

Supporting Information

Comprehensive study on the potential environmental risk of temporal antibiotic usage
through wastewater discharges

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2. MATERIALS AND METHODS

2.1. Reagents and chemicals

Table S1. Consumption of active substances of subgroup J01 systemic antibiotics during 2020 (information provided by Health Department of Castelló (Spain)). Data are expressed as defined dairy doses per 1,000 inhabitants per day (DHD).

Active substances	ATC Group Level 3	DHD
200029A - Amoxicillin + Clavulanic Acid	J01C - Antibacterial betalactamics, penicillins	2,8395
108A - Amoxicillin	J01C - Antibacterial betalactamics, penicillins	1,6304
828A - Cefuroxime	J01D - Other beta-lactam antibacterials	1,3125
7019A - Azithromycin	J01F - Macrolides and lincosamides (systemic anti-infectives)	0,7915
1395A - Doxycycline	J01A - Tetracyclines (anti-infectives for systemic use)	0,6336
2049A - Ciprofloxacin	J01M - Quinolone-derived antibacterials (system)	0,5939
2791A - Levofloxacin	J01M - Quinolone-derived antibacterials (system)	0,5423
967A - Clarithromycin	J01F - Macrolides and lincosamides (systemic anti-infectives)	0,4642
1599A - Fosfomicin	J01X - Other antibacterials (systematic anti-infectives)	0,3086
7358A - Cefditoren	J01D - Other beta-lactam antibacterials	0,2810
200127A - Cotrimoxazole (Sulfamethoxazole + Trimethoprim)	J01E – Sulfonamides and trimethoprim (systemic anti-infectives)	0,2518
2400A - Cefixime	J01D - Other beta-lactam antibacterials	0,1224
209A - Norfloxacin	J01M - Quinolone-derived antibacterials (system)	0,1095
89A - Cloxacillin	J01C - Antibacterial betalactamics, penicillins	0,1047
105A - Phenoxyethylpenicillin	J01C - Antibacterial betalactamics, penicillins	0,0786
616A - Clindamycin	J01F - Macrolides and lincosamides (systemic anti-infectives)	0,0695
1119A - Moxifloxacin	J01M - Quinolone-derived antibacterials (system)	0,0319
86A - Nitrofurantoin	J01X - Other antibacterials (systematic anti-infectives)	0,0288
1971A - Minocycline	J01A - Tetracyclines (anti-infectives for systemic use)	0,0245
1419A - Erythromycin	J01F - Macrolides and lincosamides (systemic anti-infectives)	0,0147
1804A - Josamycin	J01F - Macrolides and lincosamides (systemic anti-infectives)	0,0051
1434A - Spiramycin	J01F - Macrolides and lincosamides (systemic anti-infectives)	0,0047
825A - Cefadroxyl	J01D - Other beta-lactam antibacterials	0,0036

1619A - Fusidic acid	J01X - Other antibacterials (Systematic Anti-infectives)	0,0031
192A - Cephalexin	J01D - Other beta-lactam antibacterials	0,0027
1006A - Ampicillin	J01C - Antibacterial betalactamics, penicillins	0,0026
3276A - Cefaclor	J01D - Other beta-lactam antibacterials	0,0022
2188A - Midecamycin	J01F - Macrolides and lincosamides (systemic anti-infectives)	0,0020
372A - Amikacin	J01G - Aminoglycoside antibacterials (systemic anti-infectives)	0,0015
2223A - Ofloxacin	J01M - Quinolone-derived antibacterials (system)	0,0012
1642A - Gentamicin	J01G - Aminoglycoside antibacterials (systemic anti-infectives)	0,0011
3141A - Tobramycin	J01G - Aminoglycoside antibacterials (systemic anti-infectives)	0,0008
106A - Benzylpenicillin	J01C - Antibacterial betalactamics, penicillins	0,0008
2225A - Roxithromycin	J01F - Macrolides and lincosamides (systemic anti-infectives)	0,0005
501A - Ceftriaxone	J01D - Other beta-lactam antibacterials	0,0005
3840A - Cefotaxime	J01D - Other beta-lactam antibacterials	0,0002
3761A - Pipemidic acid	J01M - Quinolone-derived antibacterials (system)	0,0002
3197A - Vancomycin	J01X - Other antibacterials (Systematic Anti-infectives)	0,0001
189A - Ceftazidime	J01D - Other beta-lactam antibacterials	0,0001
200056A - Benzylpenicillin (Sodium - Procaine - Benzathine)	J01C - Antibacterial betalactamics, penicillins	0,0000

Table S2. Annual sales (2020) of antibiotics dispensed per pharmacy office in Castelló de la Plana (Spain).

Compound	Annual units	Percentage	Antibiotic family
Amoxicillin	700	37%	Penicillin
Azithromycin	350	19%	Macrolide
Phosphomycin	230	12%	Other antibacterial
Clarithromycin	100	5%	Macrolide
Ciprofloxacin	100	5%	Quinolone (fluoroquinolone)
Metronidazole	100	5%	Nitroimidazole
Cefuroxime	94	5%	Cephalosporin
Norfloxacin	94	5%	Quinolone (fluoroquinolone)
Levofloxacin	80	4%	Quinolone (fluoroquinolone)
Moxifloxacin	25	1%	Quinolone (fluoroquinolone)

Table S3. MS/MS conditions for antibiotics and ILIS selected. Limit of quantification (LOQ) for EWW and IWW samples. Octanol-water partition coefficient (Log K_{ow}).

Family	Compound	Log K_{ow}	CV (V)	Q transition	CE (eV)	q transitions	CE (eV)	EWW LOQ (ng L ⁻¹)	IWW LOQ (ng L ⁻¹)
β-lactams (penicillin)	Amoxicillin (AMX)	0.87*	40	349.0 > 114.0	15	349.0 > 137.0 349.0 > 165.0 349.0 > 208.0	35 20 10	400	500
	Amoxicillin- ¹³ C ₆		40	355.0 > 114.0	15				
	Ampicillin (AMP)	1.35*	20	350.0 > 106.0	20	350.0 > 160.0 350.0 > 192.0 350.0 > 114.0	10 15 25	30	70
	Ampicillin-d ₅		20	355.1 > 160.0	15				
	Cloxacillin (CLX)	2.48*	20	436.0 > 277.0	15	436.0 > 160.0 436.0 > 178.0 436.0 > 114.0	15 30 30	20	50
	Cloxacillin- ¹³ C ₄		20	440.0 > 160.0	15				
β-lactams (cephalosporin)	Cefditoren (CFT)	1.48**	20	507.0 > 241.0	20	507.0 > 197.1 507.0 > 166.0 507.0 > 210.0	25 35 15	70	500
	Cefuroxime (CFX)	-0.16*	20	364.0 > 179.0	10	364.0 > 211.0 364.0 > 165.0	15 20	70	1250
	Cefuroxime-d ₃		20	367.0 > 182.1	10				
Macrolides	Azithromycin (AZM)	4.02*	20	375.3 > 591.2	10	375.3 > 82.8 375.3 > 116.0 375.3 > 158.0	20 30 30	1000	2000
	Azithromycin-d ₃		20	377.0 > 82.9.0	15				
	Clarithromycin (CLR)	3.16*	20	748.4 > 158.0	30	748.4 > 590.3 748.4 > 82.9 748.4 > 116.0	15 40 30	20	250
	Clarithromycin-d ₃		20	751.3 > 161.1	30				
	Erythromycin (ERY)	3.06*	20	734.3 > 158.1	30	734.3 > 576.2 734.3 > 116.0 734.3 > 82.8	20 35 50	20	50
	Erythromycin- ¹³ C-d ₃		20	738.3 > 162.1	25				
	Roxithromycin (ROX)	1.7*	20	419.2 > 158.0	15	419.2 > 82.8 419.2 > 679.2 419.2 > 116.0	15 10 25	20	250
	Roxithromycin-d ₇		20	422.2 > 158.0	15				
Quinolones (Fluoroquinolones)	Ciprofloxacin (CIP)	0.28*	20	332.1 > 231.0	35	332.1 > 288.1 332.1 > 245.1 332.1 > 294.1	15 25 30	20	250
	Ciprofloxacin-d ₈		20	340.2 > 235.0	40				
	Levofloxacin (LEV)	-0.39*	20	362.1 > 261.1	25	362.1 > 318.0 362.1 > 221.1 362.1 > 205.1	20 35 40	20	250
	Levofloxacin-d ₈		20	370.1 > 265.1	25				
	Moxifloxacin (MXF)	0.95*	20	402.1 > 110.1	25	402.1 > 261.0 402.1 > 96.0 402.1 > 358.1	20 45 20	20	50
	Moxifloxacin- ¹³ C-d ₃		20	406.2 > 110.1	25				
	Norfloxacin (NFX)	0.46*	20	320.1 > 231.0	40	320.1 > 282.1 320.1 > 276.1 320.1 > 233.0	30 15 20	20	250
Norfloxacin-d ₅		20	325.1 > 231.0	35					

Lincosamide	Clindamycin (CLI)	2.16*	20	425.2 > 126.0	30	425.2 > 377.1	20	20	50
						425.2 > 81.9	50		
	Clindamycin-d ₃		20	428.1 > 129.1	30	425.2 > 69.8	50		
Tetracycline	Doxycycline (DOX)	0.63*	20	445.0 > 154.1	30	445.0 > 267.1	35	60	250
						445.0 > 201.0	40		
	Doxycycline-d ₃		20	448.0 > 155.0	30	445.0 > 97.9	40		
Nitroimidazole	Metronidazole (MTZ)	-0.02*	20	172.1 > 128.0	15	172.1 > 81.9	20	20	50
						172.1 > 80.9	40		
	Metronidazole-d ₃		20	175.0 > 131.0	15				
Sulfonamide	Sulfamethoxazole (SMX)	0.89*	20	254.0 > 156.0	15	254.0 > 91.9	25	20	50
						254.0 > 108.0	20		
	Sulfamethoxazole-d ₄		20	258.0 > 160.1	15	254.0 > 64.8	35		
Diaminopyridine	Trimethoprim (TMP)	0.91*	20	291.1 > 230.1	20	291.1 > 261.0	25	20	50
						291.1 > 123.1	25		
	Trimethoprim- ¹³ C ₃		20	294.1 > 231.1	20	291.1 > 110.1	30		

*(PubChem, 2023).

** (ChemSpider, 2023).

2.3. Wastewater samples

Table S4. IWW and EWW samples collected from the WWTP (April 2021 - January 2022).

Month	IWW samples			EWW samples		
	Code	Date	Flow (m ³ /day)	Code	Date	Flow (m ³ /day)
April	I-001	06/04/2021	33396	E-002	07/04/2021	39336
	I-002	07/04/2021	39336	E-003	08/04/2021	37738
	I-004	20/04/2021	38577	E-005	21/04/2021	46301
	I-005	21/04/2021	46301	E-006	22/04/2021	40640
May	I-007	04/05/2021	38248	E-008	05/05/2021	38254
	I-008	05/05/2021	38254	E-009	06/05/2021	42645
	I-010	18/05/2021	38918	E-011	19/05/2021	39286
	I-011	19/05/2021	39285	E-012	20/05/2021	39598
June	I-013	08/06/2021	36453	E-014	09/06/2021	38188
	I-014	09/06/2021	38188	E-015	10/06/2021	39793
	I-016	29/06/2021	36645	E-017	30/06/2021	36645
	I-017	30/06/2021	36645	E-018	01/07/2021	37721
July	I-019	13/07/2021	38779	E-020	14/07/2021	37300
	I-020	14/07/2021	37300	E-021	15/07/2021	37796
	I-022	27/07/2021	40158	E-023	28/07/2021	38772
	I-023	28/07/2021	38772	E-024	29/07/2021	38665
August	I-025	24/08/2021	37826	E-026	25/08/2021	41965
	I-026	25/08/2021	41965	E-027	26/08/2021	38037
September	I-028	07/09/2021	39403	E-029	08/09/2021	39102
	I-029	08/09/2021	39102	E-030	09/09/2021	39181
	I-031	22/09/2021	45283	E-032	23/09/2021	44919
	I-032	23/09/2021	44919	E-033	24/09/2021	44200
October	I-034	05/10/2021	43163	E-035	06/10/2021	33833
	I-035	06/10/2021	33833	E-036	07/10/2021	38974
	I-037	19/10/2021	37341	E-038	20/10/2021	36418
	I-038	20/10/2021	36418	E-039	21/10/2021	36697
January	I-040	12/01/2022	34769	E-041	13/01/2022	35066
	I-041	13/01/2022	35066	E-042	14/01/2022	32325
	I-043	26/01/2022	34185	E-044	27/01/2022	31585
	I-044	27/01/2022	31585	E-045	28/01/2022	32408

2.5 Sample analysis

A compound was considered as unequivocally identified (i.e., Level 1 of confidence identification (Celma et al., 2020)) when the protonated molecule and at least one fragment ion, both with a mass error of less than 5 ppm, were observed in the sample. Additionally, the experimental chromatographic retention time should differ less than 0.1 min from the retention time of the reference standard, and the collision cross section (CCS) error (value obtained by ion mobility) should be less than 2%. Hence, this was only feasible for those compounds for which their analytical reference standard was available.

For most of the metabolites reported in the literature, there are no commercially available reference standards. In this case, the analytes were tentatively identified based on the exact mass fragmentation observed, and the structure of the compound. In order to increase the confidence on the tentative identification, the observed fragment ions were compared with those of the parent molecule, since the metabolites usually present fragmentation patterns similar to the original (unchanged) molecule. The fragmentation observed was also compared with that described in the literature for these compounds (i.e., Level 2a of confidence (Celma et al., 2020)). In all cases, the mass error of the protonated molecule and the fragment ions used for the tentative identification should be less than 5 ppm. If no information about compound fragmentation was found in literature, and fragment ions were not shared with parent but could be justified based on the proposed metabolite structure, the compound was considered as Level 2b of confidence (Celma et al., 2020). Finally, if more than one structure can be justified based on the observed fragmentation (for example, isomeric compounds), only Level 3 can be achieved.

Table S5. Minimum Inhibitory Concentrations for bacteria obtained from the EUCAST, (2022) database (mg/L). Data for taxa with less than 30 observations for one compound were not included.

Bacterial taxa	AZM	CFT	CFX	CIP	CLR	CLI	DOX	ERY	LEV	MTZ	MXF	NFX	SMX	TMP
<i>Achromobacter xylosoxidans</i>	-	-	-	2	-	-	-	-	1	-	-	-	-	-
<i>Acinetobacter anitratus</i>	-	-	-	0.06	-	-	-	-	0.06	-	-	-	-	-
<i>Acinetobacter baumannii</i>	-	-	2	0.008	-	-	0.125	-	0.03	-	0.03	-	-	2
<i>Acinetobacter calcoaceticus</i>	-	-	-	0.06	-	-	-	-	-	-	-	-	-	-
<i>Acinetobacter lwoffii</i>	-	-	0.5	0.03	-	-	-	-	0.03	-	-	-	-	-
<i>Actinobacillus pleuropneumoniae</i>	-	-	-	-	-	-	0.5	2	-	-	-	-	-	-
<i>Actinomyces israelii</i>	-	-	-	16	0.016	0.06	-	0.03	-	-	-	-	-	-
<i>Actinomyces spp</i>	-	-	-	1	-	0.016	0.125	-	-	-	-	-	-	-
<i>Aerococcus sanguinicola</i>	-	-	-	16	-	-	-	-	16	-	-	-	-	-
<i>Aerococcus urinae</i>	-	-	-	0.25	-	-	-	-	0.5	-	-	-	-	-
<i>Alcaligenes xylosoxidans</i>	-	-	-	2	-	-	-	-	-	-	-	-	-	-
Anaerobic cocci Gram positive	-	-	-	-	-	0.03	-	-	-	0.06	-	-	-	-
<i>Bacillus cereus</i>	-	-	-	0.06	-	0.25	-	0.125	-	-	0.06	-	-	-
<i>Bacteroides caccae</i>	-	-	-	-	-	-	-	-	-	-	0.5	-	-	-
<i>Bacteroides fragilis</i>	-	-	-	2	-	0.016	-	-	0.5	0.03	0.06	-	-	-
<i>Bacteroides fragilis group</i>	-	-	-	2	0.125	0.03	-	0.5	0.5	0.03	0.125	-	-	-
<i>Bacteroides ovatus</i>	-	-	-	-	-	0.5	-	-	-	0.25	0.25	-	-	-
<i>Bacteroides spp</i>	-	-	-	-	-	-	-	-	-	-	0.06	-	-	-
<i>Bacteroides thetaiotaomicron</i>	-	-	-	-	-	0.06	-	-	2	0.06	0.5	-	-	-
<i>Bacteroides uniformis</i>	-	-	-	-	-	-	-	-	-	-	0.5	-	-	-
<i>Bacteroides vulgatus</i>	-	-	-	-	-	0.125	-	-	-	0.25	0.25	-	-	-
<i>Bifidobacterium adolescentis</i>	-	-	-	-	-	-	-	0.03	-	-	-	-	-	-
<i>Bifidobacterium longum</i>	-	-	-	-	-	0.03	-	0.06	-	-	-	-	-	-

<i>Bifidobacterium thermophilum</i>	-	-	-	-	-	0.125	-	-	-	-	-	-	-	-
<i>Bordetella bronchiseptica</i>	-	-	-	-	-	-	-	8	-	-	-	-	-	-
<i>Burkholderia cepacia</i> complex	-	-	-	0.25	-	-	-	-	1	-	-	-	-	-
<i>Burkholderia pseudomallei</i>	-	-	-	-	-	-	0.25	-	-	-	-	-	-	-
<i>Campylobacter coli</i>	0.016	-	-	0.03	-	0.03	0.06	0.06	-	-	-	-	-	-
<i>Campylobacter jejuni</i>	0.016	-	-	0.008	-	0.016	0.03	0.03	-	-	-	-	-	-
<i>Citrobacter freundii</i>	-	-	0.5	-	-	-	1	-	0.03	-	0.03	-	-	0.125
<i>Citrobacter koseri</i>	-	-	1	-	-	-	-	-	-	-	-	-	-	-
<i>Clostridioides difficile</i>	-	-	-	8	-	0.06	-	0.125	-	0.03	0.25	-	-	-
<i>Clostridium perfringens</i>	-	-	-	-	-	0.03	-	-	-	-	0.25	-	-	-
<i>Corynebacterium</i> spp	-	-	-	0.5	-	4	-	-	-	-	0.5	-	-	-
<i>Enterobacter agglomerans</i>	-	-	1	0.016	-	-	-	-	-	-	-	-	4	0.06
<i>Enterobacter cloacae</i>	-	-	0.5	0.002	-	-	0.5	-	0.03	-	0.03	-	8	0.125
<i>Enterobacter dissolvens</i>	-	-	4	0.016	-	-	-	-	-	-	-	-	8	0.25
<i>Enterobacter sakazakii</i>	-	-	8	-	-	-	-	-	-	-	-	-	-	-
<i>Enterococcus faecalis</i>	-	-	-	0.03	0.25	1	0.125	0.25	0.125	-	0.06	2	-	-
<i>Enterococcus faecalis</i> ATCC 29212	8	-	-	-	-	-	-	2	-	-	-	-	-	-
<i>Enterococcus faecium</i>	-	-	-	0.125	0.5	-	0.125	0.125	0.25	-	0.125	-	-	-
<i>Enterococcus hirae</i>	-	-	-	-	-	-	-	0.25	-	-	-	-	-	-
<i>Escherichia coli</i>	0.5	-	0.125	0.002	-	-	0.25	-	0.016	-	0.016	0.016	2	0.06
<i>Escherichia coli</i> ATCC 25922	-	-	4	-	-	-	-	-	-	-	-	-	-	-
<i>Fusobacterium</i> spp	-	-	-	-	-	0.03	-	-	-	0.03	-	-	-	-
<i>Haemophilus influenzae</i>	0.06	-	0.03	0.002	0.125	1	0.25	0.125	0.008	-	0.004	-	-	0.008
<i>Haemophilus influenzae</i> ATCC 49247	-	-	4	-	-	-	-	-	-	-	-	-	-	-
<i>Haemophilus influenzae</i> ATCC 49766	-	-	0.5	-	-	-	-	-	-	-	-	-	-	-
<i>Haemophilus parainfluenzae</i>	0.125	-	0.06	0.008	0.5	-	-	0.5	0.008	-	0.008	-	-	-
<i>Hafnia alvei</i>	-	-	2	0.008	-	-	-	-	-	-	-	0.03	-	0.5

<i>Helicobacter pylori</i>	-	-	-	0.004	0.016	-	-	-	0.016	0.016	-	-	-	-
<i>Kingella kingae</i>	-	-	0.06	0.008	0.06	-	0.06	0.06	0.016	-	-	-	-	-
<i>Klebsiella aerogenes</i>	-	-	0.5	0.008	-	-	1	-	0.03	-	0.03	-	-	0.25
<i>Klebsiella oxytoca</i>	-	-	0.25	0.008	-	-	0.5	-	0.03	-	0.03	-	16	0.125
<i>Klebsiella pneumoniae</i>	-	-	0.125	0.008	-	-	0.5	-	0.03	-	0.03	0.06	8	0.125
<i>Kluyvera spp</i>	-	-	-	0.008	-	-	-	-	-	-	-	-	-	-
<i>Kocuria kristinae</i>	-	-	-	-	-	0.06	0.125	0.125	0.25	-	-	-	-	-
<i>Lactobacillus delbrueckii</i>	-	-	-	-	-	0.125	-	0.125	-	-	-	-	-	-
<i>Lactobacillus fermentum</i>	-	-	-	-	-	-	-	0.25	-	-	-	-	-	-
<i>Lactobacillus gasseri</i>	-	-	-	-	-	1	-	0.125	-	-	-	-	-	-
<i>Lactobacillus lactis</i>	-	-	-	-	-	0.06	-	0.06	-	-	-	-	-	-
<i>Lactobacillus paracasei</i>	-	-	-	-	-	-	-	0.125	-	-	-	-	-	-
<i>Lactobacillus plantarum</i>	-	-	-	-	-	0.125	-	0.25	-	-	-	-	-	-
<i>Lactobacillus reuteri</i>	-	-	-	-	-	0.06	-	0.5	-	-	-	-	-	-
<i>Lactobacillus sakei</i>	-	-	-	-	-	-	-	0.5	-	-	-	-	-	-
<i>Lactococcus lactis</i>	-	-	-	-	-	0.06	-	0.06	-	-	-	-	-	-
<i>Legionella pneumophila</i>	0.06	-	0.5	-	0.125	-	2	0.06	0.008	-	-	-	-	-
<i>Listeria monocytogenes</i>	-	-	-	0.5	-	-	-	0.125	1	-	0.25	-	16	0.06
<i>Mannheimia haemolytica</i>	-	-	-	-	-	-	0.25	2	-	-	-	-	-	-
<i>Moraxella catarrhalis</i>	-	-	0.06	0.008	0.008	-	0.125	0.008	0.016	-	0.016	-	-	2
<i>Morganella morganii</i>	-	-	1	0.004	-	-	1	-	0.03	-	0.03	-	-	1
<i>Mycobacterium abscessus</i>	-	-	-	-	0.06	-	-	-	-	-	-	-	-	-
<i>Mycobacterium avium</i>	-	-	-	-	0.25	-	-	-	-	-	-	-	-	-
<i>Mycobacterium intracellulare</i>	-	-	-	-	0.06	-	-	-	-	-	-	-	-	-
<i>Mycobacterium marinum</i>	-	-	-	-	-	-	4	-	-	-	-	-	-	-
<i>Mycobacterium tuberculosis 7H9</i>	-	-	-	-	-	-	-	-	0.125	-	0.06	-	-	-
<i>Neisseria gonorrhoeae</i>	0.016	-	0.008	0.002	-	-	-	0.03	0.004	-	0.002	-	-	-

Shigella spp	-	-	-	0.016	-	-	-	-	-	-	-	-	-	-
Staphylococcus aureus	0.125	-	0.125	0.016	0.06	0.016	0.016	0.016	0.03	-	0.016	0.5	8	0.25
Staphylococcus aureus ATCC 29213	1	-	2	-	0.25	-	-	0.5	-	-	-	-	-	1
Staphylococcus aureus MRSA	-	-	-	0.5	-	0.06	-	0.25	-	-	-	-	-	0.25
Staphylococcus aureus MSSA	-	-	-	0.125	-	0.06	-	0.25	-	-	-	-	-	0.25
Staphylococcus capitis	-	-	0.125	0.06	-	-	-	0.06	0.125	-	0.03	-	-	-
Staphylococcus coagulase negative	-	-	-	0.06	-	0.016	0.125	-	0.06	-	0.03	0.5	-	-
Staphylococcus epidermidis	-	-	-	0.03	-	0.06	-	0.06	0.03	-	0.03	-	-	0.25
Staphylococcus epidermidis MSSE	-	-	-	0.125	-	0.06	-	0.25	-	-	-	-	-	0.25
Staphylococcus haemolyticus	-	-	-	0.06	-	0.06	0.125	0.06	0.06	-	-	-	-	-
Staphylococcus hominis	-	-	0.25	0.06	-	-	-	-	0.06	-	0.03	-	-	-
Staphylococcus hyicus	-	-	-	-	-	0.125	0.125	0.125	-	-	-	-	8	1
Staphylococcus intermedius	-	-	-	-	-	-	-	0.5	-	-	-	-	-	-
Staphylococcus lugdunensis	-	-	-	0.125	-	43	-	-	-	-	-	-	-	8
Staphylococcus pseudintermedius	-	-	-	-	-	0.06	0.06	0.125	-	-	-	-	-	-
Staphylococcus saprophyticus	-	-	1	0.125	-	-	-	0.125	0.125	-	0.06	-	-	-
Staphylococcus simulans	-	-	-	0.125	-	-	-	-	-	-	-	-	-	-
Staphylococcus warneri	-	-	0.25	0.125	-	-	-	0.06	0.125	-	0.06	-	-	-
Stenotrophomonas maltophilia	-	-	-	0.06	-	-	0.5	-	0.125	-	0.03	8	-	-
Streptococcus agalactiae	-	-	0.03	0.125	-	0.03	0.25	0.016	0.125	-	0.06	-	1	0.25
Streptococcus anginosus	-	-	-	0.25	-	0.06	-	0.06	-	-	0.03	-	-	-
Streptococcus bovis	-	-	-	0.5	-	-	-	-	1	-	0.125	-	-	-
Streptococcus canis	-	-	-	-	-	-	-	0.06	-	-	-	-	-	-
Streptococcus constellatus	-	-	-	0.25	-	0.06	-	-	-	-	0.03	-	-	-
Streptococcus dysgalactiae	-	-	-	-	-	0.06	-	0.03	-	-	0.06	-	-	-
Streptococcus equisimilis	-	-	-	-	-	-	-	0.06	-	-	-	-	-	-
Streptococcus group C	-	-	-	0.25	-	-	-	-	0.25	-	0.125	-	-	-

3. RESULTS AND DISCUSSION

Table S6. Average recoveries for QCs prepared at three fortification levels in every batch of sample analysis. RSD (%) in brackets.

	IWW			EWW		
	100 ng L ⁻¹ (n=4)	500 ng L ⁻¹ (n=4)	5000 ng L ⁻¹ (n=4)	100 ng L ⁻¹ (n=4)	500 ng L ⁻¹ (n=4)	5000 ng L ⁻¹ (n=4)
Amoxicillin	*	120 (8)	104 (6)	*	110 (3)	120 (24)
Ampicillin	132 (4)	78 (10)	97 (4)	124 (48)	103 (12)	95 (13)
Azithromycin	**	**	83 (23)	**	56 (65)	111 (24)
Cefditoren	170 (37)	104 (13)	90 (14)	140 (22)	90 (41)	86 (21)
Cefuroxime	87 (33)	90 (13)	86 (32)	***	114 (29)	133 (14)
Ciprofloxacin	137 ^a (5)	107 (20)	118 (17)	103 ^a (23)	103 (5)	82 (22)
Clarithromycin	**	51 (31)	95 (16)	53 (21)	61 ^a (2)	110 (2)
Clindamycin	66 (36)	84 (30)	108 (46)	115 (19)	108 (15)	80 (20)
Cloxacillin	66 (24)	98 (12)	107 (20)	73 (58)	102 (11)	100 (15)
Doxycycline	119 (17)	104 (32)	101 (23)	139 (32)	101 (5)	89 (13)
Erithromycin	**	82 (5)	104 (7)	63 (14)	70 (13)	126 (8)
Levofloxacin	97 ^a (13)	99 (14)	114 (15)	80 (33)	103 (3)	94 (14)
Metronidazole	112 (48)	118 (46)	114 (58)	121 (1)	108 (10)	105 (35)
Moxifloxacin	113 (17)	95 (6)	112 (13)	77 ^a (5)	96 (6)	110 (8)
Norfloxacin	84 ^a (6)	102 (4)	113 (6)	80 ^a (11)	104 (4)	108 (5)
Roxithromycin	63 (42)	94 (5)	79 (13)	234 (66)	80 (16)	109 (10)
Sulfamethoxazole	123 ^a (5)	115 (23)	119 (31)	112 (19)	108 (19)	110 (29)
Trimethoprim	90 (17)	99 (16)	99 (18)	103 (22)	105 (15)	90 (25)

Values of recoveries out of 60-140% were in bold and italic.

* No data available at the lowest spiked level, due to the lack of sensitivity for this compound.

** Not calculated due to the high analyte concentrations in the “blank” samples used for QC preparation.

*** Anomalous value.

^a Average value for n < 4 due to the presence of analyte in the blank of some QC.

Table S7. Concentration levels (ng L⁻¹) detected of antibiotics in IWW samples analyzed (April 2021- January 2022).

	April				May				June				July				August		September				October				January			
	I-001	I-002	I-004	I-005	I-007	I-008	I-010	I-011	I-013	I-014	I-016	I-017	I-019	I-020	I-022	I-023	I-025	I-026	I-028	I-029	I-031	I-032	I-034	I-035	I-037	I-038	I-040	I-041	I-043	I-044
Amoxicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ampicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Azithromycin	4113	4903	3594	3490	6171	2929	6046	6150	6565	5880	4217	3054	5298	5339	5194	4591	4571	3822	d	d	d	d	3162	1551	1645	3204	6927	3042	2420	2437
Cefditoren	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cefuroxime	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin	1254	1095	675	818	1869	524	1486	1383	1861	1849	766	683	1132	1162	1142	900	1131	1280	502	450	355	794	750	d	d	846	1438	428	398	325
Clarithromycin	714	825	598	715	855	621	961	971	1005	873	615	517	709	702	603	586	568	653	410	398	420	460	560	256	254	449	602	397	474	434
Clindamycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	d	d	d	d	54	d	d	-	-	-	-
Cloxacillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Doxycycline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Erythromycin	126	156	134	148	196	135	174	159	146	135	122	107	121	129	131	120	136	123	79	79	70	96	97	92	84	87	202	74	92	78
Levofloxacin	777	649	480	540	686	377	942	839	1251	922	618	489	789	865	745	541	856	833	306	250	d	425	414	250	d	541	1329	408	300	256
Metronidazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	50	79	-	79	50	53	75	-	58	54
Moxifloxacin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Norfloxacin	775	603	332	382	664	254	564	543	732	814	360	293	410	489	557	410	475	525	316	250	d	310	253	d	d	d	403	d	d	d
Roxithromycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sulfamethoxazole	241	369	233	299	378	204	591	545	687	569	311	259	454	556	510	349	518	474	150	141	206	535	689	50	d	455	1129	382	300	326
Trimethoprim	98	129	102	130	192	99	215	176	158	165	88	77	165	157	175	126	159	145	68	59	83	185	150	50	50	117	305	98	90	89

d, detected: concentration level < LOQ.

-, not detected.

Table S8. Concentration levels (ng L⁻¹) detected of antibiotics in EWW samples analyzed (April 2021- January 2022).

	April				May				June				July				August		September				October				January			
	E-002	E-003	E-005	E-006	E-008	E-009	E-011	E-012	E-014	E-015	E-017	E-018	E-020	E-021	E-023	E-024	E-026	E-027	E-029	E-030	E-032	E-033	E-035	E-036	E-038	E-039	E-041	E-042	E-044	E-045
Amoxicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ampicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Azithromycin	2840	3110	2720	1800	2640	2690	4180	4010	3520	3480	2560	2890	2420	2720	2490	2910	1580	1800	d	d	d	d	1239	d	d	d	1356	1557	2177	1820
Cefditoren	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cefuroxime	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin	371	271	252	141	415	374	567	511	548	623	538	511	505	509	395	486	296	455	196	166	143	50	728	176	210	167	229	167	247	197
Clarithromycin	200	214	221	223	197	188	221	203	204	211	169	167	170	171	174	167	170	169	263	259	291	268	400	249	250	253	260	263	280	262
Clindamycin	44	38	36	26	56	58	52	56	93	61	33	38	50	54	36	45	24	31	27	21	20	-	20	27	24	24	22	20	36	29
Cloxacillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Doxycycline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Erythromycin	140	130	124	97	144	125	147	148	111	113	100	101	97	96	103	100	94	99	60	60	66	63	70	64	69	69	81	74	89	76
Levofloxacin	414	331	313	143	441	399	582	605	671	670	702	641	685	646	463	560	386	534	116	108	124	75	380	164	152	110	238	192	295	240
Metronidazole	168	163	175	89	219	199	156	173	197	208	141	170	110	118	117	116	61	87	d	d	96	37	-	25	29	32	91	60	144	109
Moxifloxacin	108	38	20	d	d	d	d	d	d	d	d	d	d	d	d	d	d	-	114	40	21	23	20	d	25	23	23	d	21	d
Norfloxacin	258	140	138	73	177	180	206	197	218	241	227	201	178	181	156	193	98	160	146	82	57	30	173	45	76	44	63	58	78	59
Roxithromycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sulfamethoxazole	34	24	27	20	98	52	67	81	68	66	62	80	173	117	173	99	83	69	d	d	64	d	466	d	20	d	74	27	69	56
Trimethoprim	131	119	131	77	181	192	176	170	171	185	140	142	102	92	56	67	20	34	d	d	53	35	115	20	38	34	105	86	110	91

d, detected: concentration level < LOQ.

-, not detected.

Table S9. Daily mass loads (g/day) obtained for antibiotics in IWW samples analyzed (April 2021 - January 2022).

	April				May				June				July				August		September				October				January			
	I-001	I-002	I-004	I-005	I-007	I-008	I-010	I-011	I-013	I-014	I-016	I-017	I-019	I-020	I-022	I-023	I-025	I-026	I-028	I-029	I-031	I-032	I-034	I-035	I-037	I-038	I-040	I-041	I-043	I-044
Amoxicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ampicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Azithromycin	137	193	139	162	236	112	235	242	239	225	155	112	205	199	209	178	173	160	<u>39</u>	<u>39</u>	<u>45</u>	<u>45</u>	136	52	61	117	241	107	83	77
Cefditoren	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cefuroxime	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin	42	43	26	38	71	20	58	54	68	71	28	25	44	43	46	35	43	54	20	18	16	36	32	<u>4</u>	<u>5</u>	31	50	15	14	10
Clarithromycin	24	32	23	33	33	24	37	38	37	33	23	19	28	26	24	23	21	27	16	16	19	21	24	9	9	16	21	14	16	14
Clindamycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<u>2</u>	<u>2</u>	<u>2</u>	<u>2</u>	<u>2</u>	2	<u>2</u>	<u>2</u>	-	-	-	-
Cloxacillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Doxycycline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Erythromycin	4	6	5	7	8	5	7	6	5	5	4	4	5	5	5	5	5	5	3	3	3	4	4	3	3	3	7	3	3	2
Levofloxacin	26	27	19	25	26	14	37	33	46	35	23	18	31	32	30	21	32	35	12	10	<u>6</u>	19	18	8	<u>5</u>	20	46	14	10	8
Metronidazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	4	-	3	2	2	3	-	2	2
Moxifloxacin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Norfloxacin	26	24	13	18	25	10	22	21	27	31	13	11	16	18	22	16	18	22	12	10	<u>6</u>	14	11	<u>4</u>	<u>5</u>	<u>5</u>	14	<u>4</u>	<u>4</u>	<u>4</u>
Roxithromycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sulfamethoxazole	8	15	9	14	14	8	23	21	25	22	11	9	18	21	20	14	20	20	6	6	9	24	30	2	<u>1</u>	17	39	13	10	10
Trimethoprim	3	5	4	6	7	4	8	7	6	6	3	3	6	6	7	5	6	6	3	2	4	8	6	2	2	4	11	3	3	3
Sum/day*	270	345	238	303	420	197	427	422	453	428	260	201	353	350	363	297	318	329	113	106	112	177	263	89	95	217	432	173	145	130

*Sum of the daily mass loads (g/day) of antibiotics studied.

The underlined mass loads were obtained from concentrations below its LOQ and above its LOD; a concentration equivalent to half the LOQ value was considered.

-, not detected.

Table S10. Daily mass loads (g/day) obtained for antibiotics in EWW samples analyzed (April 2021- January 2022).

	April				May				June				July				August		September				October				January			
	E-002	E-003	E-005	E-006	E-008	E-009	E-011	E-012	E-014	E-015	E-017	E-018	E-020	E-021	E-023	E-024	E-026	E-027	E-029	E-030	E-032	E-033	E-035	E-036	E-038	E-039	E-041	E-042	E-044	E-045
Amoxicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ampicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Azithromycin	112	117	126	73	101	115	164	159	134	138	94	109	90	103	97	113	66	68	<u>20</u>	<u>20</u>	<u>22</u>	<u>22</u>	42	<u>19</u>	<u>18</u>	<u>18</u>	48	50	69	59
Cefditoren	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cefuroxime	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin	15	10	12	6	16	16	22	20	21	25	20	19	19	19	15	19	12	17	8	7	6	2	25	7	8	6	8	5	8	6
Clarithromycin	8	8	10	9	8	8	9	8	8	8	6	6	6	6	7	6	7	6	10	10	13	12	14	10	9	9	9	8	9	8
Clindamycin	2	1	2	1	2	2	2	2	4	2	1	1	2	2	1	2	1	1	1	1	1	-	1	1	1	1	1	1	1	1
Cloxacillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Doxycycline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Erythromycin	5	5	6	4	6	5	6	6	4	5	4	4	4	4	4	4	4	4	2	2	3	3	2	2	3	3	3	2	3	2
Levofloxacin	16	12	14	6	17	17	23	24	26	27	26	24	26	24	18	22	16	20	5	4	6	3	13	6	6	4	8	6	9	8
Metronidazole	7	6	8	4	8	9	6	7	8	8	5	6	4	4	5	5	3	3	<u>0,4</u>	<u>0,4</u>	4	2	-	1	1	1	3	2	5	4
Moxifloxacin	4	1	1	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	<u>0,4</u>	-	4	2	1	1	0,7	<u>0,4</u>	1	0,8	0,8	<u>0,3</u>	0,7	<u>0,3</u>
Norfloxacin	10	5	6	3	7	8	8	8	8	10	8	8	7	7	6	7	4	6	6	3	3	1	6	2	3	2	2	2	2	2
Roxithromycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sulfamethoxazole	1	1	1	1	4	2	3	3	3	3	2	3	6	4	7	4	3	3	<u>0,4</u>	<u>0,4</u>	3	<u>0,4</u>	16	<u>0,4</u>	1	<u>0,4</u>	3	1	2	2
Trimethoprim	5	4	6	3	7	8	7	7	7	7	5	5	4	3	2	3	1	1	<u>0,4</u>	<u>0,4</u>	2	2	4	1	1	1	4	3	3	3
Sum/day*	185	170	192	110	176	190	250	244	223	233	171	185	168	176	162	185	117	129	57	50	64	48	124	50	52	46	90	80	112	95

*Sum of the daily mass loads (g/day) of antibiotics studied.

The underlined mass loads were obtained from concentrations below its LOQ and above its LOD; a concentration equivalent to half the LOQ value was considered.

-, not detected.

Tabel S11. Concentration levels (ng L⁻¹) detected of antibiotics in IWW samples analyzed across the world.

Antibiotic	Our study	Australia (Li et al., 2023)	Peru (Lima) (Nieto-Juárez et al., 2021)	Peru (Cusco) (Nieto-Juárez et al., 2021)	China (Xing et al., 2022)	South Africa (Oharisi et al., 2023)
Amoxicillin	-	/	/	/	/	70-120
Ampicillin	-	470-810	/	/	/	0-110
Azithromycin	d-6927	/	2520-3930	1290-5270	13-7	110-250
Cefditoren	-	/	/	/	/	/
Cefuroxime	-	/	/	/	/	/
Ciprofloxacin	d-1869	360-590	2910-4700	2860-7220	0-1	190-660
Clarithromycin	254-1005	/	1400-2860	1320-3490	1-3	/
Clindamycin	d-54	10-21	70-180	30-70	1-11	/
Cloxacillin	-	/	/	/	/	/
Doxycycline	-	/	/	/	18-36	34900-120000
Erithromycin	70-202	/	200-820	820-1270	-	210-580
Levofloxacin	d-1329	d-67	/	/	19-220	0-90
Metronidazole	50-79	28-120	37-1540	430-870	/	-
Moxifloxacin	-	d-78	/	/	/	/
Norfloxacin	d-814	69-120	470-780	420-1420	0-259	0-160
Roxithromycin	-	/	-	-	9-79	/
Sulfamethoxazole	d-1129	200-1300	940-3410	4360-10360	2-32	780-96800
Trimethoprim	50-305	350-730	1930-5990	6800-12020	0-0.13	120-9960

d, detected.

-, not detected.

/, not studied.

3.2. Metabolite screening

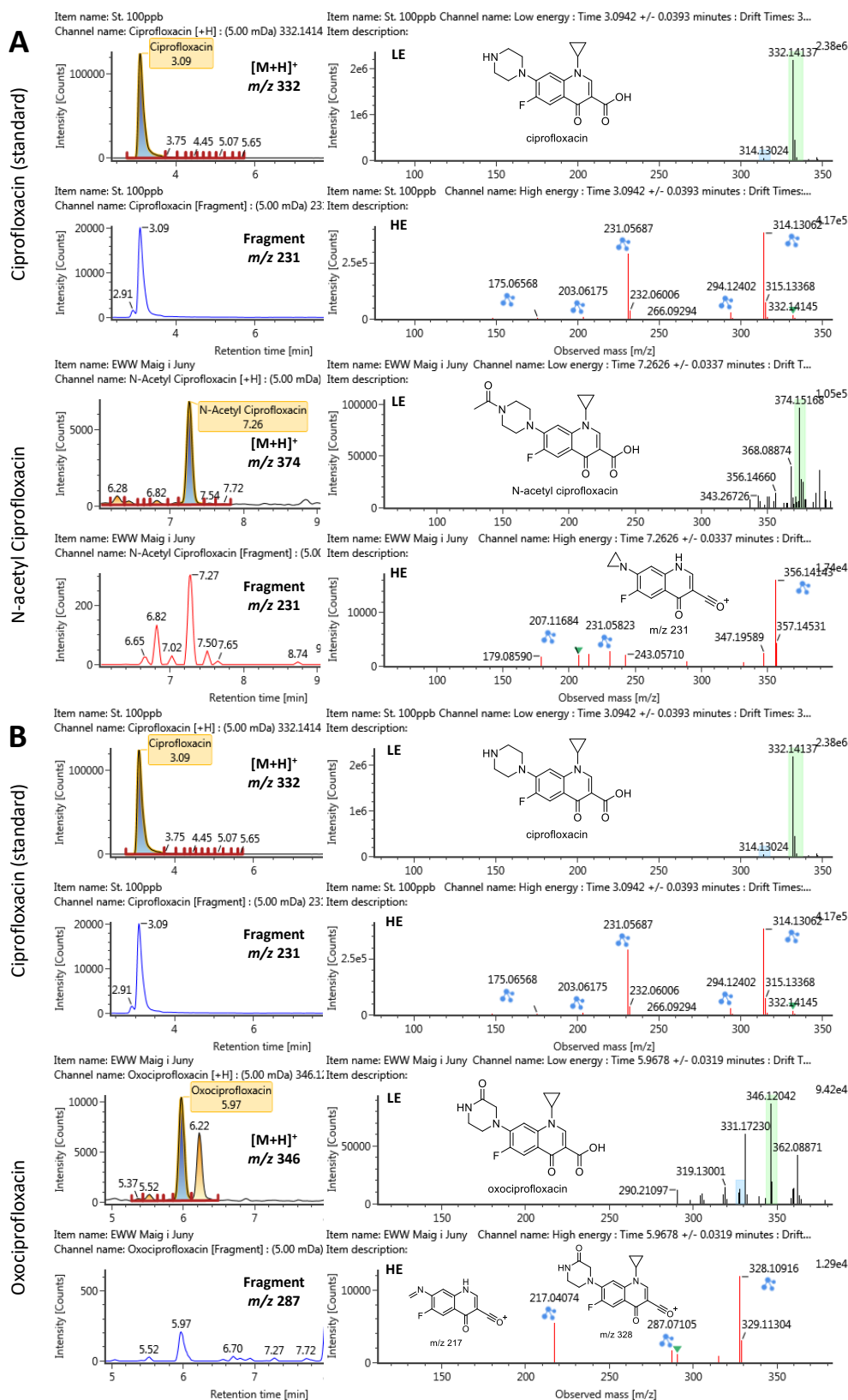


Figure S1. Examples of antibiotic metabolites identification during UHPLC-IMS-HRMS screening based on accurate-mass fragmentation compared with parent compounds. **A** *N*-acetyl ciprofloxacin (Level 2b). **B** Oxociprofloxacin (Level 3).

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