlated with mean temperature ($r = 0.16$; $P = 0.008$), relative humidity ($r = 0.24$; $p < 0.0001$), total precipitation ($r = 0.22$; $p < 0.0001$) and being closer to the equator ($r = (-)0.34$; $p < 0.0001$) [94].

In 2018, Mork et al. [95] performed a cross-sectional study assessing risk-factors for colonization of household members of index patients with MRSA infection. Increased odds of MRSA colonization among households members (OR, 1.2; 95% CI, 1.03–1.5) was seen per degree increase in temperature (°F) (95]. Finally, in 2020, Bloomfield et al. [96] performed a cross-sectional analysis of 57,557 MRSA isolates in Western Australia from 2004–2018. Incidence rate ratio for MRSA cases (infection and colonization) increased as the climactic zone became more humid, and warmer (incidence rate ratio, 9.11; 95% CI, 7.22–11.49) for the hottest, warmest climate after adjusting for IRSAD [96].

Carbapenem-resistant *Enterobacteriaceae*. None identified.

Clostridioides difficile. Five studies assessed impact of temperature, humidity, or season on human infection or colonization with *Clostridioides difficile*. In 2011, Norman et al. [42] performed a cross-sectional sampling of human composite wastewater in Texas from 2004–2007 comparing two closed populations of humans who work with swine with those who do not. On multi-level mixed effect logistic regression, greater odds for *Clostridum difficile* presence in human waste water was observed during spring months (OR,1.75; 95% CI, 1.06–2.91) [42]. In 2012, Reil et al. [97] performed a cross-sectional analysis of stool samples from a single laboratory processing samples from northern Bavaria. January, February, and March (all $p < 0.01$) had greater numbers of isolates submitted and greater numbers of positive patients although no comparative statistical values were reported [97].

In 2014, Furuya-Kanamori et al. [98] published two articles describing seasonality of CDI. The first study was a retrospective cross-sectional analysis of stool samples submitted for *Clostridioides difficile* toxin gene detection from Queensland, Australia, from 2003–2012 [98]. *Clostridioides difficile* infection peaked in summer (December–February) and reached its nadir in autumn opposite from trends seen in countries in the Northern Hemisphere [98]. Infection was associated with greater rainfall (OR, 1.08; 95% CI, 1.01–1.14) [98]. In the second study, a systematic review of 18 studies evaluating seasonality of CDI was performed [99]. Infection rates peaked during March to April in the Northern Hemisphere and October to November in the Southern Hemisphere with an XCORR peak at 0.6 at lags = 8 suggesting an eight-month lag in infection peaks between hemispheres. This same group developed a mechanistic compartmental model of *Clostridioides difficile* transmission in a hospital and surrounding community, exploring impact of seasonal antibiotic prescription [100]. Halving seasonal excess antibiotic prescriptions reduced incidence of CDI by 6%–18%, suggesting proportional reduction of infections

and that some, but not all of the seasonality observed in CDI is from antibiotic prescriptions [100].

Human population migration and travel

Synopsis: Increased human population migration and travel has been documented to be associated with colonization or infection by MRSA and CRE. Given these associations, similar associations may be present with *Clostridioides difficile* although additional data are currently lacking.

Methicillin-resistant *Staphylococcus aureus*. Eight studies assessed associations between travel and population migration with MRSA. In 2005 Maier et al. [101] performed a prospective survey of 127 patients with PVL-positive MRSA isolates obtained in Germany. Of these, 19 (15%) were found to be travel-related after epidemiologic investigation, which was further supported after multi-locus sequence typing (MLST), although no controls were identified enabling comparative analysis [99]. In 2007, Gustafsson et al. [102] described a prospective cross-sectional screening survey of 151 children adopted from foreign countries to Swedish families. Among 23 children who screened positive for MRSA, 13 (57%) had contact with a foreign hospital in the previous six months before arrival, although again no controls were identified to enable comparative analysis [102]. Similarly, in 2012 Hagleitner et al. [103] retrospectively reviewed all children adopted within the referral area of a single center in The Netherlands screened for MRSA within one month after arrival. Seventeen (13%) children were positive, compared with 2% of Dutch travelers hospitalized abroad, although no comparison was performed with control children [103].

In 2013, Chroboczek et al. [104] performed a retrospective cross-sectional assessment of epidemiologic risk factors associated with 85 MRSA isolates from Guadeloupe, Martinique, Jamaica, Trinidad and Tobago, and the Dominican Republic. In the French West Indies (n = 72), most strains were identical based on MLST isolated from mainland France (Lyon [n = 35] and Geraldine [n = 11] strains) [104]. Strains isolated from other islands (n = 13) corresponded with strains with worldwide endemic spread [104]. The authors proposed clonal resemblance of MRSA strains in the French (Guadeloupe and Martinique) and non-French West Indies (Jamaica, Trinidad and Tobago) is different and strains most closely resemble those found in home countries of traveling visitors [104].

In 2014, Larsson et al. [105] performed a retrospective study of positive MRSA cultures obtained in Skåne County, Sweden, from 2000–2010 identifying strain geographic origin using molecular typing. Only 231 (24%) index cases were of Swedish origin and contracted in Sweden although no statistical comparison was performed [105]. In the previously described Tosas Auguet et al. [81] study, development of CA-MRSA was associated with recent immigration to the United Kingdom (RR = 1.77; 95% CI, 1.19–2.66). In 2019, Moller et al. [106] reported an unusual outbreak with PVL-positive MRSA in 37 patients. After typing and epidemiologic investigation, cases were linked to a healthcare worker from Denmark who traveled to Southeast Asia on holiday, picked up an endemic strain, and brought it back to Denmark [106]. Finally, in 2020, Junnila et al. [107] performed a retrospective study of reported MRSA cases in Finland. Immigrants, refugees, and residents of foreign countries accounted for 32% of cases, but no statistical analysis was performed to address associations [107].

Carbapenem-resistant *Enterobacteriaceae*. Five studies assessed relations between travel and population migration with CRE. In 2015, Lofmark et al. [108] performed a retrospective analysis of all meropenem-resistant *Enterobacteriaceae* submitted to the Swedish Public Health Agency from 2007–2011. Of 94 cases identified, 76 (81%) had a history of travel abroad and 84% had been hospitalized abroad, although no statistical comparison was presented [108]. Also, in 2015, Ruppe et al. [109] performed a pre- to post-trip analysis of French travelers traveling abroad using fecal samples. Of 574 travelers who did not have multi-drug–resistant organisms before their trip, 292 (51%) carried multi-drug–resistant organisms after their trip, of which three (1%) were CRE [109]. Although not isolated to only CRE, the region visited (no OR provided; $p < 0.001$), β-lactam use during travel (OR, 4.08; 95% CI, 1.39–11.97), diarrhea during travel (OR, 1.90; 95% CI, 1.31–2.75), and type of travel (all-inclusive resorts vs. others; $p = 0.03$) influenced odds of multi-drug–resistant organism acquisition [109]. In 2016, Van Hattem et al. [110] reported a prospective multi-center cohort study of healthy travelers and non-traveling household members from The Netherlands. Of 2,001 travelers, five (0.2%) developed CRE, with one traveler carrying the same strain for six months post-travel [110]. Concerningly, this strain was transmitted to the traveler's spouse. No statistical comparison was performed with a comparator group [110].

In 2016, Reuland et al. [111] performed a prospective cohort study of Netherlands citizens traveling overseas, comparing stool sample or rectal swab pre-travel to a comparable sample post-travel. Only one traveler returned with a carbapenemase-producing *Enterobacteriaceae*, limiting assessment of CRE [109]. However, 98 (23%) travelers acquired extended-spectrum β-lactamase–producing organisms after travel with increased odds of acquisition associated with development of traveler's diarrhea treated with antibiotic agents (OR, 5.69; 95% CI, 1.29–24.99) and travel to Asia (OR, 3.14; 95% CI, 1.73–5.71) [111]. In 2019, Schaumburg et al. [112] enrolled international travelers leaving Germany and The Netherlands in a prospective cohort study from 2016–2018. No travelers were colonized with CRE before travel. Twenty-six (19.5%) travelers acquired CRE during travel, although most were intermittent carriers (24/26) [112]. On adjusted analysis, travel to Asia (OR, 0.2; 95% CI, 0.1–0.6) or vomiting during travel (OR, 0.1; 95% CI, 0–0.4] were associated with increased risk of CRE acquisition. An exclusively vegetarian diet (OR, 0.1; 95% CI, 0.01–0.6) was protective against colonization [112].

Clostrodium difficile. A single study assessed influence of travel and population migration with colonization by *Clostridioides difficile*. In the previously described Schaumburg et al. [112] study, pre- and post-travel carriage of *Clostridioides difficile* was assessed, however no *Clostridioides difficile* was identified in any stool samples, limiting analysis [112].

Built healthcare environment

Synopsis: Exposure to built healthcare environments has been documented to be associated with colonization and infection with MRSA and *Clostridioides difficile*. No studies were identified associating prior exposure to the built healthcare environment to CRE colonization or infection, although this risk factor is plausible based on associations for MRSA and *Clostridioides difficile*.

Methicillin-resistant *Staphylococcus aureus*. Five studies evaluated associations between exposure to the built healthcare environment and carriage or infection with MRSA. In the previously discussed Hidron et al. [48] case-control study, hospitalization within the last year was associated with increased odds of MRSA colonization (OR, 4.0; 95% CI, 2.0–8.2). Similarly, in the previously described Schinasi et al. [52] study, the greatest odds of carriage were seen among patients living with household members who were hospitalized in the last 12 months or had used antibiotic agents within the last four weeks (OR, 3.27; 95% CI, 1.24–8.57). In 2016, Holtfreter et al. [113] performed a population-based cross-sectional study of the northeastern German population (n = 3,891) to assess epidemiologic risk factors for MRSA carriage while performing whole genome sequencing of isolates to evaluate lineages. Contact with the built healthcare environment was associated with carriage of MRSA (0.69% of population exposed vs. 0.14% not exposed; $p = 0.04$), and most strains belonged to the pandemic ST22 strain suggesting healthcare exposure was a risk factor for carriage [113]. In the previously mentioned Reynaga et al. [32] study, hospital admission within the last 12 months was associated with MRSA carriage (47% vs. 26%; $p = 0.015$) on univariable analysis, although this was not found to be associated with tetracycline-resistant MRSA.

In line with these reports, in the previously described systematic review and meta-analysis performed by Wu et al. [35], regular visits to a healthcare facility was associated with highest odds of MRSA colonization (OR, 23.83; 95% CI, 2.72–209.01), followed by having a household member work in a healthcare facility (OR, 8.98; 95% CI, 1.4–55.63).

Carbapenem-resistant *Enterobacteriaceae*. None identified.

Clostridioides difficile. Six studies assessed associations between the built healthcare environment on human infection or colonization with *Clostridioides difficile*. In the Kutty et al. [62] study described earlier, a history of outpatient visits was associated with the second greatest odds of development of CA-CDI (OR, 5.1; 95% CI, 1.5–17.9) after antibiotic exposure. In the previously discussed Sǿes et al. [43] matched case-control study of Danish patients, prior hospitalization was associated with the second highest odds of CDI after a history of prior antibiotic administration (OR, 5.0; 95% CI, 2.5–9.9. In the 2015 Freedberg et al. [67] study discussed previously, prior hospitalization was associated with increased odds of CDI infection among persons younger than 17 years of age (OR, 2.51; 95% CI, 1.59–3.97). Also in 2015, Zacharioudakis et al. [114] performed a systematic review and meta-analysis to explore risk factors for colonization with toxigenic *Clostridioides difficile* upon hospital admission and risk of CDI. From 19 studies comprising 8,725 patients, history of hospitalization during the preceding three months was associated with highest risk of colonization (RR = 1.63; 95% CI, 1.13–2.34) [114]. In the previously described Anderson et al. [44] study from 2017, proximity to nursing homes (model estimate, −0.019; standard error [SE] = 0.009; $p = 0.04$) was identified as a risk factor for presence of CA-CDI. Also in the previously mentioned study by Adams et al. [69] study, prior outpatient visits were associated with increased odds of CDI (OR, 1.35; 95% CI, 1.31–1.39) among children in the U.S. military healthcare system.

Population density and urbanization

Synopsis: Living in a rural setting compared with an urban setting may increase infection or colonization with MRSA and *Clostridioides difficile*. The number of studies supporting this association is low and those studies that also assessed livestock exposure found that livestock exposure many have caused the difference in association rather than the rural setting itself. No data were found documenting association between colonization or infection with CRE and population density or rural–urban status although this association is plausible given data on MRSA and *Clostridioides difficile*.

Methicillin-resistant *Staphylococcus aureus*. Six studies assessed impact of population density or urbanization on human infection or colonization by MRSA. In 2009, Tong et al. [115] performed a matched case-control study to compare risk factors for infection with MRSA and MSSA infection at a single-institution in Australia. After adjusting for patient ethnicity, remote residence was associated with a 33-fold increase in odds for MRSA infections (95% CI, 11–129; $p < 0.01$) [115]. Between January and June 2014, Hussein et al. [116] performed a cross-sectional population-based survey of secondary students evaluating for MRSA carriage in rural and urban areas of Kurdistan, Iraq. Carriage rate in urban students was 2% compared with 22% in rural students (OR, 0.07; 95% CI, 0.009–0.6; $p = 0.02$) although no multivariable analysis was performed [116].

In 2017, See et al. [83] published a retrospective analysis of the CDC's Emerging Infections Program surveillance data to determine census tract factors associated with differences in invasive CA-MRSA cases. Although not the primary outcome, living in a rural area was associated with a rate ratio of invasive community-acquired MRSA infection of 0.36 (95% CI, 0.25–0.52; $p < 0.001$), contrary to many of the other reviewed studies [83]. Abiye et al. [117] performed a community-based cross-sectional survey of 622 urban and rural elementary schoolchildren in Gondar, Ethiopia. Frequency of MRSA was 1% in urban schoolchildren compared with 9% in rural schoolchildren (OR, 0.11; 95% CI, 0.013–0.866) [117]. In 2018, Anker et al. [31] published a geospatial analysis of clinical human infection with PVL-negative MRSA clonal complex 398 (CC398) without direct livestock exposure in three municipalities with high swine-farm density. Cases tended to be geographically clustered in rural areas (Global Moran's z-score 11.03; $p < 0.001$), but there was no difference in odds of infection among cases or controls in areas with high-density swine farming, suggesting human-to-human community transmission of PVL-negative CC398 was present [31]. Also in 2018, Lin et al. [118] performed a multi-stage, stratified, clustered cross-sectional

analysis of eight elementary schools in Guangzhou, China. In this study, the authors did not find any difference in the odds of MRSA colonization between urban or rural students (OR, 1.13; 95% CI, 0.61–2.10) [118].

Carbapenem-resistant *Enterobacteriaceae*. None identified.

Clostridioides difficile. Two studies evaluated associations between population density or urbanization on human infection or colonization with *Clostridioides difficile*. In 1990, Oguike et al. [119] performed a fecal survey of rural and urban children (<5 years of age) with diarrhea from Anambra State, Nigeria. Presence of *Clostridioides difficile* was common and similar between rural and urban areas (48%–53% vs. 42%–48%) although no statistical comparison was performed and no assessment of toxin-creating capacity of isolates was performed [119]. In 2017, in the Anderson et al. [44] study described earlier, lower population density was associated with greater odds of infection (model estimate [ME] = –0.029; SE = 0.14; p = 0.04), which may have been largely driven by the positive influence from closer proximity to livestock farms (ME = –0.021; SE = 0.009; p = 0.01), and farming raw material services (ME = –0.011; SE = 0.005; p = 0.02) [44].

Limitations

There are numerous important limitations to this scoping review. In accordance with our scoping review question, no attempt was made to acquire, synthesize, or describe studies that did not demonstrate association between social or environmental determinants of health and colonization or infection with MRSA, CDI, or CRE. This selection bias was introduced intentionally to encourage hypothesis generation and emphasize potential avenues for further research. Performing a comprehensive quantitative analysis of positive and negative associations between socioeconomic and environmental variables and colonization or infection with MRSA, CDI, and CRE will be an important next step. Environmental sampling studies without association, linkage, or causal inference made to human colonization were excluded, thus limiting our ability to describe potential environmental sources capable of harboring pathogens ultimately able to cause human disease. In accordance with scoping review methodology, no attempt was made to quantify effect of a given social or environmental determinant of health on human colonization or infection, which limits our ability to use our findings to predict impact of determinants on distribution of colonization or infection. There is also the risk of introducing ecological fallacy when individual-level phenomena are described at larger aggregate spatial units as is frequently performed when assessing population level socioeconomic or environmental variables. Finally, articles describing both human colonization and infection were included introducing heterogeneity into our articles and our findings. It is likely that risk factors for colonization and infection exist along a spectrum, so association between a given determinant of health and these phases of human interaction should be interpreted with caution.

Conclusions

Socioeconomic and environmental determinants of health have been documented to be associated with human infection or colonization with common antibiotic-resistant or antibiotic-associated pathogens. Across all seven categories of socioeconomic and environmental determinants of health, data supporting associations with MRSA or *Clostridioides difficile* were more common than for CRE. Transmission of MRSA or *Clostridioides difficile* between humans and livestock and non-livestock animals was well-documented with increased exposure to livestock and non-livestock animals increasing human colonization and infection. Antibiotic exposure, including exposure outside of the built healthcare environment was documented to increase infection or colonization with MRSA, CRE, or *Clostridioides difficile*. Greater colonization or infection by MRSA was documented to be associated with lower socioeconomic status or education level. Although race may be associated with greater colonization or infection by MRSA, this association was more commonly described when race itself was associated a lower socioeconomic status. It is unclear how *Clostridioides difficile* or CRE infection or colonization may be impacted by socioeconomic status, race, or education as existing literature is discrepant and sparse for each pathogen respectively. Higher temperatures and humidity were documented to increase colonization and infection with MRSA. Although seasonality was reported to effect colonization or infection with *Clostridioides difficile,* this association varied by Southern and Northern Hemispheres. More frequent human population migration and travel was documented to be associated with colonization or infection by MRSA and CRE. Exposure to built healthcare environments was reported to be associated with colonization and infection with MRSA and *Clostridioides difficile*. Finally, living in a rural setting compared with an urban setting may increase infection or colonization with MRSA and *Clostridioides difficile* although livestock exposure, rather than rurality in and of itself, may have been responsible for the observed difference. Although articles outlining socioeconomic and environmental drivers of antibiotic-resistant and antibiotic-associated infection are still disconcertedly few, evidence of such as an association is overwhelming for MRSA and CDI, and supportive for CRE. Additional research is needed to investigate the role and importance of different potential socioeconomic and environmental drivers of antibiotic-resistant and antibiotic-associated infections and colonization in humans.

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Supplementary Material

Supplementary Appendix SA1

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