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SMART Antibiotic Resistance Goals to Drive Meat Safety Improvement

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Abstract: Concerns that food-animal production significantly contributes to antibiotic-resistant human infections have persisted for more than 20 years. Most antibiotic resistance concerns are generalized, not specific. By their nature, non-specific concerns are unfalsifiable and can never be scientifically alleviated or remediated. Therefore, antibiotic resistance meat safety improvement begins with defining SMART (Specific, Measurable, Attainable, Relevant, and Time bound) antibiotic resistance goals. Two SMART goals related to high-priority antibiotic resistance in beef production are described as an example to facilitate scientific goal attainment.

Key words: antibiotic resistance, food safety, *Salmonella*, *Escherichia coli*, beef
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Introduction

Numerous governmental and nongovernmental organizations have identified antibiotic resistance as a critically important public health threat (WHO, 2018; CDC, 2019). The Centers for Disease Control and Prevention (CDC) attributes approximately 2.9 million infections and 49,000 deaths to antibiotic resistance annually in the United States (CDC, 2019). Longstanding concerns exist that antibiotic use during food-animal production significantly contributes to antibiotic-resistant infections (both human and animal) (WHO, 2000; Spellberg et al., 2008; Davies, 2013). Organizations including the CDC (2019), the Tripartite Collaboration on antimicrobial resistance by the World Organization for Animal Health/Food and Agriculture Organization/World Health Organization (FAO, 2015), the US Food and Drug Administration (FDA, 2018), and the US Department of Agriculture (USDA, 2014) declare antibiotic resistance to be a "One Health" problem since resistant bacteria may spread among animals, humans, and the environment. Specifically, the CDC defines One Health as "a collaborative, multisectoral, and trans-disciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment" (CDC, 2019).

Over the last 10 years, numerous actions have been taken in the US to address these One Health antibiotic resistance concerns: in 2011, the National Institute for Animal Agriculture began holding annual symposiums focused on antibiotics; in 2012, bans on certain specific antibiotic applications in food animals were adopted (FDA, 2012b); in 2013, the National Antimicrobial Resistance Monitoring System (NARMS) surveillance program, which is focused on meat production and processing chains, was expanded (FSIS, 2013); in 2014, the President's Council of Advisors on Science and Technology published the *National Strategy for Combating Antibiotic-Resistant Bacteria* (PCAST, 2014); in 2015, the Food and Drug Administration published the Veterinary Feed Directive final rule improving

US antibiotic use stewardship (FDA, 2015); in 2019, the National Institute of Antimicrobial Resistance Research and Education was founded; and in 2020, the NARMS program was expanded further (FSIS, 2020). Concurrently, numerous studies have found that antibiotic use during food-animal production has small to no sustained impact on antibiotic resistance levels, with a few cited here (Schmidt et al., 2013, 2020; Tang et al., 2017, 2019; Vikram et al., 2017, 2018, 2019; Miller et al., 2018, 2019; Vikram and Schmidt, 2018; Levent et al., 2019; Ohta et al., 2019; Rovira et al., 2019).

Antibiotic resistance is an ancient, natural, and intrinsic bacterial trait and predates human use of antibiotics (D'Costa et al., 2011). Accordingly, antibiotic resistance genes and antibiotic-resistant bacteria can be detected in any bacterial-inhabited environment, including relict prairie (Agga et al., 2015), air in major cities (Li et al., 2018), household dust (Ben Maamar et al., 2020), 120,000-year-old Greenland ice cores (Miteva et al., 2004), soils undisturbed for more than 3 million years (Brown and Balkwill, 2009; Bhullar et al., 2012), and remote indigenous communities with very low or no antibiotic exposure (Davis and Anandan, 1970; Bartoloni et al., 2009; Clemente et al., 2015). However, antibiotic-resistance–related recommendations tend to be generalized and do not identify specific high-priority antibiotic-resistant bacteria or antibiotic resistance genes. Commonly accepted normal, safe, background, or basal level definitions for the >2,000 individual antibiotic-resistant bacteria and antibiotic resistance genes do not exist (Bengtsson-Palme and Larsson, 2015; Martinez et al., 2015; Zhang et al., 2019). Unhelpfully, without such standards, the One Health concept can be used to exaggerate perceived risks and lead to ineffective recommendations when ubiquitous antibiotic resistance is detected (Chainier et al., 2017; Ben Maamar et al., 2020). The resulting diffuse, unspecific, and generalized food safety antibiotic resistance concerns are inherently unfalsifiable and can never be scientifically alleviated or remediated. Identification of SMART antibiotic resistance goals will enable tangible meat safety improvements. SMART is an acronym (Specific, Measurable, Attainable, Relevant, and Time bound) used in management to provide criteria to guide goal formulation (Doran, 1981). The objective of this manuscript was to describe 2 antibiotic-resistance–related SMART goals for beef production to serve as examples of how meat safety may be improved by addressing antibiotic resistance concerns.

SMART Goal 1

SMART goal 1 was as follows.

- Specific: Develop a robust method to identify beef products harboring antibiotic-resistant nontyphoidal *Salmonella enterica* (hereafter *Salmonella*) seriously threatening human health.
- Measurable: Use beef manufacturing trimmings and ground beef samples currently tested for Shiga toxin–producing *Escherichia coli* and increasingly tested for *Salmonella*.
- Attainable: Use and improve existing technologies to isolate antibiotic-resistant *Salmonella* seriously threatening human health. Beef production system (feeding operations and dairies) samples or hide samples can be used to isolate *Salmonella* to identify unique DNA sequences and develop rapid screening protocols (analogous to Shiga toxin–producing *Escherichia coli* testing).
- Relevant: The CDC considers beef the dominant source of azithromycin-resistant and ceftriaxone-resistant *Salmonella* seriously threatening human health.
- Time bound: Amenable to discrete deadlines since all technologies exist and samples are easily obtained.

Of the 18 specific antibiotic-resistant organisms seriously threatening human health (as defined by CDC), only infections caused by *Salmonella* can be linked to beef consumption (CDC, 2019). The CDC identifies *Salmonella* resistant to azithromycin, ceftriaxone, or ciprofloxacin as serious threats to human health, with an estimated 212,500 infections and 70 deaths per year (CDC, 2019). Source attribution estimates identified beef as a source in 6.4% of 811 foodborne *Salmonella* outbreaks from 1998 to 2017 (IFSAC, 2019). However, the CDC concluded that beef is the predominant source of ceftriaxone-resistant *Salmonella* because the 2 most dominant serotypes (Newport [40.2%] and Typhimurium [25.9%]) among 978 ceftriaxone-resistant *Salmonella* isolated from humans between 1996 and 2013 were cattle associated (Iwamoto et al., 2017). The CDC has also concluded that beef is the likely source of ceftriaxone-resistant *Salmonella* Dublin associated with severe clinical outcomes (Harvey et al., 2017). A 2019 multistate outbreak (255 cases, 60 hospitalizations, 2 deaths) of azithromycin-resistant *Salmonella* Newport was attributed to ground beef consumption (Plumb et al., 2019).

Several studies have demonstrated that antibiotic use during cattle production does not impact occurrences of *Salmonella* resistant to azithromycin, ceftriaxone, or ciprofloxacin (Vikram et al., 2017, 2018; Levent et al., 2019; Ohta et al., 2019). Contrary to CDC conclusions, *Salmonella* (regardless of antibiotic resistance status) was detected in just 197 (1.1%) of the 21,225 retail ground beef samples NARMS tested between 2002 and 2017 (FDA, 2019a). Ceftriaxone-resistant *Salmonella* were detected in only 29 (0.1%) samples. Azithromycin-resistant *Salmonella* and ciprofloxacin-resistant *Salmonella* were not detected. While beef is extremely rarely contaminated by *Salmonella* resistant to azithromycin, ceftriaxone, or ciprofloxacin, the hazards to human health and public perception of the beef industry are very high. The appropriate SMART goal is to adapt current testing of beef manufacturing trimmings and ground beef to identify and remove lots harboring *Salmonella* resistant to azithromycin, ceftriaxone, or ciprofloxacin. A major obstacle is the lack of rapid tests that specifically identify *Salmonella* resistant to azithromycin, ceftriaxone, or ciprofloxacin.

Fortunately, a clear path to these goals using existing technologies exists. Some companies already screen many (>100,000 per year) lots for *Salmonella* in order to reduce significant threats to public health. A logical first step is to subject samples from *Salmonella*-positive lots to additional culture methods to isolate *Salmonella* resistant to azithromycin, ceftriaxone, or ciprofloxacin (Vikram et al., 2017, 2018). However, additional samples must be obtained to account for the expected extremely infrequent detection of *Salmonella* resistant to azithromycin, ceftriaxone, or ciprofloxacin in beef manufacturing trimmings and ground beef. Azithromycin-, ceftriaxone-, or ciprofloxacin-resistant *Salmonella* detection is likely to be more frequent on hides or in surface soils obtained from cattle pens. Preliminary research detected ceftriaxone-resistant *Salmonella* in surface soil samples obtained from pens at 8 of 23 cattle feeding operations (J. W. Schmidt, unpublished data, 2020). Azithromycin-resistant *Salmonella* was detected at 1 cattle feeding operation. Importantly, these ceftriaxone-resistant *Salmonella* and azithromycin-resistant *Salmonella* populations were small subpopulations within larger, generally pansusceptible diverse *Salmonella* populations (J. W. Schmidt, unpublished data, 2020). Similar sampling regimes throughout fed and cull beef production and processing continuums will be required to achieve the related high-priority goal of defining a *Salmonella* baseline, which is key to the formulation of a quantitative microbial risk assessment.

The most affordable and efficient mechanism for identifying high-quality DNA markers specific to azithromycin-, ceftriaxone-, and ciprofloxacin-resistant *Salmonella* strains posing the highest human health risks is next-generation sequencing, often referred to as whole-genome sequencing. Liability concerns surrounding whole-genome sequencing can be mitigated by obtaining samples in an anonymous manner.

SMART Goal 2

SMART goal 2 was as follows.

- Specific: Determine whether beef is a significant source of human pathogenic ceftriaxone-resistant *E. coli* in the US.
- Measurable: Ceftriaxone-resistant *E. coli* can be isolated from ground beef, beef manufacturing trimmings, hides, and cattle pen surface soils using existing methods.
- Attainable: Whole-genome sequencing demonstrated that United Kingdom retail meat and food-animal ceftriaxone-resistant *E. coli* isolates were distinct from *E. coli* isolated from human bacteremia patients.
- Relevant: Despite little evidence, several scientific manuscripts have concluded that meats are a significant source of ceftriaxone-resistant extraintestinal pathogenic *E. coli* causing human infections.
- Time bound: Amenable to discrete deadlines since all technologies exist and samples are easily obtained.

Cephalosporins (ceftriaxone, cefotaxime, ceftiofur) are inactivated by extended-spectrum beta-lactamases. Extended-spectrum beta-lactamase–producing Enterobacteriaceae, predominantly ceftriaxone-resistant *E. coli*, are a serious antibiotic resistance threat and caused an estimated 197,00 hospitalizations and 9,100 deaths in 2017 (CDC, 2019). The *E. coli* strains that cause these infections are termed extraintestinal pathogenic *E. coli*. Unlike Shiga-toxigenic *E. coli* and enterohemorrhagic *E. coli*, there is no discrete set of genetic markers that can be used to distinguish extraintestinal pathogenic *E. coli* from commensal *E. coli* (Kaper et al., 2004; Johnson and Russo, 2005; Croxen and Finlay, 2010; Johnson et al., 2015, 2019). This complexity has led to the measurement of levels of ceftriaxone-resistant *E. coli*, since ceftriaxone is the preferred

therapy for many human extraintestinal *E. coli* infections.

The CDC does not implicate beef (or meat generally) as a source of ceftriaxone-resistant *E. coli* threatening human health. In the US, cephalosporins account for less than 1% of the medically important antibiotics used in food-animal production, and the mass of cephalosporins used in human medicine is at least 10 times greater than that used in food-animal production (FDA, 2012a, 2019b). Numerous studies have demonstrated that antibiotic drug uses (including cephalosporin uses) during beef production either do not increase, transiently increase, or marginally increase ceftriaxone-resistant *E. coli* shed by cattle (Schmidt et al., 2013, 2020; Agga et al., 2016a, 2016b; Vikram et al., 2017; Ohta et al., 2019; Taylor et al., 2019). Beef processing sanitary dressing and processing interventions have been demonstrated to effectively reduce ceftriaxone-resistant *E. coli* (Schmidt et al., 2015). Ceftriaxone-resistant *E. coli* were detected at similar ($P = 1.00$) low rates in ground beef produced with (1.1%) and without (0.6%) antibiotics (Vikram et al., 2018). Nevertheless, several other groups have concluded that meat is a significant source of ceftriaxone-resistant extraintestinal pathogenic *E. coli* causing human infections and have suggested that antibiotic uses during beef production may increase occurrences (Hammerum and Heuer, 2009; Leverstein-van Hall et al., 2011; Overdevest et al., 2011; Nordstrom et al., 2013; Lazarus et al., 2015; Horigan et al., 2016; Johnson et al., 2017).

Despite the lack of specific genetic markers, extraintestinal pathogenic *E. coli* are strongly associated with specific lineages (akin to serotypes) known as sequence types (Johnson et al., 2015, 2019; Day et al., 2016). Furthermore, ceftriaxone resistance in extraintestinal pathogenic *E. coli* is strongly correlated with specific extended-spectrum beta-lactamase alleles. The most efficient mechanism to determine *E. coli* sequence types and extended-spectrum beta-lactamase alleles is whole-genome sequencing. A recent whole-genome sequencing study of 936 UK isolates concluded that the sequence types and extended-spectrum beta-lactamase gene alleles of *E. coli* isolated from human bacteremia patients matched human fecal and municipal sewage isolates but were distinct from retail meat (including beef) and food-animal (including dairy fecal slurry) isolates (Day et al., 2019). The authors concluded that UK food chain interventions were unlikely to reduce human infections.

These findings strongly suggest that US beef is not a significant source of ceftriaxone-resistant extraintestinal pathogenic *E. coli*. The appropriate SMART goal would utilize the same samples as SMART goal 1 focused on *Salmonella* (beef manufacturing trimmings, ground beef, hides, and cattle pen surface soils) to conclusively determine the occurrence of ceftriaxone-resistant extraintestinal pathogenic *E. coli* in the beef production continuum. Ceftriaxone-resistant *E. coli* are reliably isolated using proven methods (Schmidt et al., 2015, 2020; Vikram et al., 2018). Determining sequence type and extended-spectrum beta-lactamase alleles is attainable. The US Meat Animal Research Center has developed a whole-genome sequencing and annotation pipeline to rapidly obtain these data from *E. coli* and *Salmonella* isolates (J. W. Schmidt and A. Dickey, unpublished data, 2020). Obtaining these data for >1,000 US ceftriaxone-resistant *E. coli* isolated from beef and cattle should be sufficient to determine whether beef is a significant source of human pathogenic ceftriaxone-resistant *E. coli* in the US. These data, including whole-genome sequencing data, are required to generate a quantitative microbial risk assessment that accurately estimates the probability and magnitude of exposure to ceftriaxone-resistant extraintestinal pathogenic *E. coli* via beef consumption in the US (Collineau et al., 2019). Importantly, publication of this research is not contingent on depositing whole-genome sequences in a public database. No whole-genome sequences were released for the UK study published in *The Lancet Infectious Diseases* (Day et al., 2019). The successful completion of this work will either demonstrate that cattle and beef are not significant sources of ceftriaxone-resistant extraintestinal pathogenic *E. coli* in the US or provide critical data needed to develop rapid screening protocols.

Conclusions

Devoting resources to assuage ambiguous antibiotic resistance concerns will not inform tangible actions to improve meat safety. Antibiotic resistance is an intrinsic bacterial trait, and bacterial populations are an inherent component of meat production continuums. Therefore, antibiotic resistance can never be eliminated from most segments of the meat production continuum, including fresh meats. The example SMART antibiotic resistance goals defined here and analogous goals for other meat commodities offer the best mechanisms to definitively contribute to One Health goals by ensuring that meats do not increase the

occurrences of human infections complicated by antibiotic resistance.

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Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of product, and the use of the name by the USDA implies no approval of the product to the exclusion of others that may also be suitable. The USDA is an equal opportunity employer and provider.

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