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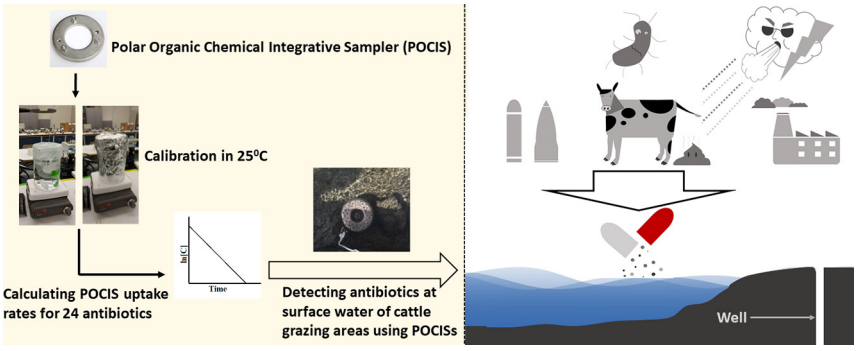
HIGHLIGHTS

- Laboratory uptake rates of 24 antibiotics using POCIS were determined.
- Except monensin, none of the detected antibiotics were prescribed in US MARC.
- Detecting other antibiotics might be due to natural production or transfer by wind.
- Highest concentration of antibiotics was detected in August–September.
- Highest concentrations coincided with the highest number of precipitation events.

GRAPHICAL ABSTRACT



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ABSTRACT

A wide variety of antibiotics and other pharmaceuticals are used in livestock production systems and residues passed to the environment, often unmetabolized, after use and excretion. Antibiotic residues may be transported from manure-treated soils via runoff and are also capable of reaching surface and groundwater systems through a variety of pathways. The occurrence and persistence of antibiotics in the environment is a concern due to the potential for ecological effects and proliferation of environmental antibiotic resistance in pathogenic organisms. In the present study, the occurrence and seasonal variation of 24 commonly-used veterinary antibiotics was evaluated in surface water adjacent to several livestock production systems using Polar Organic Chemical Integrative Samplers (POCIS). Uptake rates for all compounds, nine of which have not been previously reported, were measured in the laboratory to permit estimation of changes in the time-weighted average (TWA) antibiotic concentrations during exposure. The antibiotics detected in POCIS extracts included sulfadimethoxine, sulfamethoxazole, trimethoprim, sulfamerazine, sulfadiazine, lincomycin, erythromycin, erythromycin anhydro- and monensin. The maximum TWA concentration belonged to sulfadiazine (25 ng/L) in the August–September sampling period and coincided with the highest number of precipitation events. With the exception of monensin that showed an increase in concentration over the stream path, none of the detected antibiotics were prescribed to livestock at the facility. The detection of antibiotics not prescribed by the facility may be

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attributable to the environmental persistence of previously used antibiotics, transfer by wind from other nearby livestock production sites or industrial uses, and/or the natural production of some antibiotics.

1. Introduction

The use of antibiotics in livestock production to promote animal growth and prevent disease has likely resulted in development of antibiotic resistance in human pathogens (Qiao et al., 2018), potentially reducing their effectiveness in treating infections (Martinez, 2009). The use of antibiotics has undoubtedly resulted in increasing the occurrence of these compounds in the environment, where they are considered important emerging pollutants (Yan et al., 2019). Regardless of the relatively short half-lives of antibiotics that vary from hours to hundreds of days (Ji et al., 2010), their residues can remain in the environment as persistent organic contaminants, with implications for public health (Hamscher et al., 2002). Among different classes of antibiotics, sulfonamides, tetracycline, macrolides and beta-lactams are among the most frequently used antibiotics for veterinary purposes and consequently are detected in the environment (Charuaud et al., 2019; Peng et al., 2019; Pinheiro et al., 2017; Ravikumar et al., 2019).

Livestock manure is a significant source of crop nutrients and is applied to cropland globally (Miller et al., 2019). Antibiotics that were administrated to animals can be excreted in urine or feces (Zhao et al., 2010), and may occur in manure at concentrations up to hundreds of mg/kg (Zhou et al., 2013). The use of livestock manure and wastewater as fertilizers are among the greatest potential sources of antibiotics entering agroecosystems (Ashbolt et al., 2013; Ben et al., 2019).

The measurement of antibiotics in aqueous environments is often performed via active sampling approaches such as grab sampling; however, this approach which mostly includes collecting samples into or through a convenient medium (Górecki and Namieśnik, 2002); results in a snapshot of the contaminant concentrations at the sampling time points. In addition, grab sampling is expensive and difficult if large sample volumes are required. These problems can be addressed with the use of passive samplers (Xie et al., 2018). As opposed to grab samplers, passive samplers are easy to deploy/retrieve and more cost-effective. Moreover, no power source is required for their operation during the deployment time. Based on the type of the passive samplers, they can either provide information on the concentration of the analytes around the retrieval time of the sampler, or on the time-weighted average (TWA) concentration of the analytes during the sampler deployment period (Salim and Górecki, 2019). Passive sampling was developed to measure a wide range of organic compounds in aqueous environments (Criquet et al., 2017). Moreover, since passive sampling methods accumulate compounds over time, they can be used to measure very low contaminant concentrations (Miège et al., 2015).

In the past two decades, techniques for passive sampling for polar compounds have been used broadly for environmental monitoring (Fauvelle et al., 2017; Mali et al., 2017; Wang et al., 2017). There are different types of passive samplers namely silicone rubber, polar organic chemical integrative sampler (POCIS) and Chemcatcher. Several factors should be taken into account while choosing the passive samplers including the purpose of the study and the uptake of the target compounds to the passive sampler which is highly related to the hydrophobicity. The more hydrophilic the compound (low K_{ow}), the better it will be detected by POCIS samplers (Ahrens et al., 2015).

POCIS samplers rely on diffusion of compounds from the aqueous phase to an organic phase that is separated by a permeable membrane, which allows the transfer and accumulation of analytes due to concentration gradients across the membrane (Valenzuela et al., 2019). One limitation of POCIS is that determination of time-weighted average concentrations from POCIS requires a laboratory determined uptake rate, and uptake in the field may differ due to changes in ambient conditions.

In this study, POCIS samplers were used to investigate the occurrence and seasonal variation of antibiotics (with log $K_{ow} < 10$) in surface water within a cattle grazing area at the U.S. Meat Animal Research Center (US MARC) near Clay Center, Nebraska, by sampling at five locations along a stream in the facility from April to September 2018. The objectives of this project were to (1) measure laboratory uptake rates for 24 antibiotics in POCIS samplers; (2) document the presence of antibiotics in the stream located adjacent to cattle grazing areas; and (3) identify seasonal variation in the types and concentrations of antibiotics detected.

2. Materials and methods

2.1. POCIS samplers

POCIS samplers that were utilized in this study were purchased from Environmental Sampling Technologies (St. Joseph, MO, USA). The POCIS contained a solid sequestration media (Oasis HLB™ copolymer, Waters Corporation, Milford, MA, USA). The sorbent is sandwiched between two polyethersulfone membranes held together by stainless steel compression rings. POCIS contain 200 mg of sorbent medium with an effective surface area of 41 cm^2. The POCIS samplers were stored at −20 °C until use.

2.2. Laboratory uptake rate experiments

2.2.1. Procedure for determining uptake rates

The experimental procedure for determining POCIS uptake rates was based on the method described by Macleod et al. (2007) and used in Bartelt-Hunt et al. (2011). In brief, an aqueous mixture of the target antibiotics including virginiamycin M1, tylosin, tiamulin, penillic acid, penicillin, novobiocin, monensin, erythromycin Anhydro-, erythromycin, ceftiofur, lincomycin, oxytetracycline, ractopamine, sulfadimethoxine, sulfamethazine, tetracycline, trimethoprim, sulfamethizole, sulfamerazine, sulfamethoxazole, sulfathiazole, sulfadiazine and chlortetracycline, was prepared in a beaker. Each antibiotic had a concentration of 5 μg/L and a POCIS sampler was submerged in the beaker. Togola and Budzinski (2007) demonstrated that there was no effect of analyte concentration on POCIS uptake rates; therefore, uptake rates determined at this concentration were relevant to uptake in the field even where environmentally-relevant concentrations may be low. One set of experiments was performed for macrolide and beta-lactam compounds and another was performed for tetracycline and sulfonamide compounds. Although the experimental conditions were the same, tetracycline/sulfonamide and beta-lactam/penicillin compounds were analyzed in two separate experimental set ups because of the two different extraction methods they needed. Monensin was evaluated in both sets of experiments and its calculated R_s from both analysis methods were very close showing that the methods were in close agreement.

A 1 mM mixture of sodium dihydrogen phosphate and disodium hydrogen phosphate was used to buffer 1.6 L of water at pH 7 for performing the uptake experiments. Prior to use in the uptake experiments, the glassware and stir bars were soaked in diluted 2% Citranox solution for 24 h. A saturated ethylenediaminetetraacetic acid (EDTA) solution was added to glassware used for tetracycline uptake. The experiments were performed in in triplicate at room temperature (24 °C) and at an estimated flow rate of 84 cm/s. For control experiments, where decay of the contaminants unrelated to POCIS uptake was monitored, a 2 L beaker without POCIS and containing the same aqueous concentration of contaminants was used. The beakers were covered with parafilm and foil to prevent evaporation and

photodegradation. Fifty milliliters of water was removed from each beaker at 0, 1, 3, 7, 14, and 28 d and stored in an amber jar at −20 °C until analysis. The POCIS was removed at the end of the 28-d exposure period, and stored at −20 °C until analysis. Preliminary experiments demonstrated limited (0.5%) evaporation occurred over the 28-d experiment.

2.2.2. Calculation of sampling rates and TWA

The aqueous concentration over time was modeled using a first order decay model to determine the first-order decay coefficient (K). There were also concentration changes due to processes other than uptake by POCIS, such as degradation of the antibiotics. Therefore, control experiments were used to determine the rate of this concentration change (k_D) (Bartelt-Hunt et al., 2011). The rate of uptake by POCIS (k_U) was determined as:

$$K = K_U + K_D$$

The POCIS uptake rate (R_s) was calculated as:

$$R_s = K_U V_T$$

where V_T was the total volume of the water in the beaker. Volume changes in the beakers due to sampling during the sampling events were considered by adjusting the values of V_T. The POCIS sampling rates were calculated from the slope of concentration versus time using all data created over the 28-d exposure (Bartelt-Hunt et al., 2011).

2.3. Analytical methods

There were two groups of veterinary pharmaceuticals in this study. Categorizing them was based on their eluting conditions from POCIS sorbent, their chemical classes and adaptability to solvents (Dungan et al., 2017). The group of analytes that were categorized as macrolide/penicillin in this study, included ampicillin, virginiamycin M1, tylosin, tiamulin, penillic acid, penicillin, novobiocin, monensin, erythromycin Anhydro-, erythromycin and ceftiofur. The second group of compounds that were categorized as tetracycline/sulfonamide in this study was lincomycin, oxytetracycline, ractopamine, sulfadimethoxine, sulfamethazine, tetracycline, trimethoprim, sulfamethizole, sulfamerazine, sulfamethoxazole, sulfathiazole, sulfadiazine and chlortetracycline. Solvents and standards were purchased from ThermoFisher Scientific (St. Louis, MO) and Sigma-Aldrich (St. Louis, MO). Isotopically-labelled internal standards were purchased from Cambridge Isotopes (Tewksbury, MA). For the macrolide/penicillin compounds, surrogate was oleandomycin and internal standards were roxithromycin, salinomycin, and penicillin V. For tetracycline/sulfonamide compounds, surrogate was sulfachloropyridazine and demeclocycline, and the internal standards were sulfamethazine-$^{13}C_6$, doxycycline, and salinomycin. In order to make the spiking solutions of internal standard, mixed analytes and surrogates, the first step was to prepare the stock solutions with a concentration of 1 μg/μL. For macrolide/penicillin compounds, 10 mg of each compound was accurately weighted and dissolved in 10 mL of HPLC grade acetonitrile. For tetracycline/sulfonamide compounds, accurately weighed compounds (10 mg) were dissolved in 10 mL of Optima™ high purity methanol. The stock solutions were pipetted and diluted in either methanol or acetonitrile and were stored in silane treated amber vials at −20 °C.

2.3.1. Extraction of aqueous samples for tetracycline/sulfonamide compounds

Approximately 0.1 g of EDTA was added to 20 g of aqueous sample, mixed thoroughly, and then spiked with 100uL of 1 ng/uL tetracycline/sulfonamide surrogate spikes. Samples were extracted through 200 mg HLB cartridges (Waters Corporation, Milford, MA), which were preconditioned with 5 mL methanol followed by 5 mL distilled

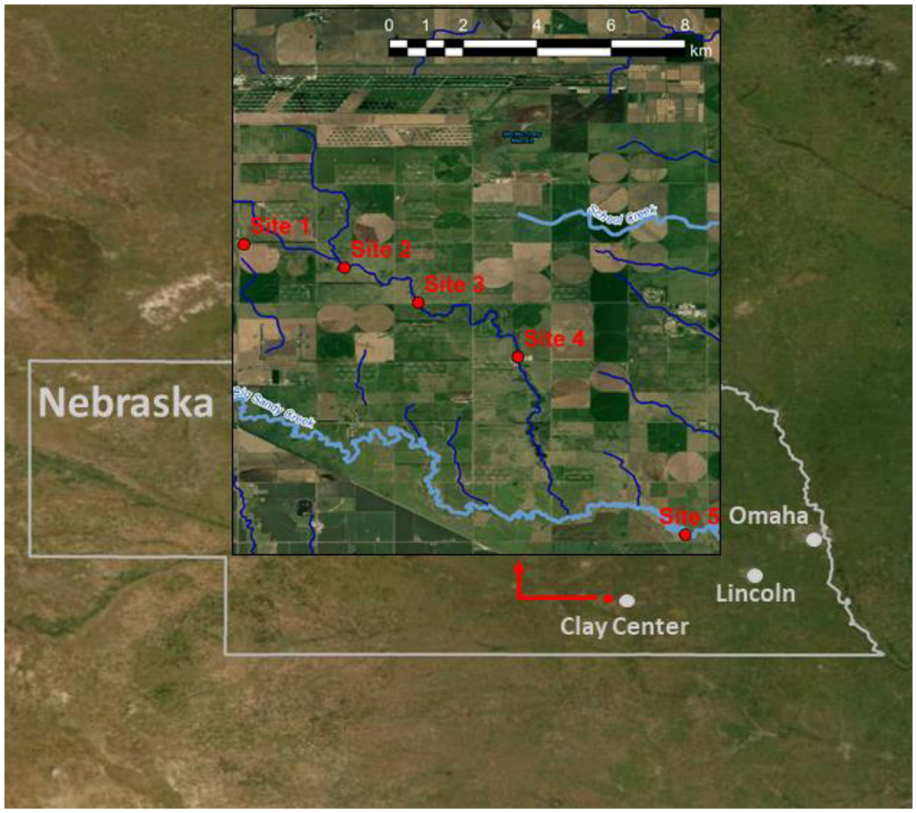

Fig. 1. Magnified map of sampling site locations in Nebraska.

deionized water. The cartridges were then eluted to glass culture tubes with 5 mL of 0.5% formic acid in methanol. The extract was evaporated to 500 μL via N_2 stream and then spiked with 100 μL of 1 ng/μL tetracycline/sulfonamide Internal Standard spike and vortexed to mix. Samples were then evaporated to 100 μL, and 300 μL of 1:33 mM ammonium citrate were added to each sample, vortexed to mix and transferred to autosampler vials fitted with a 200 μL conical spring insert and stored at −20 °C until analysis by liquid chromatography tandem mass spectrometry (LC/MS-MS). Quality assurance samples, including a lab duplicate (LD2), a lab fortified blank (LFB), a lab fortified matrix (LFM) and a lab reagent blank (LRB) were each prepared and analyzed with a frequency of 1 in 20 samples. Recoveries in LFBs analyzed with POCIS extracts ranged from a low of 56.5 ± 45.8% for chlortetracycline to 124.3 ± 134.6% for tetracyclin, with most compounds averaging above 75%.

2.3.2. Extraction of aqueous samples for macrolide/beta-lactam compounds

Approximately 0.1 g of ammonium acetate was mixed with 20 g of sample and then spiked with 100 μL of 1 ng/μL macrolide/penicillin surrogate spike. Samples were extracted using 200 mg HLB SPE cartridges, preconditioned with 5 mL dichloromethane (DCM), 5 mL of acetonitrile (ACN) followed by 5 mL of distilled deionized water. The cartridges were then eluted to glass culture tubes with 10 mL of 80:20 DCM/Acetone solvent followed by 3 mL of ACN. Extracts were evaporated sequentially to 100 μL and then combined with 100 μL of 1 ng/μL macrolide/penicillin Internal Standard spike and vortex to mix. Samples were evaporated to 100 μL, and mixed with 300 μL of 1:33 mM ammonium acetate vortex to mix and transferred to autosampler vials fitted with a conical spring insert and stored in −20 °C freezer for analyses by LC/MS-MS. Recoveries in LFBs analyzed with POCIS extracts ranged from a low of 32 ± 30% for penillic acid to 108 ± 16% for erythromycin anhydride, with most compounds averaging above 75%.

2.3.3. POCIS extraction and analysis

Field-deployed POCIS were extracted sequentially for two groups of compounds and extracts combined using methods describe previously (Dungan et al., 2017). Macrolides and beta-lactams were measured first to minimize the risk of hydrolysis from methanol and formic acid. Briefly, each POCIS device was carefully disassembled and HLB resins were transferred by rinsing the membrane with reagent water into individual glass extraction columns containing a small quantity of glass wool and Teflon stopcock. The water was allowed to drain and then solvents added for extraction and analysis of the sorbent. Macrolide/beta-lactam compounds were extracted using 50 mL of 80:20 DCM/acetone followed by 30 mL of ACN into glass RapidVAP (Labconco, Kansas City, MO) evaporation tubes, spiked with 100 μL of 1 ng/μL macrolide/beta-lactam surrogate spike, and then evaporated under nitrogen at 55% speed, 40 °C to approximately 1 mL. The concentrated extract was quantitatively transferred to glass culture tubes using additional ACN rinses. Internal standards (100 μL of 1 ng/μL) were added and the volume further reduced to approximately 200 μL. Extracts were transferred to autosampler vials containing conical inserts.

The POCIS resin was then extracted with 50 mL of 0.5% formic acid in methanol eluted into glass RapidVAP tubes and spiked with 100 μL of 1 ng/μL tetracycline/sulfonamide surrogate spike and then evaporated under nitrogen at 55% speed, 40 °C to approximately 1 mL. 100 μL of 1 ng/μL of internal standards were added and the volume further reduced to approximately 200 μL. The extract from the first extraction was combined with the second to ensure quantitative recovery of all compounds.

Recovery of each analyte group from the POCIS resin was checked by spiking and processing as described above. Quality controls were analyzed at a rate of 5%, including laboratory fortified blanks (LFBs) spiked with 100 μL of 100 ng/μL of each compound. The same extraction procedure was applied to POCIS from uptake rate experiments.

The TWA concentration of each compound is calculated as follows:

$$TWA\ concentration = \frac{Mass\ of\ the\ extracted\ \ compound}{R_s \times deployment\ \ time}$$

2.3.4. Instrumental methods

Extracts were analyzed in two groups both by liquid chromatography tandem mass spectrometry. Macrolides and beta-lactams were quantified using a Waters 2659 PLC interfaced with a Quattro Micro triple quadrupole mass spectrometer in positive ion mode electrospray ionization. Gradient separation was achieved using a Thermo HyPURITY C18 column (250 mm × 2.1 mm ID, 5 μm particle size) at a temperature of 50 °C and a flow rate of 0.20 ml/min. Mobile phase solvents: A) 0.1% (v/v) formic acid in acetonitrile, B) 0.1% (v/v) formic acid in water. Initial conditions at 5%A, hold until 1 min, then step to 50%A, hold until 3 min followed by linear gradient to reach 75%A at 14 min, then step to 100%A and hold until 20 min, then immediately back to initial conditions (0% A), hold for 8 min. Total run time is 28 min. Mass spectrometer conditions: collision gas: Argon at 4.0 × 10–3 Torr; desolvation gas: N_2 at 700 L/h; desolvation temperature: 500 °C; cone gas: N_2 at 30 L/h; source temperature: 120 °C; and capillary voltage: 4 kV. Cone voltages and collision energies used for each standard and analyte are given in Table S1. Injection volume was 25 μL. Instrument detection limits, determined from the standard deviation of the lowest calibration standard, ranged from 7 to 56 picograms.

Tetracycline and sulfonamide group compounds were analyzed on an Agilent 1100 HPLC interfaced to a 6410 triple quadrupole mass spectrometer. Gradient separation used a Thermo HyPURITY C18 column

Table 1
R_s values determined in current study compared with previous research.

Compound	R_s at 24 °C (L/d)	Literature R_s values in flowing condition	R^2	Mass balance (%)
Virginiamycin M1	0.271	NA	0.95	69
Tylosin	0.336	1.52 (Washington et al., 2018); 1.33 (Bartelt-Hunt et al., 2011)	0.60	92
Tiamulin	0.342	0.314 (Bartelt-Hunt et al., 2011)	0.96	33.9
Penillic acid	0.036	NA	0.60	69.6
Penicillin G	0.183	NA	0.95	95.2
Novobiocin	0.266	NA	0.97	157
Monensin*	0.277	0.205 (Bartelt-Hunt et al., 2011)	0.99	74.3
Erythromycin Anhydro-	0.171	NA	0.88	31.7
Erythromycin	0.186	0.0163 (Bueno et al., 2009); 0.911 (Macleod et al., 2007)	0.87	35.7
Ceftiofur	1.09	NA	0.82	114
Ampicillin	0.088	NA	0.6	71
Lincomycin	0.117	0.233 (Bartelt-Hunt et al., 2011)	0.93	133.3
Oxytetracycline	0.810	0.023 (Bueno et al., 2009)	0.63	219
Ractopamine	0.200	0.302 (Bartelt-Hunt et al., 2011)	0.92	125.4
Sulfadimethoxine	0.140	0.091 (Macleod et al., 2007); 0.291 (Bartelt-Hunt et al., 2011)	0.84	124
Sulfamethazine	0.094	0.114 (Macleod et al., 2007), 0.18 (Bartelt-Hunt et al., 2009)	0.85	98.8
Tetracycline	0.344	0.071 (Bueno et al., 2009)	0.99	70.67
Trimethoprim	0.145	0.36 (Macleod et al., 2007); 0.411, 0.213, 0.436 (Li et al., 2010)	0.89	121.8
Sulfamethizole	0.019	0.21 (Bartelt-Hunt et al., 2009)	0.65	105.9
Sulfamerazine	0.055	0.2 (Bartelt-Hunt et al., 2009)	0.83	101.5
Sulfamethoxazole	0.031	0.291, 0.339 and 0.348 (Li et al., 2010); 0.21 (Bartelt-Hunt et al., 2009); 0.085, 0.093, 0.113, 0.092, 0.094, 0.08 (Bailly et al., 2013)	0.62	116.4
Sulfathiazole	0.061	0.22 (Bartelt-Hunt et al., 2009)	0.83	97.3
Sulfadiazine	0.016	NA	0.402	106.9
Chlortetracycline	0.114	NA	0.97	199

* Monensin's uptake rate was evaluated in both sets of experiments (tetracycline/sulfonamide and beta-lactam/penicillin) and although the calculated R_s from both analysis methods were very close, the current R_s value is an average of them

(250 mm × 2.1 mm ID, 5 um particle size) at a temperature of 50 °C and a flow rate of 0.20 ml/min. Mobile phase solvents: A) 0.01% (v/v) formic acid in methanol, B) 1 mM ammonium citrate in water. Initial conditions at 0%A, hold until 1.0 min followed by linear gradient to reach 80%A at 3 min and 95%A at 12 min, hold until 23 min then immediately back to initial conditions (0%A) and hold for 5 min. Total run time is 28 min. Tandem mass spectrometry is used for identification and quantitation. The Agilent 6410 mass spectrometer had an electrospray ionization and detection was in positive ion mode. Desolvation gas: N_2 at 12 L/min; gas temperature: 350 °C; nebulizer: 40 psi; and capillary voltage: 4 kV. Fragmentation and collision energies used for each standard and analyte are given in Table S2. Injection volume was 25 μL, and

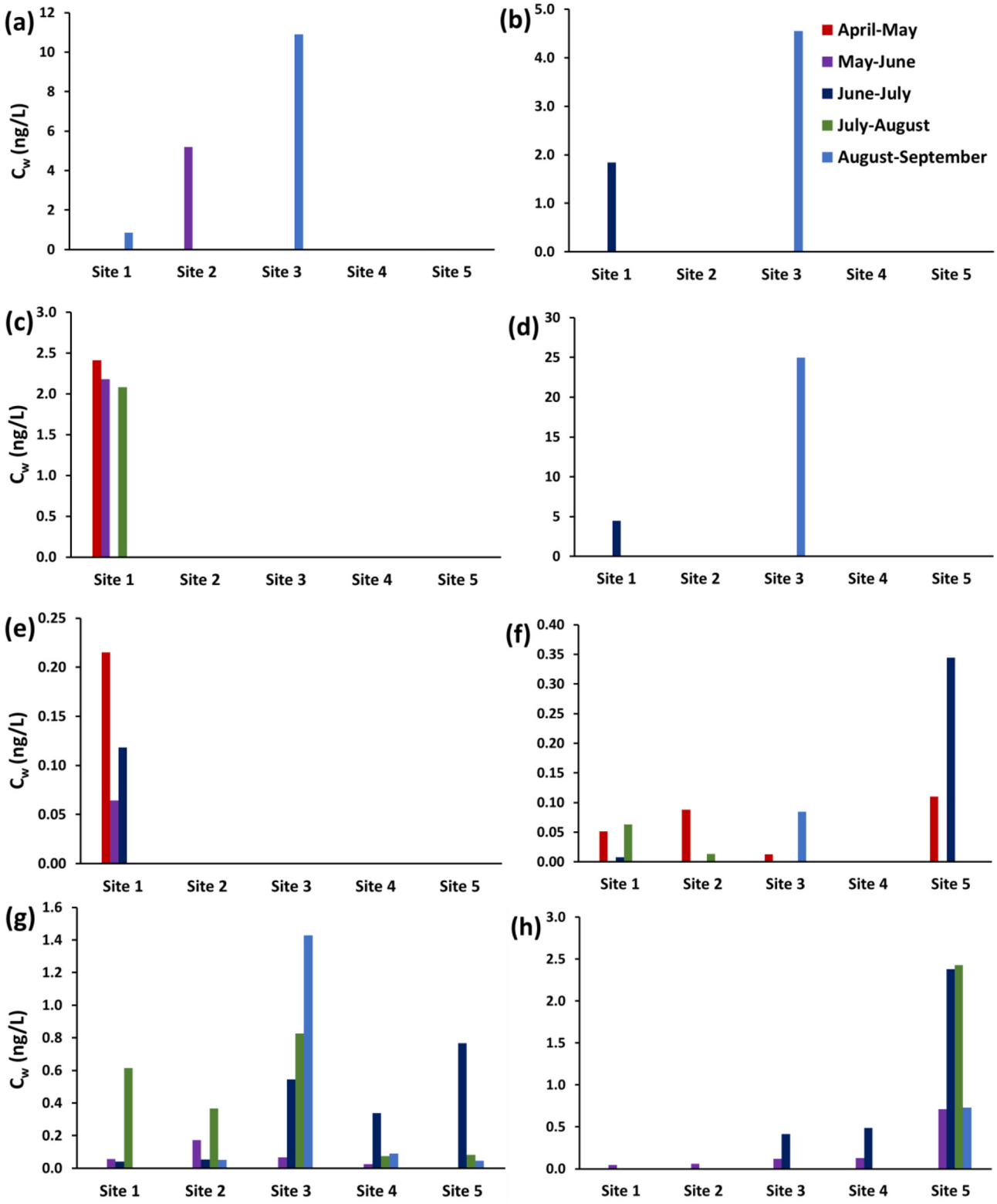

Fig. 2. Concentrations of a) lincomycin b) sulfamerazine, c) sulfamethoxazole, d) sulfadiazine, e) sulfadimethoxine, f) erythromycin, g) erythromycin-anhydro, and h) monensin in different locations and time intervals.

instrument detection limits determined from the standard deviation of the lowest calibration standard, ranged from 1 to 32 picograms injected.

2.4. Field deployment of POCIS samplers

POCIS samplers were deployed at the 34,000-acre US MARC in Clay Center, NE. The site was formerly a World War II Naval Ammunition Depot (NAD), and munitions manufacturing during that time resulted in two plumes of contaminated groundwater (USACE, 2010). In 2014, the U.S. Army Corp of Engineers completed a water treatment facility and implemented a groundwater remediation plan involving beneficial reuse of the treated water by the USMARC. The remediation plan includes discharge of the treated water into an existing stream and the construction of nine grade structures (GCS) to reduce erosion rates and increase the water storage capacity of the stream. The treated water is discharged at site 1, which is where the modified stream system begins (Fig. 1). The water flows 15 km through pasture down to a 0.81 km^2 reservoir, where the water is stored for irrigation. Samplers were deployed at five different sites in the stream that is fed by treated groundwater. Sites 1 and 5 are at the discharge point and reservoir, respectively, and sites 2–4 are located at GCSs along the stream. The USMARC has approximately 8000 breeding-age cows on pasture, and a 6000-head feedlot located approximately 3.8 km northeast of the groundwater discharge point and 3.2 km north of the stream at the shortest distance. The feedlot manure is accumulated and applied in fall or early winter to amend soils of the fields used to grow corn, hay, and other forage for feeding cattle. These crop fields are located throughout the US MARC.

POCIS were deployed at the five locations monthly from April 16 to September 18, 2018. The deployment duration of samplers ranged from 28 to 36 days. Field blanks were not deployed. At the conclusion of each deployment period, the POCIS were rinsed, wrapped in foil and stored at −20 °C until extraction. After POCIS were extracted and analyzed based on the methods described above, the water concentration of compound of interest was calculated using the R_s values from the uptake rate experiments and the mass of compound extracted per POCIS as described above.

2.5. Flow monitoring

Hydrologic monitoring was conducted at each of the five study sites. The flow at site 1 was measured using a flowmeter as it was discharged to the stream. Water depth at sites 2 through 5 were measured using HOBO pressure transducers (Onset HOBO, Bourne, MA, USA). Discharge at sites 2 and 4 were calculated using the Kindsvater-Carter equation suppressed rectangular, sharp-crested weir,

$$Q = \left(0.4000\left(\frac{H}{P}\right) + 3.220\right)(L - 0.003)(H + 0.003)^{3/2},$$

where Q = flowrate (cfs), H = water level (ft), P = height of the weir (ft) and L = length of the weir crest (ft). Discharge at site 3 could not be calculated since there was no weir and, therefore, the weir equation could not be applied either at site 3 or at site 5 in the reservoir.

3. Results and discussion

3.1. POCIS uptake rates

R_s values were determined for 24 compounds. Fig. S1 shows some examples of the uptake data used to calculate R_s values, which are given in Table 1. The mass balance for all experiments was in the range of 32% to 219% (Table 1) and the average mass balance of all the compounds was 102.64%. For virginiamycin M_1, penillic acid, penicillin G, novibiocin, erythromycin anhydro-, ceftiofur, ampicillin, sulfadiazine and chlortetracycline there were no R_s values previously available in the literature. For the rest of the antibiotics the R_s values determined in this study were within 30 to 50% of those previously reported. Uptake rates are influenced by properties such as pH and water flow (Washington et al., 2018) which can vary between studies. Another factor that might also affect the uptake rates is pK_a values of each compound (Li et al., 2011). For acidic compounds, pH has been shown to affect the uptake rates of compounds with pKa values below five (Li et al., 2011). Therefore, for some acidic compounds investigated in this study (penicillin G, novobiocin, ceftiofur, oxytetracycline, tetracycline, sulfamethizole and sulfamethoxazole) uptake rates might be underestimated at pH 7.

The experimental designs for uptake studies vary in the literature and ranges from flow-through systems to stirred water in beakers. These experimental methods may affect the final R_s values. It was reported by Macleod et al. (2007) that uptake rates calculated under flowing conditions were up to 10 times larger than those calculated under quiescent conditions. In addition, in many studies, the velocity adjacent to the membrane surface, which will affect the thickness of water, was not measured or only estimated. Therefore, comparing uptake results between studies can be challenging and uncertain (Li et al., 2010).

One more factor that may alter the R_s values is water temperature; however, many studies demonstrate that the uptake rates will not dramatically change with changes in water temperature. It was previously reported that although temperature increased 500%, uptake rates were increased by <20% (Li et al., 2010; Togola and Budzinski, 2007).

Because uptake occurs by diffusion across the water boundary layer and POCIS membrane, there may be a relationship between the molecular weight of the compounds and the POCIS uptake (Bartelt-Hunt et al., 2011). In this study, no linear relationship was observed between the uptake rates and molecular weights of the antibiotics investigated ($R^2 < 0.3$). Macleod et al. (2007) and Bartelt-Hunt et al. (2011) reported similar results.

Uptake rates with R^2 values >0.75 are considered linear over 28-d exposure time (Bartelt-Hunt et al., 2011). Therefore, except for penicillic acid, sulfamethoxazole, sulfadiazine, sulfamethizole, ampicillin, tylosin and oxytetracycline with R^2 values between 0.6 and 0.75, other compounds followed linear decay function.

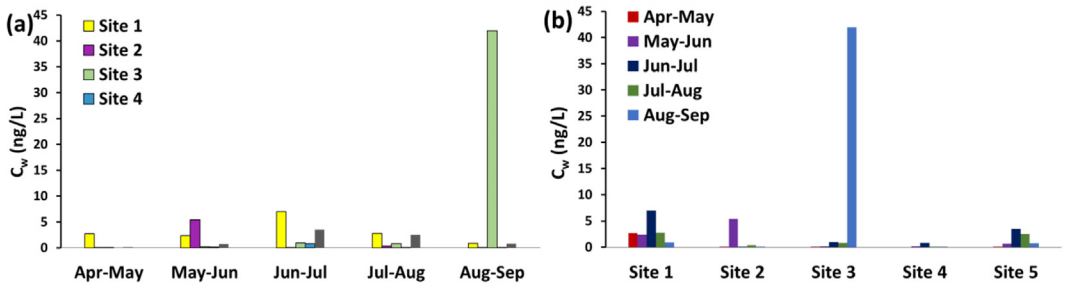

Fig. 3. Total antibiotic concentration distribution in a) different time intervals, and b) sampling locations.

As it is shown in Table 1, among the compounds with non-linear uptakes, only sulfamethoxazole, sulfamethizole, tylosin and oxytetracycline R_s values were previously reported.

3.2. Field samples analysis

Of the 24 antibiotics compounds evaluated, 10 were detected at least at one sampling site. Ceftiofur, novobiocin, penicillin G, penillic acid, tylosin, virginiamycin M1, chlortetracycline, oxytetracycline, tetracycline, ractopamine, sulfamethazine, sulfamethizole, and sulfathiazole were not detected in any of the POCIS residues.

Fig. 2 shows the antibiotics detected in the sampling sites along the stream flowing through the cattle grazing area. In addition to the compounds shown in the graph, trimethoprim was also detected at site 1 in the June–July time interval at a concentration of 0.5 ng/L. Fig. 3 illustrates the total antibiotic distribution in different time intervals and sampling locations. As it is shown in Figs. 3 and 4, sulfadiazine was detected at the highest concentration (>24 ng/L) followed by lincomycin (10.9 ng/L), which both occurred in Aug-Sep at site 3. The concentration of monensin followed an increasing trend from site 1 to 5. The greatest frequency of detection among all antibiotics and all time intervals occurred at site 1. In addition, none of the sulfonamide compounds were detected at site 4 and 5. In the literature, there are only a few studies investigating the fate and transport of veterinary antibiotics from cattle grazing areas to surface runoff. For instance, in a study conducted by Bair et al. (2017), the occurrence of chlortetracyline and oxytetracycline in surface waters affected by irrigated pasture was investigated. They reported that the concentration ranges of chlortetracycline and oxytetracycline were 0.001–0.7 and 0.001–1.3 μg/L, respectively. In another study, Popova et al. (2013) simulated pasture systems by applying manure to grass grown soil boxes and aimed to detect veterinary pharmaceuticals (chlortetracycline and oxytetracycline) in surface runoff and leachate from simulated pasture areas. They reported concentrations of the antibiotics to be <0.5 μg/L. Therefore, the detected concentration ranges in present study are comparable to the results reported in the literature.

Fig. 4 depicts the mass loading rates for sites 1, 2 and 4. The mass loading rates were calculated by multiplying the antibiotic concentrations by the average flow rate of each sampling location in each time interval which are presented in Table 2. The mass loading rate distribution pattern approximately follows the same trend that was found for the concentrations distribution illustrated in Fig. 3. It also shows that there is a seasonal variation in the mass loading rate, meaning that the antibiotics that were accumulated during winter in the field were flushed out via the rainfall events during spring and after July, the mass loading declined by 68% of the initial value for site 1 and almost zero for sites 2 and 4.

Fig. 5 presents the ambient conditions of the sampling locations, including the average relative humidity, air temperature, wind speed, number of precipitation events, and quantity of precipitation for each time interval. Surface water levels can be affected by air temperature, wind speed and relative humidity and these ambient conditions might have affected antibiotic detection, especially in the June–July and August–September time periods that had the highest air temperature and relative humidity, respectively.

As shown in Fig. 5 the highest average precipitation occurred in the June–July time interval and the highest number of precipitation events occurred in August–September. During the precipitation events, runoff can transport antibiotics and other contaminants from the soil to surface water. This is also consistent with the results shown in Fig. 3 that antibiotics were detected during the June–July period in all of the sampling sites. Although the highest number of precipitation events occurs in August–September (Fig. 5), the average precipitation is lower than in the June–July interval, possibly leading to the higher antibiotics concentrations detected in the August–September time interval.

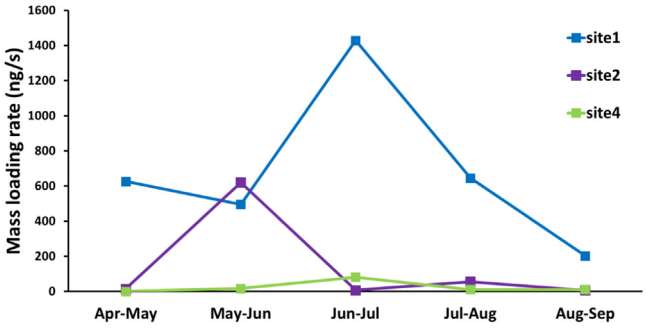

Fig. 4. Total mass loading rates in each time interval and sampling site.

Table 3 presents the usage and administration for the antibiotics at the US MARC facility. Interestingly, except monensin, none of the antibiotics prescribed at US MARC were detected during the sampling period. The concentration of monensin increased from site 1 to site 5 (Fig. 2). The highest concentration of monensin was observed downstream at site 5 where the stream discharges to the reservoir. Furthermore, other unadministered antibiotics including sulfadiazine were not prescribed in the facility. One possible explanation is that some antibiotics prescribed in prior years persisted in the environment as similarly reported by Guo et al. (2013).

In the calibration process of POCIS samplers, it was shown that sulfamethazine had relatively low uptake rates of 0.094 L/d which may limit detection of this compound by POCIS. Chlortetracycline has high adsorption affinity in clay loam with a k_d value ranging from 1280 to 2386 (L/kg). The soils at US MARC have an appreciable clay content (Berry et al., 2007); hence, it is possible for chlortetracycline to accumulated in soil (Pan and Chu, 2017), and consequently, not be detected by POCIS.

Tylosin and oxytetracycline were also not detected in any of the sampling sites. In a study conducted by Rabølle and Spliid (2000), the mobility of tylosin and oxytetracycline was investigated. They reported that oxytetracycline and tylosin are strongly adsorbed to all types of soils regardless of the type pf the soil and consequently they were shown to be immobile. This could be a possible reason explaining why tylosin and oxytetracycline were not flushed out from the pasture areas or manure-amended fields via rainfall events and did not reach surface water.

As it is illustrated in Fig. 2, none of the sulfonamide compounds were detected in sites 2, 4 and 5. A study led by Bai et al. (2019), showed that the sulfonamide compounds are likely to be degraded in anoxic conditions and elongated flow paths. At sampling sites 2, 4 and 5, the POCIS were submerged either in deep water on the upstream side of the GCS (sites 2 and 4) or in the lake (site 5); hence, there may have been low levels of dissolved oxygen which leads to anoxic conditions and also, due to their distance from the discharge point, it is possible that sulfonamide compounds were degraded.

Among all antibiotics that were detected but not prescribed at the US MARC facility, sulfadiazine was present at the highest concentration. Several sulfonamide compounds were detected during this study that

Table 2
Average flow rates in each time interval (L/s).

Time intervals	Site 1	Site 2	Site 3	Site 4
April–May	233.43	160.01	110.42	136.82
May–June	210.63	114.17	83.14	106.79
June–July	205.67	110.41	77.64	98.34
July–August	233.43	144.04	88.20	137.47
August–September	233.43	109.34	112.83	113.70

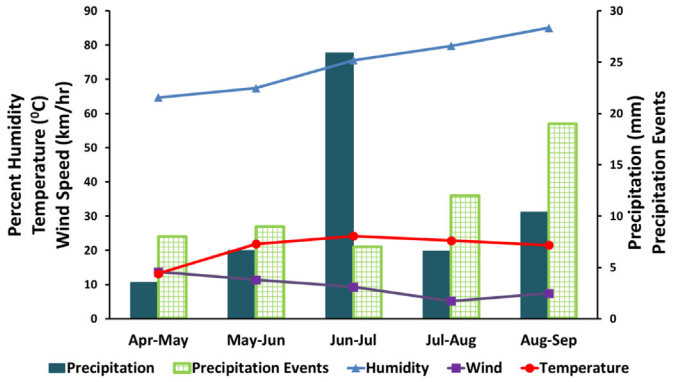

Fig. 5. Average percent humidity, wind speed and temperature of the sampling location in different time intervals of sampling.

was not administered to USMARC livestock. There are other potential sources of sulfur-containing compounds to the site. For instance, sulfonamide and related sulfa-drugs are commonly used in swine production. There have been large scale swine production facilities to the west and north of USMARC for many years. This and other nearby livestock facilities are potential sources of sulfonamide compounds. Likewise, manufacturing activities in the vicinity of US MARC are possible sources of sulfonamide compounds in the environment. One example is a hide processing facility in the area. The initial steps of processing hides involve sulfuric acid. In addition, azo dyes used in leather colorants for hide dying are capable of being converted to sulfonamide compounds (Chung, 2016).

Previous studies have reported the detection of sulfonamide compounds in areas adjacent to the sampling sites of this study. A study conducted by Brown et al. (2015), showed detection of sulfonamide compounds in a river that receives discharge from the Hastings, Nebraska waste water treatment plant, providing evidence for a source in to the region west of the US MARC facility. In a separate study by Zhang et al. (2013), grab samples of water and sludge were collected from beef feedlot and swine confinement wastewater lagoons at USMARC and sulfonamide compounds were detected. In short, these studies identify other possible sources of these compounds near the sampling sites of the current study.

There are also other possibilities that may explain the detection of antibiotics other than the ones prescribed in the facility. For example, the detection of some classes of antibiotics may reflect their production by endogenous soil bacteria. In case of erythromycin and erythromycin-anhydro that were both found in the streams, there are studies showing that some bacteria are capable of producing them naturally in the environment (Schafhauser et al., 2018). It was also demonstrated that in wastewater treatment plants, erythromycin can attach to biosolids that are eventually used as fertilizers in agroecosystem, and ultimately reach the groundwater overtime (Yan et al., 2014). In another study, conducted by (Kuchta et al., 2009), it was shown that lincomycin found in manure can persist in the environment for several months and reach groundwater. Therefore, lincomycin might have transferred from sources adjacent to the facility (either from applied biosolids or manure). In addition, since the average wind speed is high in the sampling location area (Fig. 5), there might be the possibility of antibiotics being transported from other livestock production sites via windborne particulates (McEachran et al., 2015).

Table 3
The usage, administration and detection status of the studied antibiotics.

Compound	Usage	Administrated (A)/not administrated (NA)	Detected (D)/not detected (ND)
Virginiamycin M1	–	NA	ND
Tylosin	Cattle, swine	A	ND
Tiamulin	–	NA	ND
Penillic acid	–	NA	ND
Penicillin G	Swine	A	ND
Novobiocin	–	NA	ND
Monensin	Cattle	A	D
Erythromycin Anhydro-	–	NA	D
Erythromycin	–	NA	D
Ceftiofur	Cattle, swine	A	ND
Ampicillin	Swine	A	ND
Lincomycin	–	NA	D
Oxytetracycline	Cattle, swine, sheep	A	ND
Ractopamine	–	NA	ND
Sulfadimethoxine	–	NA	D
Sulfamethazine	Cattle	A	ND
Tetracycline	–	NA	ND
Trimethoprim	–	NA	ND
Sulfamethizole	–	NA	ND
Sulfamerazine	–	NA	D
Sulfamethoxazole	–	NA	D
Sulfathiazole	–	NA	ND
Sulfadiazine	–	NA	D
Chlortetracycline	Cattle, sheep	A	ND

4. Conclusions

Uptake rates were measured for 24 antibiotics using POCIS samplers, nine of which did not have uptake rates previously reported in the literature. POCIS samplers were also used to evaluate the fate and occurrence of four categories of antibiotics in a stream fed by treated groundwater that traverses a cattle grazing area at the U.S. Meat Animal Research Center, Clay Center, Nebraska.

The antibiotics detected were sulfadimethoxine, sulfamethoxazole, trimethoprim, sulfamerazine, sulfadiazine, lincomycin, erythromycin, erythromycin anhydro- and monensin. According to mass loading rate results, the highest number of detected antibiotics occurred in site 1, which is the groundwater discharge point. The maximum detected concentration belonged to sulfadiazine (25 ng/L) and it occurred in August–September, which was the sampling period that had the highest number of precipitation events.

Among the antibiotics prescribed for livestock at US MARC, only monensin was detected during any sampling period. Monensin concentration had an increasing trend from site 1 which is the discharge location to site 5, which is a reservoir at the terminus of the stream. Among the antibiotics that were prescribed at the facility but not detected, some of them such as tylosin and oxytetracycline may have been adsorbed by soil and therefore not transported to surface water. Other prescribed antibiotics such as chlortetracycline and sulfamethazine may have not been detected due to their low R_s values. The detection of some classes of antibiotics that were not used to treat US MARC livestock may indicate their production by endogenous soil bacteria. These results highlight the importance of linking environmental occurrence of antibiotics to local sources as well as the potential for some antibiotics to be transported significant distances, as the majority of the antibiotics detected were not prescribed or used on site.

CRediT authorship contribution statement

Nasrin Naderi Beni: Investigation, Writing - original draft, Writing - review & editing. **Daniel D. Snow:** Resources, Supervision. **Elaine D. Berry:** Investigation, Resources. **Aaron R. Mittelstet:** Investigation,

Supervision. **Tiffany L. Messer:** Investigation, Supervision. **Shannon Bartelt-Hunt:** Project administration, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.138296.

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