Population driven biochemical burden in a multi-city study: antibiotics, ARGs and implications for One Health actions

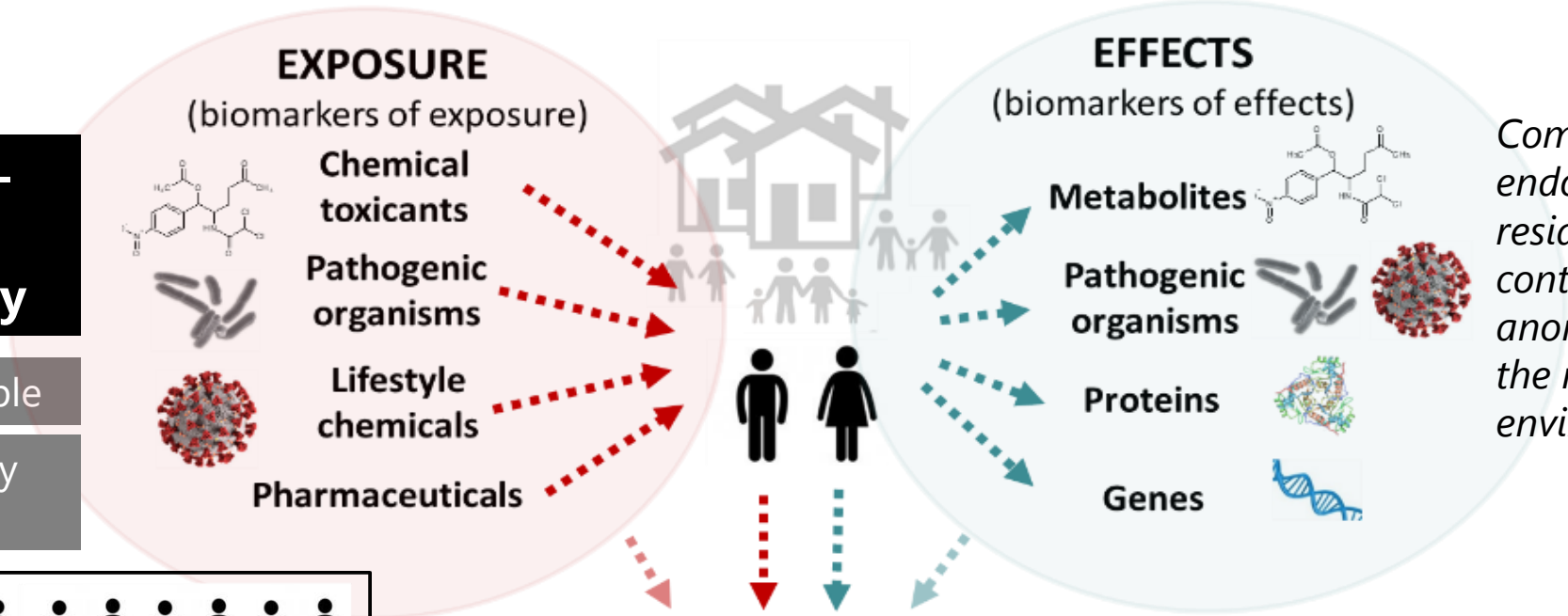
Barbara Kasprzyk-Hordern[1], Natalie Sims[1], Kishore Jagadeesan[1], Felicity Elder[1], Ruth Barden[2]
[1]Environmental Chemistry & Public Health Research Group
University of Bath
[2]Wessex Water

Wastewater-Based Epidemiology

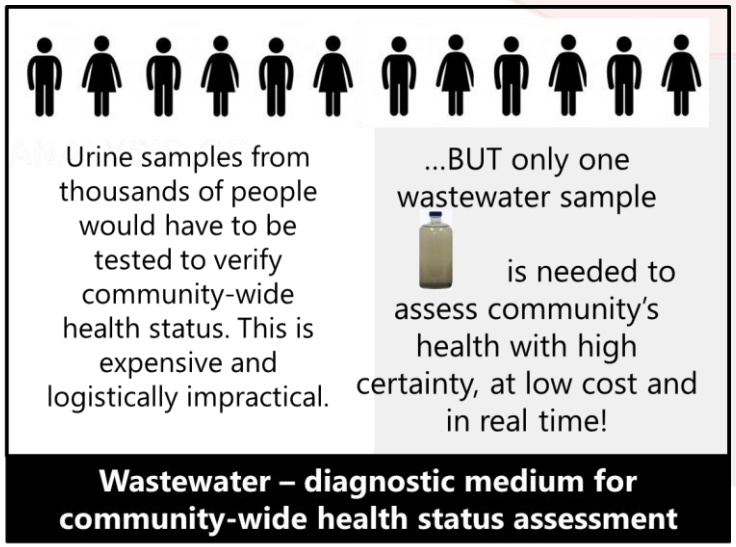
Wastewater-Based Epidemiology

Conceptually simple

Methodologically sophisticated



Community derived endo- and exogenous residues are continuously and anonymously pooled by the receiving environment



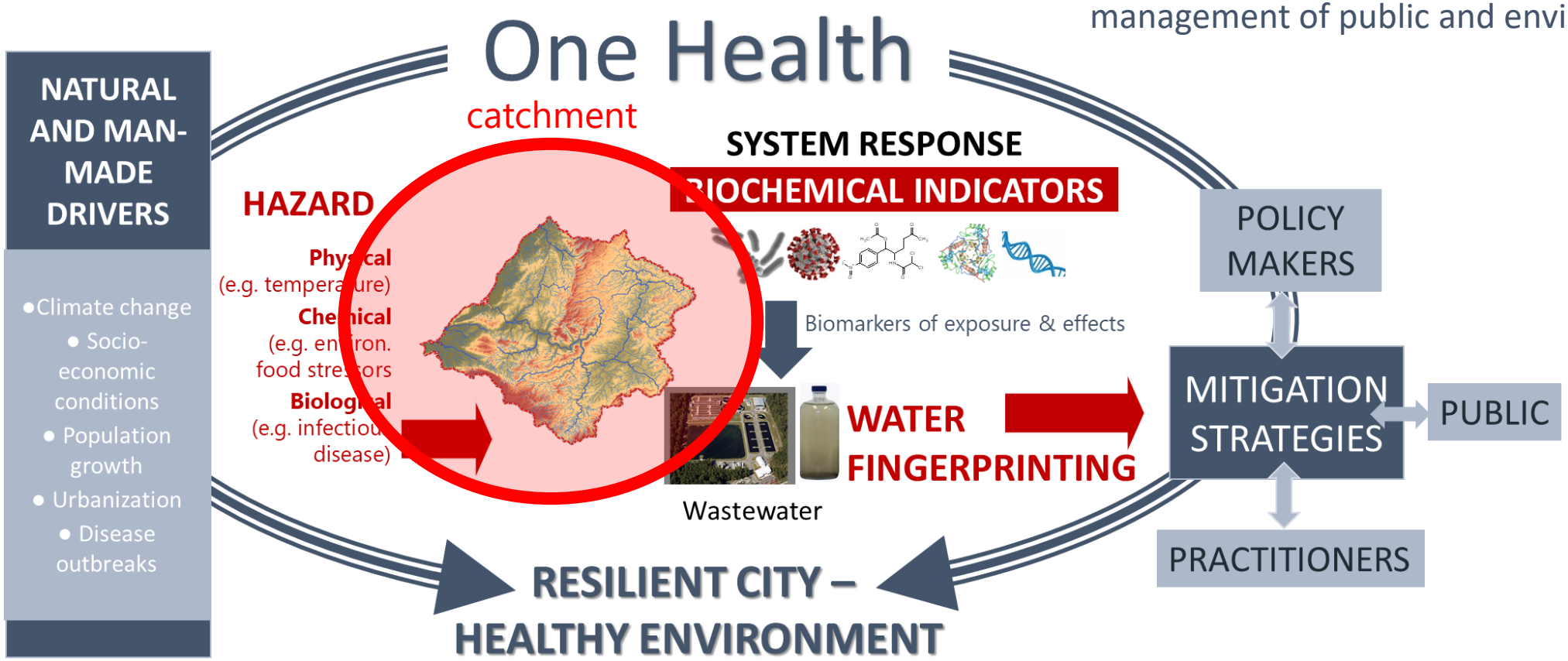
Wastewater is a fingerprint of community's health and lifestyle

comprehensive | continuous | anonymous | near real-time | objective | unbiassed

B.Kasprzyk-Hordern@bath.ac.uk

Water-Based Epidemiology and One Health

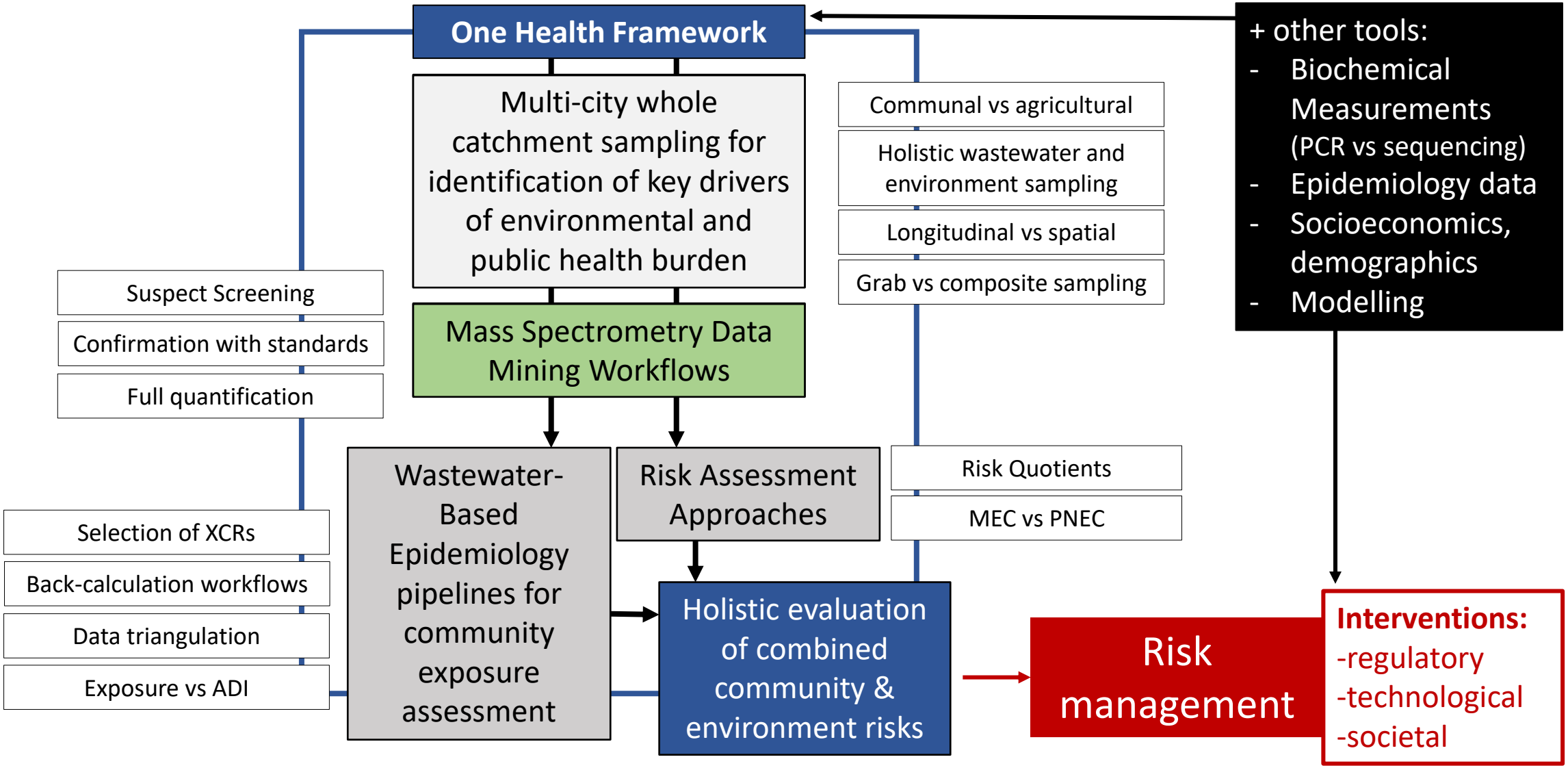
One Health is a cross sectoral and multidisciplinary effort aimed at a holistic understanding and management of public and environmental health



~~Waste~~Water-Based Epidemiology – an enabler of One Health

1 Evaluate env/public health status
2. Inform One Health actions
3. Evaluate mitigation strategies

One Health framework for holistic evaluation of combined community & environment risks



Biochemical Indicators

Class	Compound
UV Filter	Benzophenone-1
	Benzophenone-2
	Benzophenone-3
	Benzophenone-4
Parabens	Methylparaben
	Ethylparaben
	Propylparaben
	Butylparaben
Plasticizer	Bisphenol-A
	Bisphenol A sulphate
Steroid Estrogens	E1
	E2
	EE2
Antibiotics and Antibacterial	Sulfasalazine
	Clarithromycin
	Azithromycin
	Trimethoprim
	Sulfamethoxazole
	Triclosan
	Triclosan sulphate
	Amoxicillin
	Metronidazole
	Sulfadiazine
	Cefalexin
	Ofloxacin
	Ciprofloxacin
	Tetracycline
	Danofloxacin
	Oxytetracycline
	Chloramphenicol
	Penicillin G
	Penicillin V
	Erythromycin
	Prulifloxacin
	Norfloxacin
	Nalidixic acid
Antifungal	Griseofulvin
	Ketoconazole
Hypertension	Valsartan
	Irbesartan
	Lisinopril

Class	Compound
NSAIDs	Ketoprofen
	Ibuprofen
	Naproxen
	Diclofenac
	Acetaminophen
Lipid regulator	Bezafibrate
	Atorvastatin
Anti-hyperlipidemic	Gemfibrozil
Anti-hyperintensive	Candesartan Cilexetil
Antihistamine	Fexofenadine
	Cetirizine
GUD/ED	Sildenafil
Diabetes	Metformin
	Gliclazide
	Sitagliptin
Cough suppressant	Pholcodine
Beta-blocker	Atenolol
	Metoprolol
	Propranolol
	Bisoprolol
H2 receptor agonist	Ranitidine
	Cimetidine
X-ray contrast media	Iopromide
Various	Buprenorphine
Drug precursor	Ephedrine/pseudoephedrine
	Norephedrine
Anti-cancer	Azathioprine
	Methotrexate
	Ifosfamide
	Tamoxifen
	Imatinib
	Capecitabine
	Bicalutamide
Genes/ARGs	16SRNA
	ermB
	qnrS
	Sulf
	catA

UNIVERSITY OF BATH

Class	Compound
Anaesthetic and metabolite	Ketamine
	Norketamine
Anti-depressants	Venlafaxine
	Desvenlafaxine
	Fluoxetine
	Norfluoxetine
	Sertraline
	Mirtazapine
	Citalopram
	Desmethylcitalopram
	Paroxetine
	Duloxetine
	Amitriptyline
	Nortriptyline
	Norsertraline
Anti-epileptic	Carbamazepine
	Carbamazepine10,11-epoxide
	10,11-Dihydro-10-hydroxycarbamazepine
Calcium-channel blocker	Diltiazem
	Verapamil
Hypnotic	Temazepam
	Oxazepam
	Diazepam
Anti-psychotic	Quetiapine
	Risperidone
Dementia	Donepezil
	Memantine
Creatinine	Creatinine
Lifestyle Chemicals	Nicotine
	Caffeine
	Cotinine
	1,7 dimethylxantine
Analgesics and Metabolites	Morphine
	Dihydromorphine
	Normorphine
	Methadone
	EDDP
	Codeine
	Norcodeine
	Dihydrocodeine
	Tramadol
	N-desmethyltramadol
	O-desmethyltramadol

Pharma & prescription vs social prescribing
Antibiotics, ARGs and pharma compliance
Endogenous markers: DNA damage, oxidative stress, metabolites
Pathogen RNA: Sars-Cov-2
Proteins: CRP

Class	Compound
Stimulants and metabolites	Amphetamine
	Methamphetamine
	MDMA
	MDA
	Cocaine
	Benzoylecgonine
	Anhydroecgonine methylester
	Cocaethylene
	Mephedrone
	MDPV
Opioid and metabolite	Heroin
	6-acetylmorphine
Pesticides, fungicides and herbicides	Thiamethoxam
	Imidacloprid
	Clothianidin
	Metazachlor
	Terbuthylazine
	Methiocarb
	Dichlofluanid
	Flufenacet
	Oxadiazon
	Chlorpyrifos
	Triallate
	3PBA (3-phenoxybenzoic acid)
Veterinary Pharma	Tylosin
	Sulfapyridine
	Sarafloxacin
	Ceftiofur
	Diazinon
WQIs	Ammonia N
	COD
	N total
	Nitrite as N
	Nitrate as N
	Orthophos
	Chloride

B.Kasprzyk-Hordern@bath.ac.uk

…more markers added via retrospective mass spectra mining

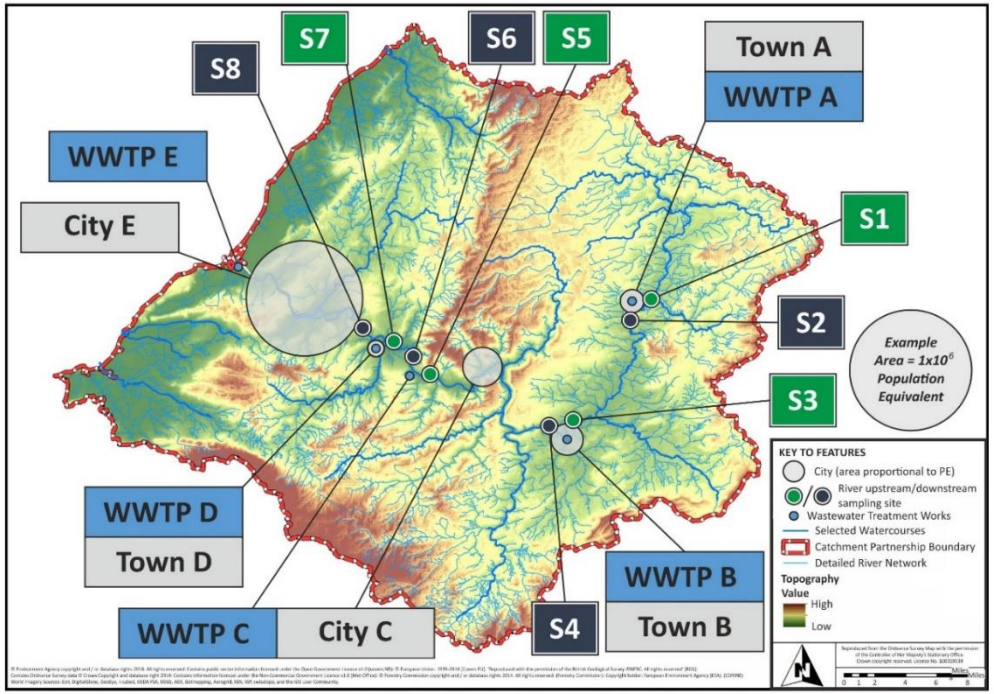
Studied antimicrobial agents

Antiretroviral (ARV);
nitrofuran (NIT);
cycline (CYC);
amphenicols (Phen);
β-lactams (β-lact);
tuberculosis-related drugs (TB);
aminoglycoside (AMG);
sulfonamide (Sulf);
trimethoprim (TMP);
macrolide (Mac);
lincosamide (Linc);
fluoro/quinolones (FQ)

ARV
NIT, CYC, & Phen
Azoles
β-lact
TB
AMG
Sulf & TMP
Mac & Linc
FQ

Grouping	Chemical	Grouping	Chemical
Sulphonamide & Trimethoprim	Sulfadiazine	**TB (1st line)**	Isoniazid
	Sulfapyridine		Pyrazinamide
	Sulfamethoxazole		Ethambutol
	Sulfasalazine		Rifampicin
	Trimethoprim		Rifabutin
	N-acetyl sulfadiazine		Isonicotinic acid
	N-acetyl sulfapyridine		Acetyl-isoniazid
	N-acetyl sulfamethoxazole		5-Hydroxy-pyrazinoic acid
	4-hydroxy-trimethoprim		25-desacetyl rifampicin
Macrolide & Lincosamide	Azithromycin		25-O-desacetyl rifabutin
	Erythromycin	**TB (MDR)**	Capreomycin IA
	Clarithromycin		Capreomycin IB
	Clindamycin		Gentamycin C1
	N-desmethyl azithromycin		Gentamycin C1a
	N-desmethyl erythromycin A		Gentamycin C2 C2a C2b
	N-desmethyl clarithromycin		Kanamycin A
	N-desmethyl clindamycin		Streptomycin A
β-lactams			D-cycloserine
Penicillin	Amoxicillin	**TB (other)**	Delamanid
	Ampicillin		Bedaquiline
	Flucloxacillin		Linezolid
	Penicillin G		Thalidomide
	Penicillin V	**OTHER**	
	Amoxicilloic acid	**Amphenicol**	Chloramphenicol
	Ampicilloic acid		Florfenicol
	Penicilloic G acid		2-Amino-1-(4-nitrophenyl)-1,3-propanediol
Quinolone	Besifloxacin	**Cycline**	Doxycycline
	Ciprofloxacin		Oxytetracycline
	Danofloxacin		Tetracycline
	Enrofloxacin	**Nitrofuran**	Nitrofurantoin
	Flumequine		1-(2-nitrobenzylidenamino)-2,4-imidazolidinedione
	Gatifloxacin	**Azole**	Metronidazole
	Lomefloxacin		Ketoconazole
	Moxifloxacin		Hydroxy-metronidazole
	Nadifloxacin		Deacetyl-ketoconazole
	Nalidixic acid	**Antiretroviral**	Emtricitabine
	Norfloxacin		Lamivudine
	Ofloxacin (Levofloxacin) *	**Cephalosporin**	Cefalexin
	Prulifloxacin		Cefixime
	Sarafloxacin		Ceftiofur
	Desethylene ciprofloxacin		Ceftriaxone
	Hydroxy-norfloxacin	**Monobactam**	Aztreonam
	Ofloxacin N-oxide	**Carbapenem**	Imipenem
	Desmethyl-ofloxacin		Meropenem
	Ulifloxacin		

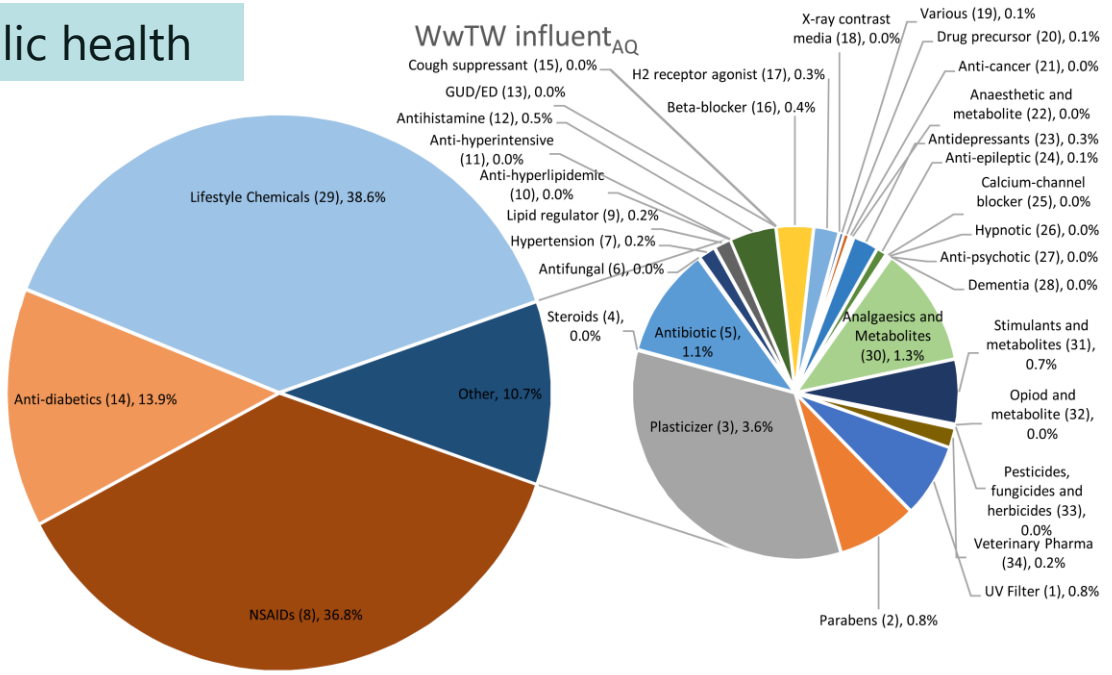
141 Chemicals of Emerging Concern in South West UK river catchment



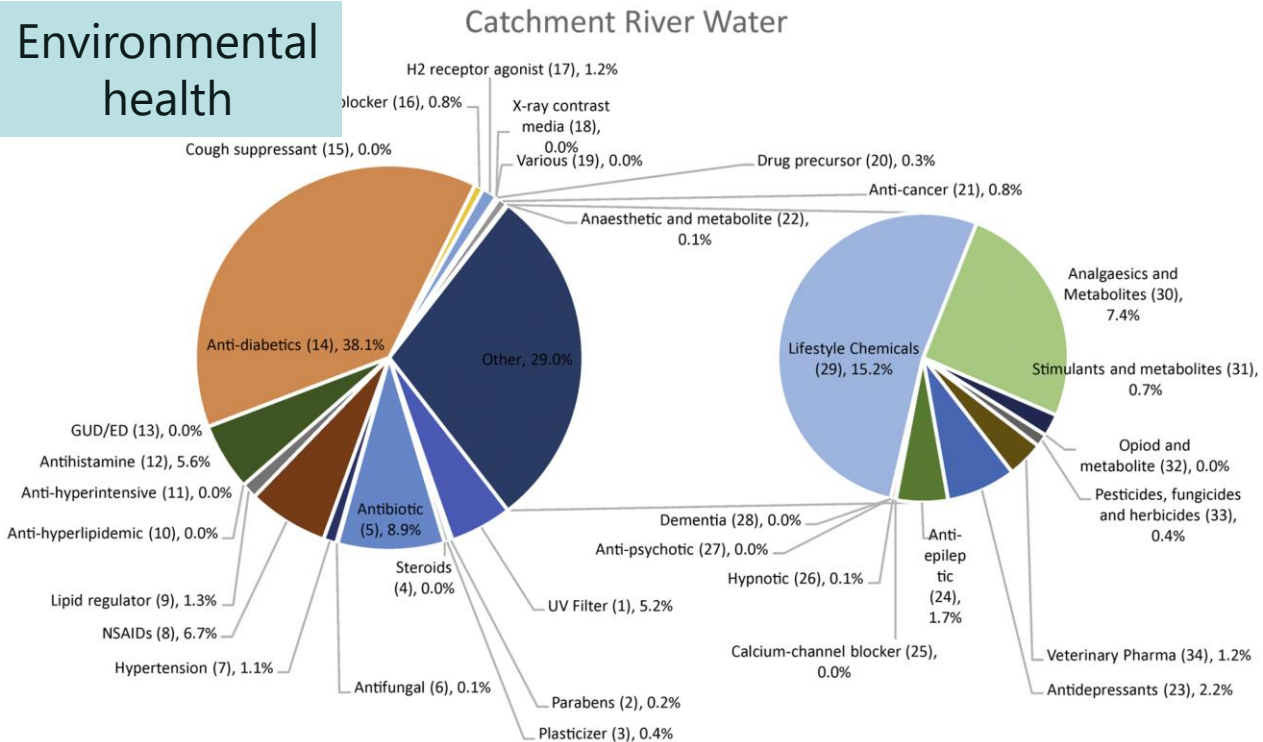
Population: 1,14 mln
Catchment: 362 km^2
Study area: 75% of total population in the catchment

Proctor et al. Journal of Hazardous Materials 401 (2021) 123745

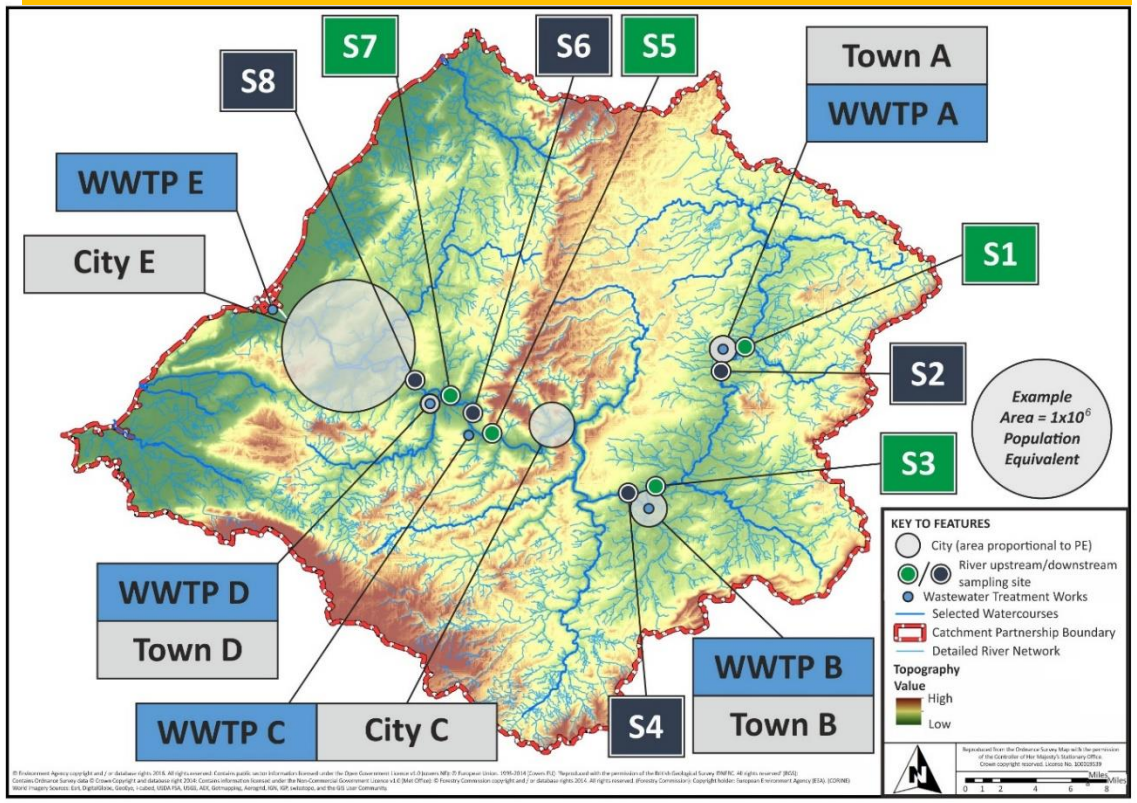
Public health



Environmental health



141 Chemicals of Emerging Concern (CECs) in South West UK river catchment



Population: 1,14 mln
Catchment: 362 km^2
Study area: 75% of total population in the catchment

169.3 kg/d of CECs entering the WwTWs:
167.9 kg/d in liquid phase 1.4 kg/day in SPM

155 kg/d removed

14 kg/day of CECs discharged into surface waters:
from 0.2 kg/d at WwTW A to 7.3 kg/d at WwTW E

Antibiotics

EXPOSURE

ERA

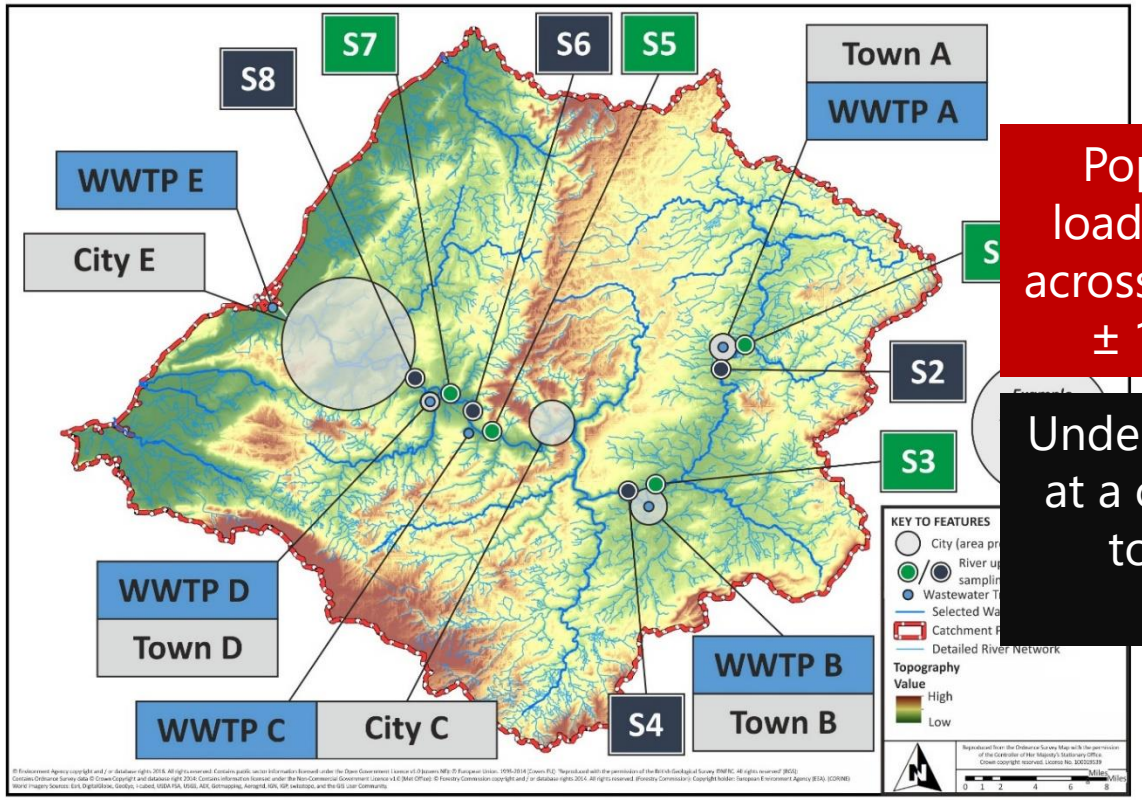
HAZARD

Ciprofloxacin, clarithromycin, azithromycin and erythromycin requlary exceed PNEC^{enviro} and PNEC^{MIC} in wastewater and sporadically in receiving waters

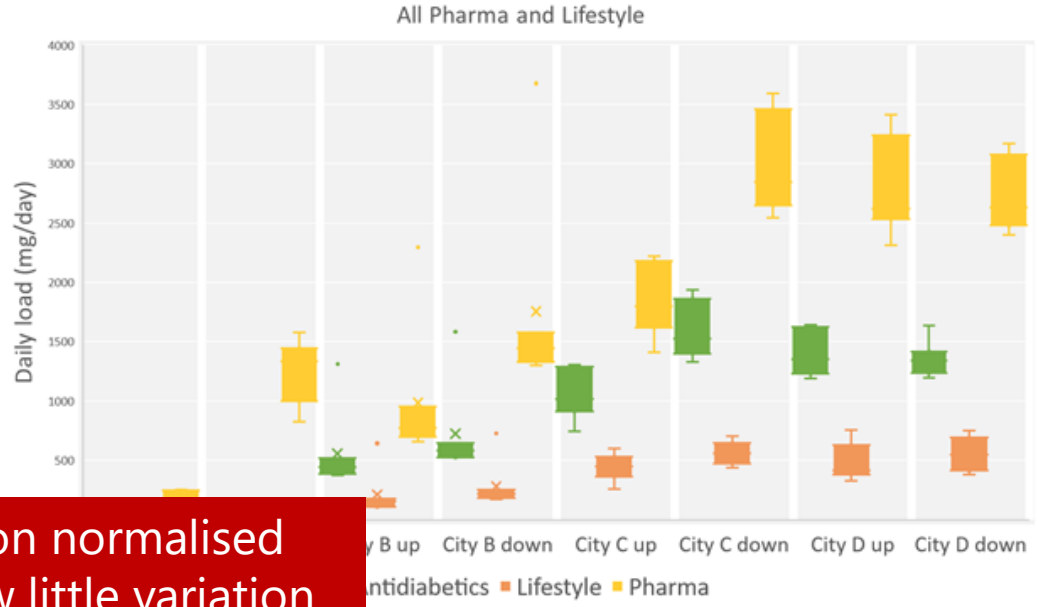
Proctor et al. Journal of Hazardous Materials 401 (2021) 123745

Elder et al. Water Research 203 (2021) 117933

Population size as a key driver of chemical burden in the receiving environment

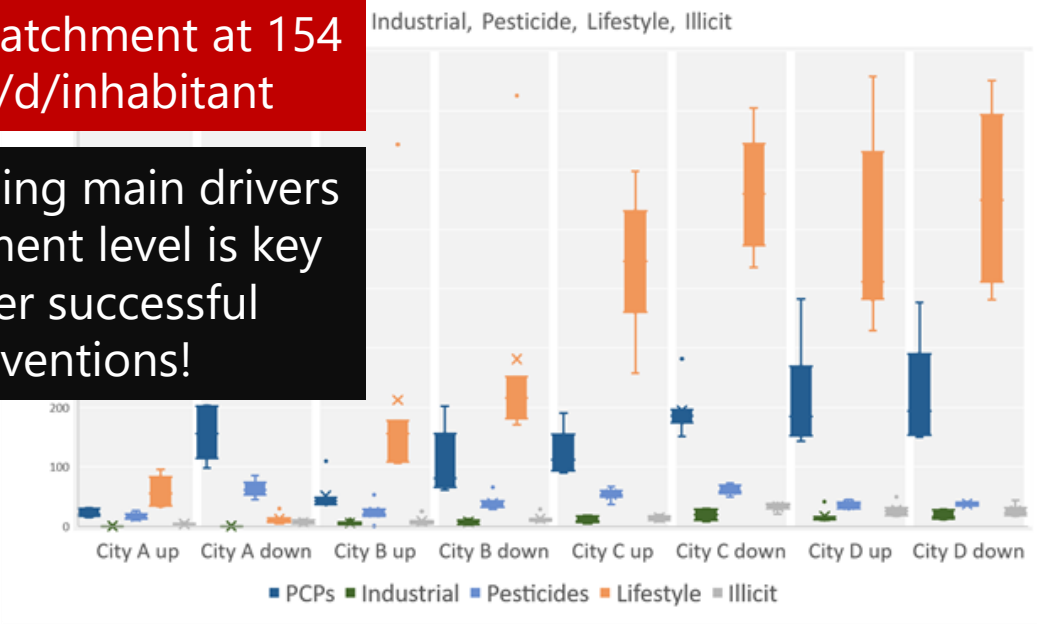


SPATIAL



Population normalised loads show little variation across the catchment at 154 ± 12 mg/d/inhabitant

Understanding main drivers at a catchment level is key to deliver successful interventions!



Kasprzyk-Hordern et al. J Haz Mat 429 (2022) 127882

Proctor et al. Journal of Hazardous Materials 401 (2021) 123745

Antibiotics and AMR

SPATIAL

Drivers: Population size

Population size as a key driver of antibiotics and ARGs in WWTP influent…..

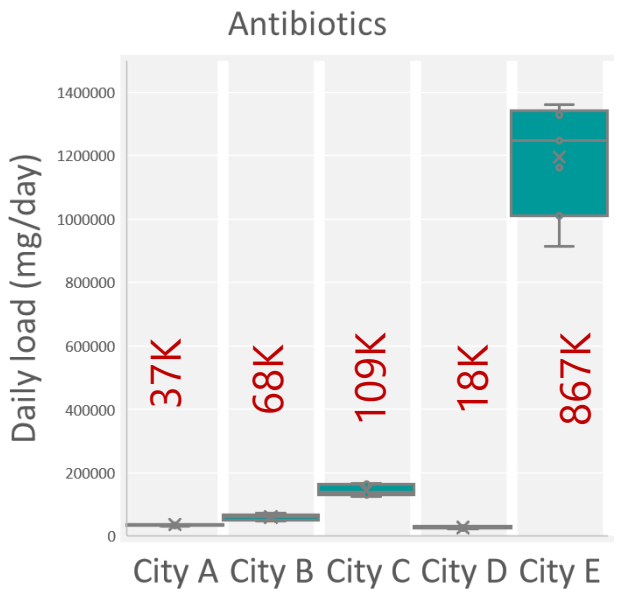
Pearson correlation between AB, ARG and PE

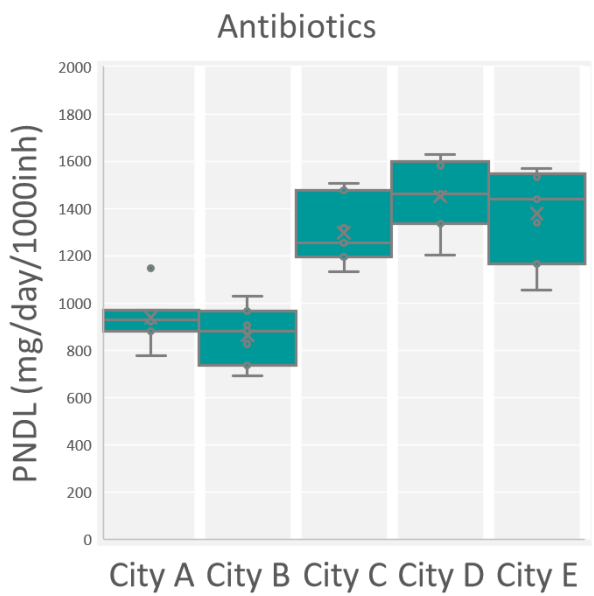
Pearson coefficient		
	Population	Sulfamethoxazole
Sulfamethoxazole	0.998704	1
Sul1	0.727473	0.694801
	Population	Chloramphenicol
Chloramphenicol	0.995464	1
catA	0.984915	0.967056
	Population	Macrolides
Macrolides	0.999576	1
ermB	0.996935	0.994663
	Population	Fluoroquinolones
Fluoroquinolones	0.998584	1
qnrS	0.980448	0.976258

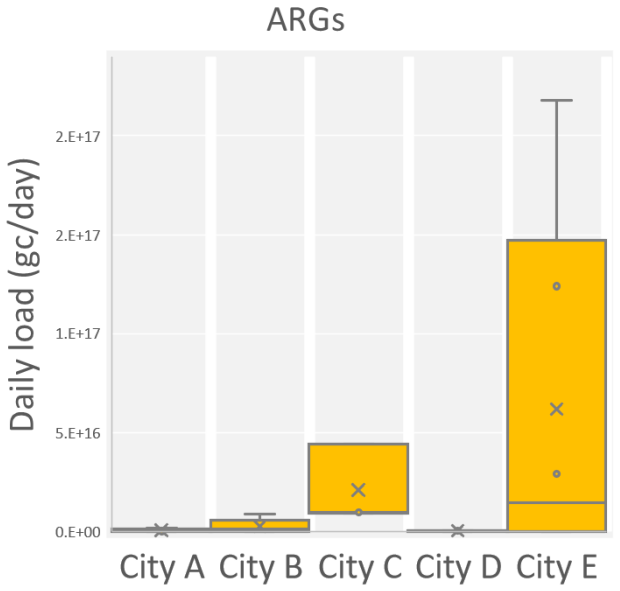
Strong correlation observed between combined daily loads of antibiotics, ARGs and population size served by individual WWTPs

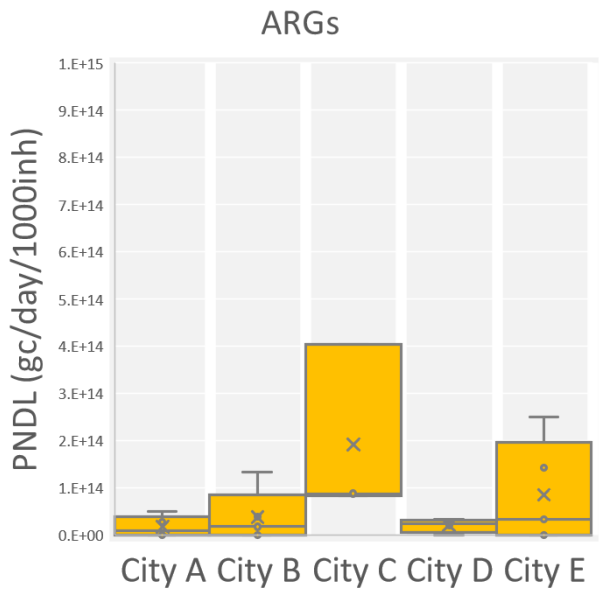
… One Health actions could focus on the reduction in antibiotics prescription …..

Kasprzyk-Hordern et al. J Haz Mat 429 (2022) 127882









Daily loads of antimicrobials by class and associated antibiotic resistance genes (ARGs) in influent wastewater (Bath)

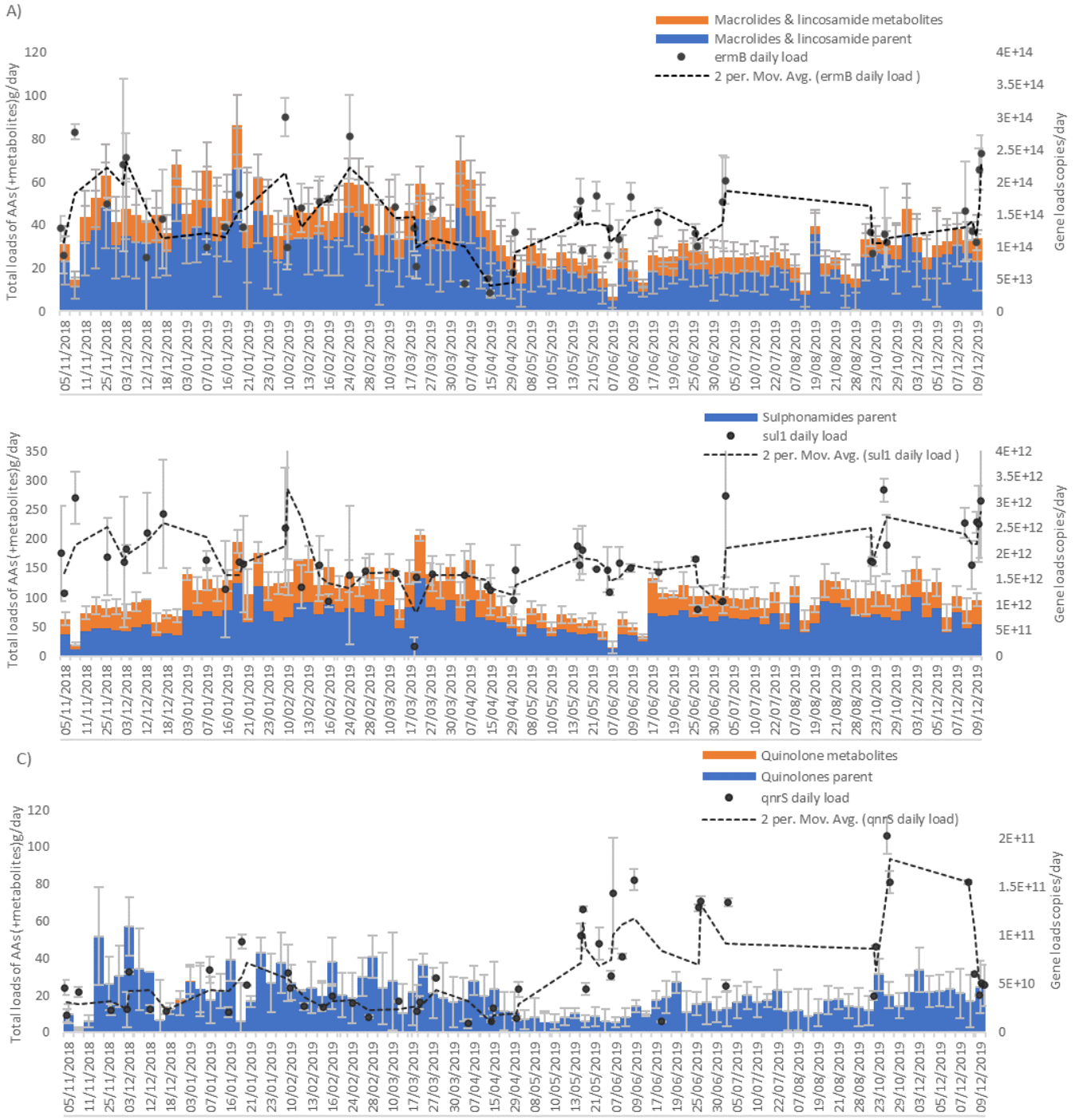
TEMPORAL

Seasonal changes in AB usage observed but not ARG prevalence

Weak/no positive correlations between AAs and ARGs

Population size is the key driver for AAs and ARGs

ARG levels are endemic, community dependent with low impact from seasonal changes in AA usage



Sims et al. Environmental Pollution, 333 (2023) 122020

UNIVERSITY OF BATH

Wessex Water YTL GROUP

Comparison of Population Normalised Daily Loads to the monthly catchment prescription data

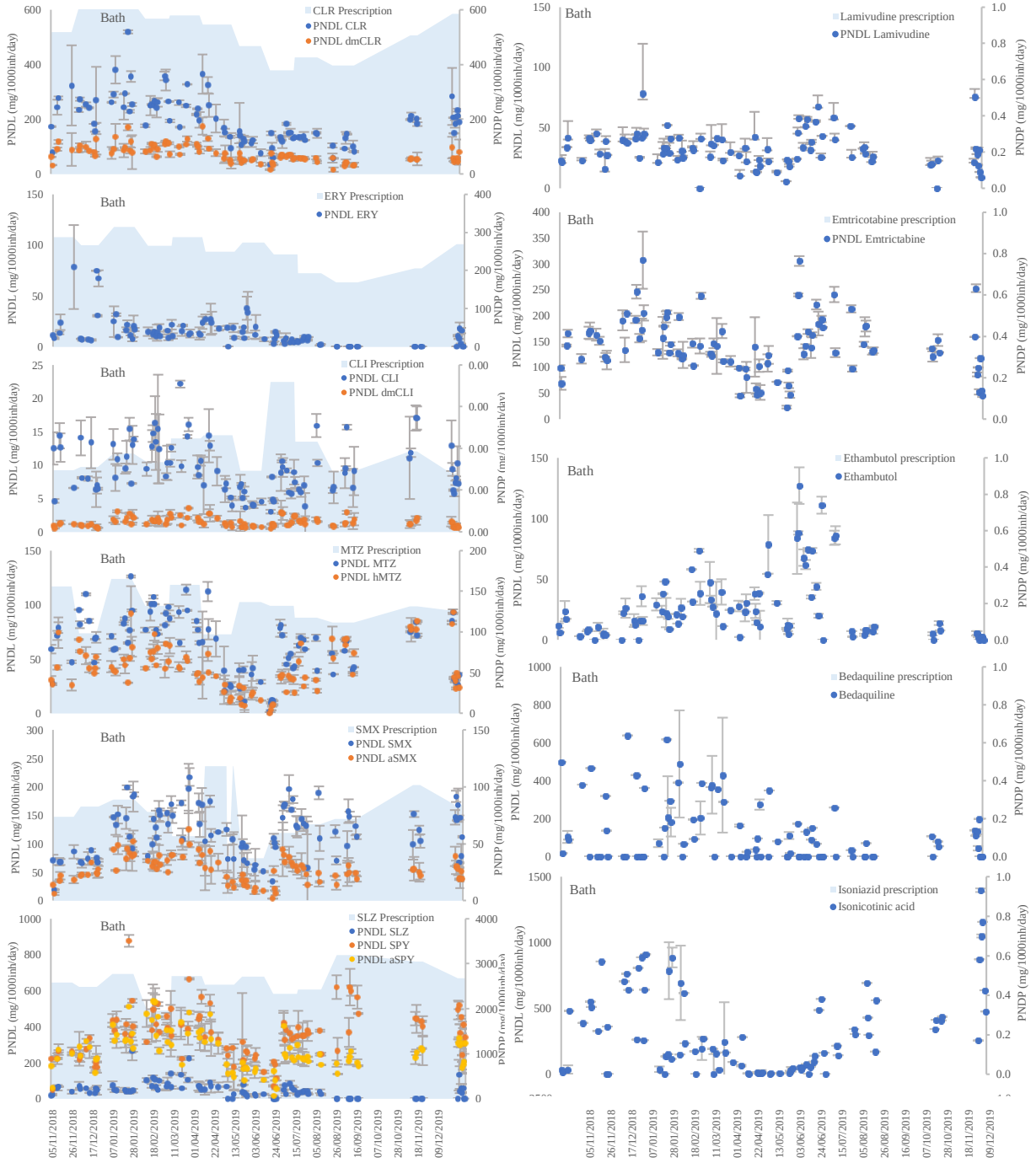
UNIVERSITY OF BATH

Wessex Water
YTL GROUP

WBE and prescription data shows similar seasonal trends but with low correlation in intake due to variable prescribing patterns and/or lack of patient compliance

WBE provides estimates of true community-wide antibiotic usage

Sims et al. Journal of Hazardous Materials, 454 (2023) 131461

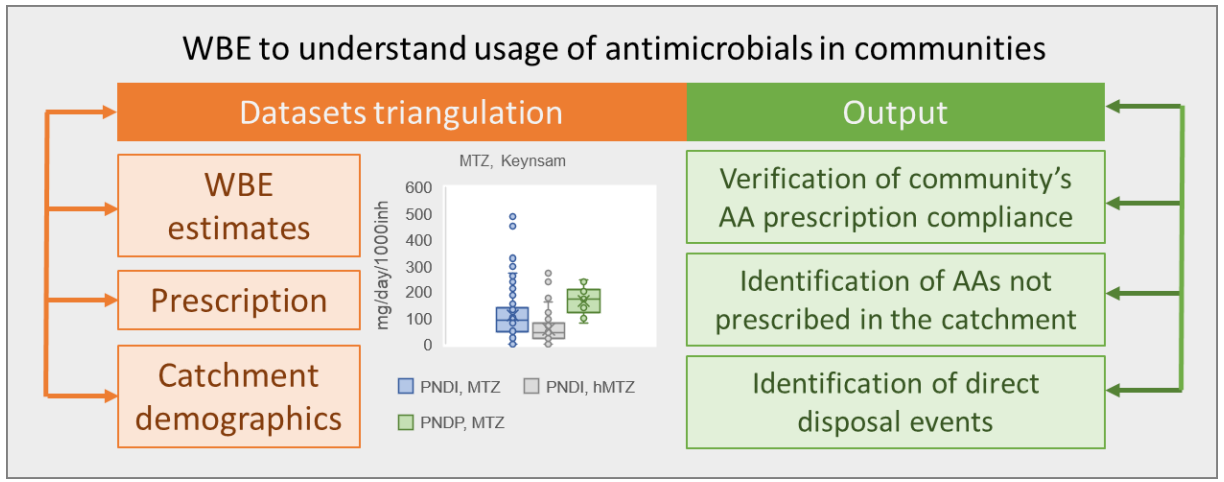


We regularly quantify antimicrobial agents (e.g. HIV and TB drugs) that are not prescribed in the catchment (either prescribed outside of the monitoring catchment, purchased over-the-counter or sourced illegally).

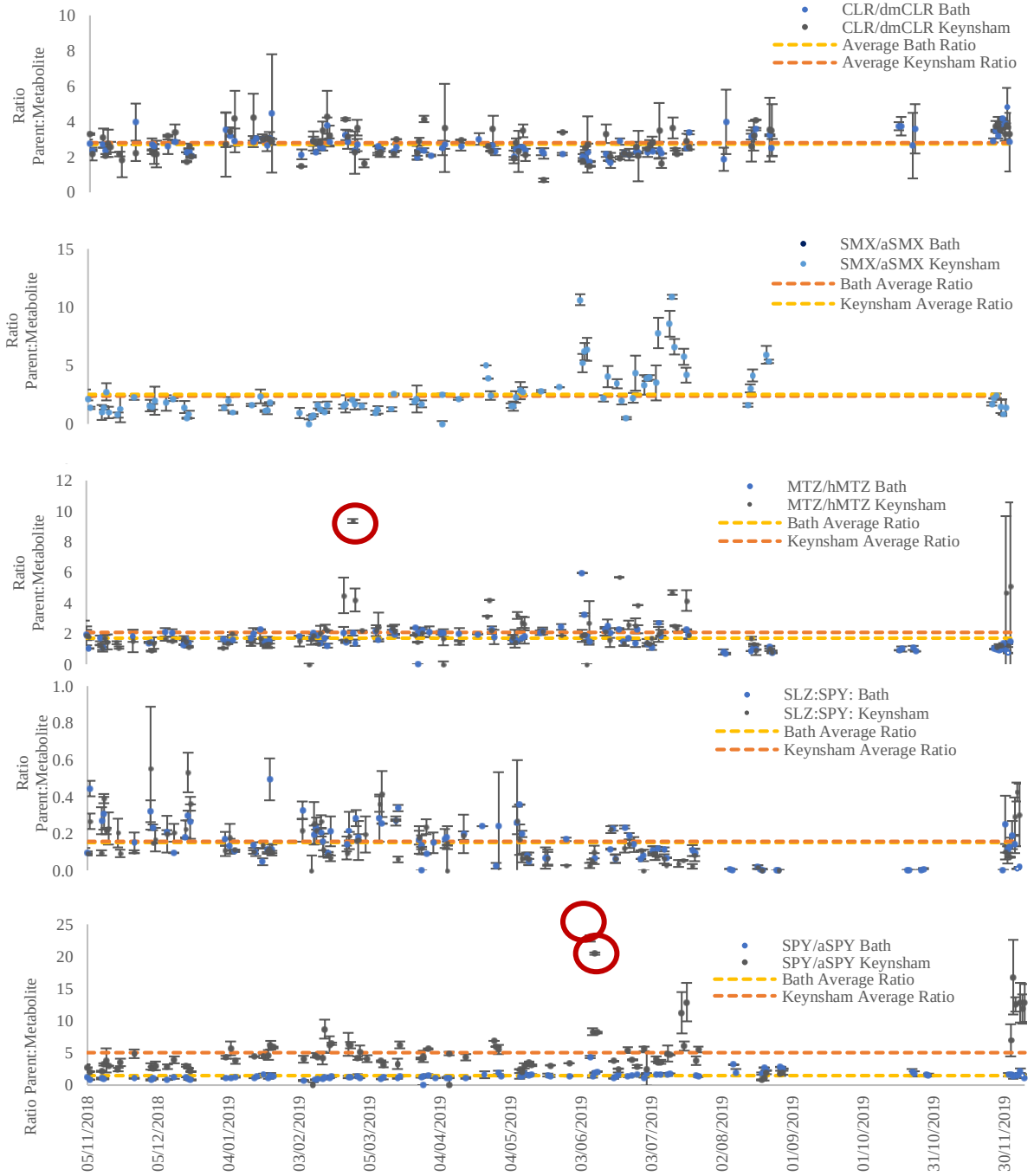
Examples:

Lamivudine (3TC)
Emtricitabine (FTC)
Ethambutol (EMB)
Bedaquiline (BDQ)
Isonicotinic acid (INa)
5-hydroxy-pyrazinoic acid (hPZA)

Antimicrobials in communities - a longitudinal study of two cities (down-the-drain disposal)



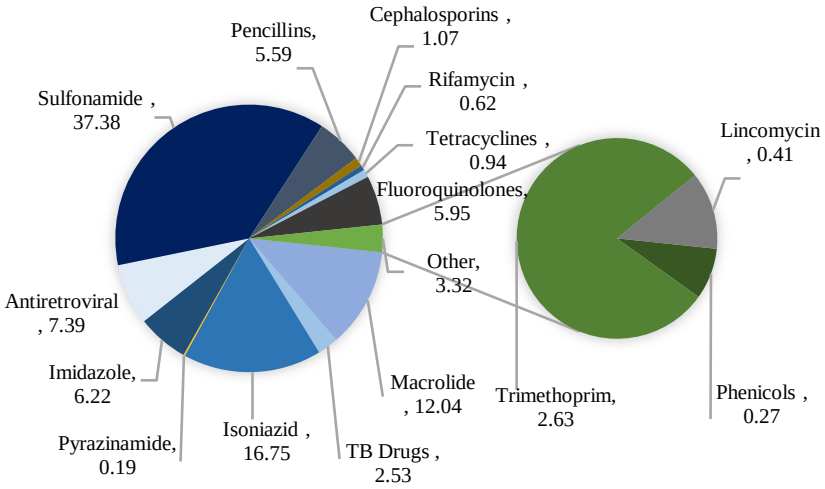
- Antimicrobials are disposed of down-the-drain.
- Due to the nature of AA prescribing (intermittent rather than continuous) as well as variable oral, intravenous or topical applications, it is more difficult to pinpoint all the disposal events.
- Education and awareness of the environmental risks of incorrect disposal is essential.



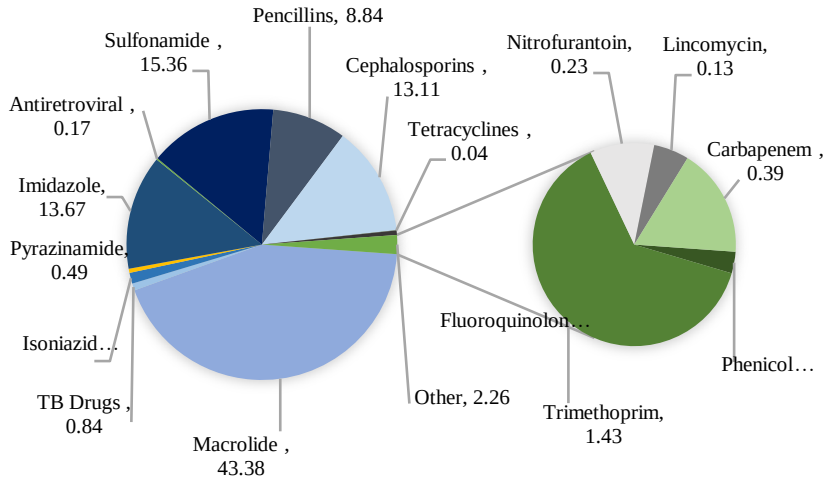
Sims et al. Journal of Hazardous Materials, 454 (2023) 131461

Average concentrations of antibiotics in hospital effluent and community wastewater compared with PNECs (Predicted No-Effect Concentrations)

AAs - Community wastewater (Bath WWTP influent)



AAs - Hospital wastewater



Antibiotics in both hospital and community wastewater exceed PNECs.

Hospital wastewater is an important consideration in AMR surveillance as could be high risk areas for AMR.

Bath Antimicrobials	Average Wastewater Concentration (ug/L) Hospital	Community	Predicted No-Effect Concentration (ug/L) PNEC-MIC	PNEC-ENV	Lowest PNEC
Chloramphenicol	0.18 ± 0.09	0.15 ± 0.17	8	N/A	8
Sulfamethoxazole	**1.47 ± 1.58**	0.46 ± 0.19	16	0.6	0.6
Azithromycin	**39.5 ± 41.56**	**0.31 ± 0.30**	0.25	0.02	0.02
Clarithromycin	**0.47 ± 0.32**	**0.72 ± 0.31**	0.25	0.08	0.08
Erythromycin	**2.20 ± 2.31**	0.06 ± 0.05	1	0.5	0.5
Ciprofloxacin	**0.93 ± 1.66**	**0.52 ± 0.24**	0.064	0.57	0.064
Ofloxacin	0.04 ± 0.05	0.04 ± 0.03	0.5 (levofloxacin)	10	0.5 (levofloxacin)
Amoxicillin	**11.13 ± 8.92**	-	0.25	N/A	0.25
Clindamycin	**0.27 ± 0.43**	0.04 ± 0.02	1	0.1	0.1
Metronidazole	**12.49 ± 3.40**	**0.23 ± 0.09**	0.125	N/A	0.125
Nitrofurantoin	**0.52 ± 0.51**	-	64	N/A	64
Oxytetracycline	0.05 ± 0.03	0.24 ± 0.16	0.5	18	0.5
Tetracycline	0.03 ± 0.01	0.13 ± 0.08	1	3.2	1
Ethambutol	0.07 ± 0.05	0.11 ± 0.12	2	N/A	2
Sulfadiazine	-	0.008 ± 0.007	N/A	13	13
Trimethoprim	**3.25 ± 2.76**	0.33 ± 0.12	0.5	100	0.5
Flucloxacillin	**5.66 ± 5.97**	**0.44 ± 0.23**			

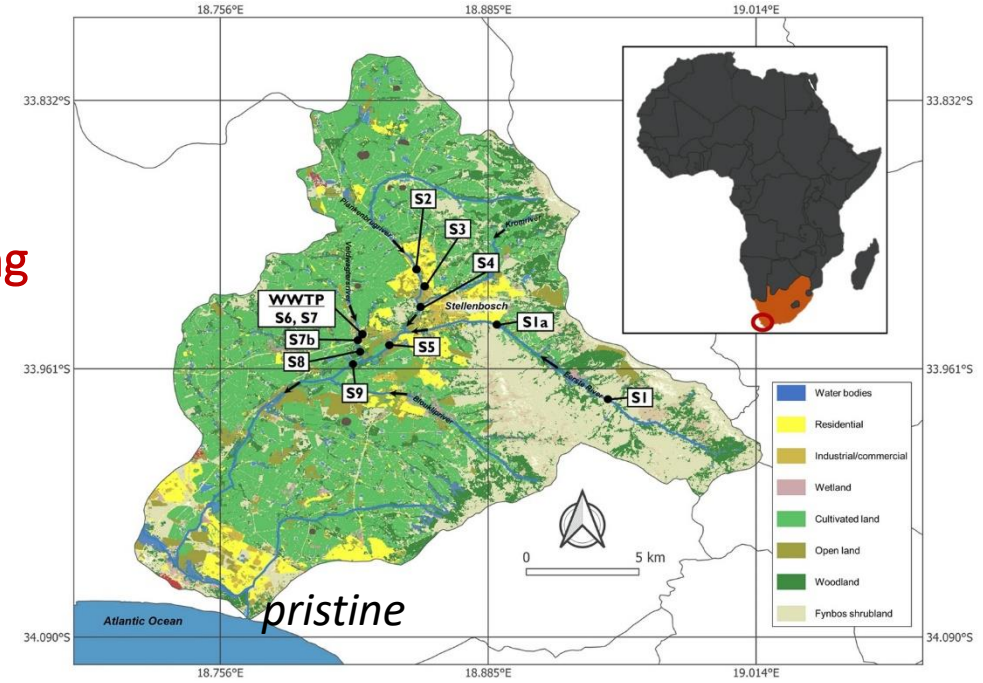
Sims et al. Environmental Pollution, 333 (2023) 122020

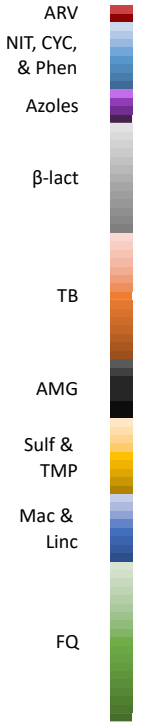
UNIVERSITY OF BATH

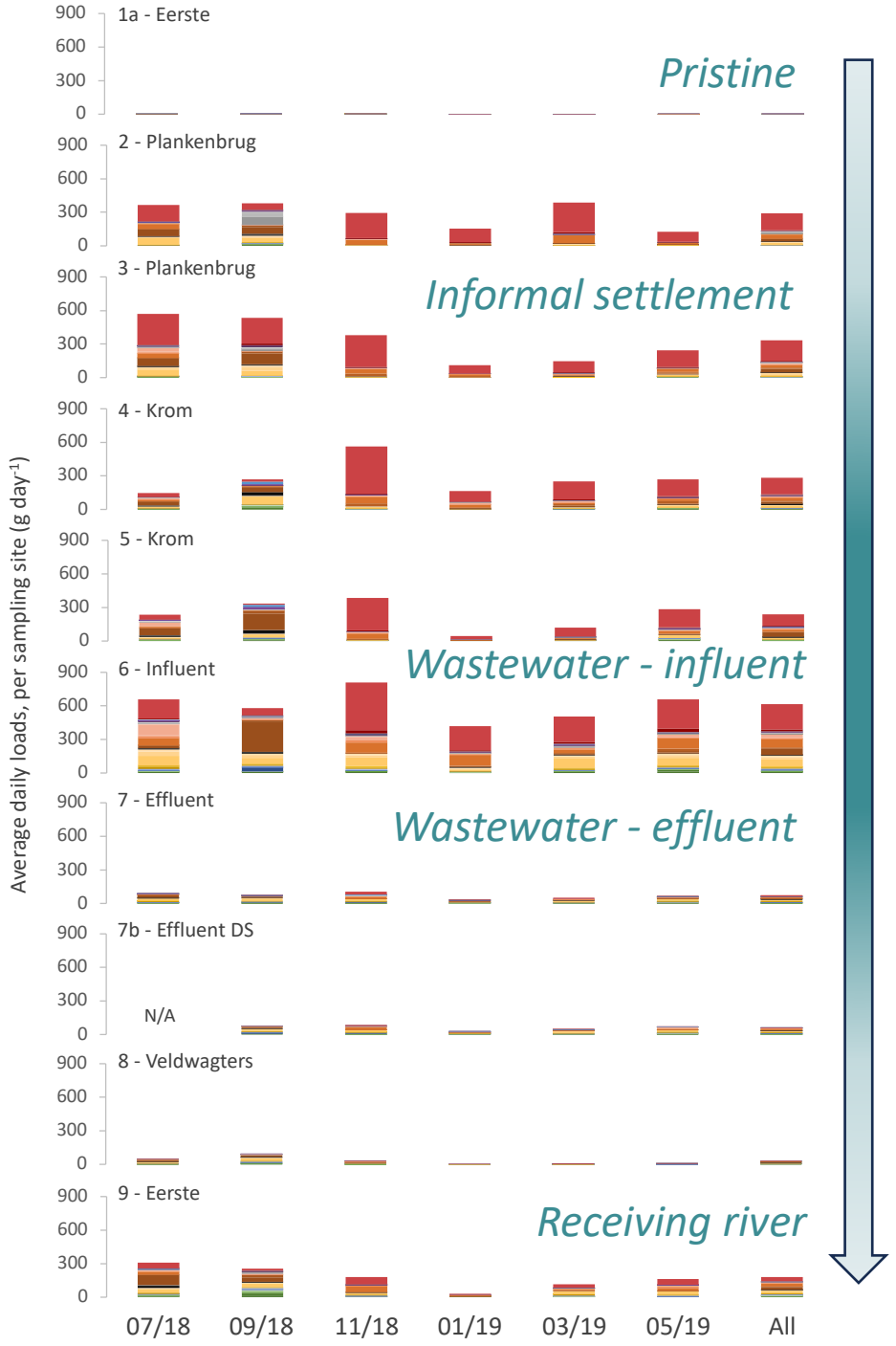
Wessex Water YTL GROUP

Antimicrobials usage globally

Case study:
Stellenbosch, SA
The River Eerste
1 year monitoring







1. WBE accounts for total drug mass in the region, independent of prescription access, compliance, or movement of people.
2. Much higher usage of antimicrobials in the informal settlement vs sewage connected city residents.
3. Comparing UK and SA prescription and WBE datasets indicates higher prevalence of macrolides usage in the UK vs antiretrovirals usage in SA.

Holton et al Environ International 164 (2022) 107227
Holton et al Journal of Hazardous Mat 436 (2022) 129001
Holton et al Water Research 240 (2023) 120110

UNIVERSITY OF BATH

UNIVERSITEIT iYUNIVESITHI STELLENBOSCH UNIVERSITY

ACKNOWLEDGMENTS

Environmental Chemistry @ Bath

NETWORKS/PROJECTS

FUNDERS