Mr Ben Harris

Honorary Lecturer
University of Otago

A/Professor David Holland

Clinical Head of the Infectious Diseases Service
Middlemore Hospital

Professor Jack Heinemann

Genetics and Molecular Biology
School of Biological Sciences
University of Canterbury

A/Professor Siouxsie Wiles

Microbiologist
Head of the Bioluminescent Superbugs Lab
University of Auckland

Dr Bryan Betty

General Practitioner
Wellington

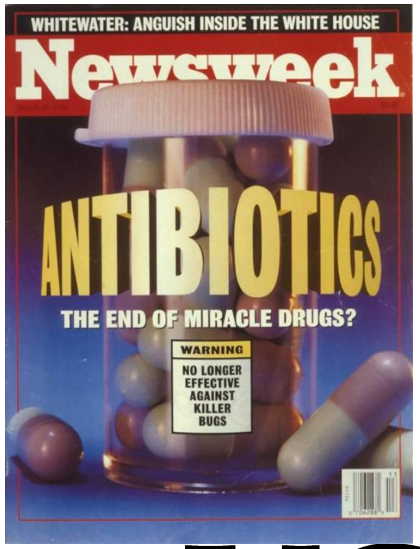
Sunday, August 11, 2019 (Room 9)

8:30 - 10:30 WS #147: Pharmac Session: Antimicrobial Resistance - Global Threat or Myth? (120mins, not repeated)

Environmental Sources of Antibiotic Resistance: implications for public safety

He taura whiri kotahi mai anō te kopunga tai no i te pu au

From the source to the mouth of the sea all things are joined together as one



Jack Heinemann
Centre for Integrated Research in Biosafety
School of Biological Sciences

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

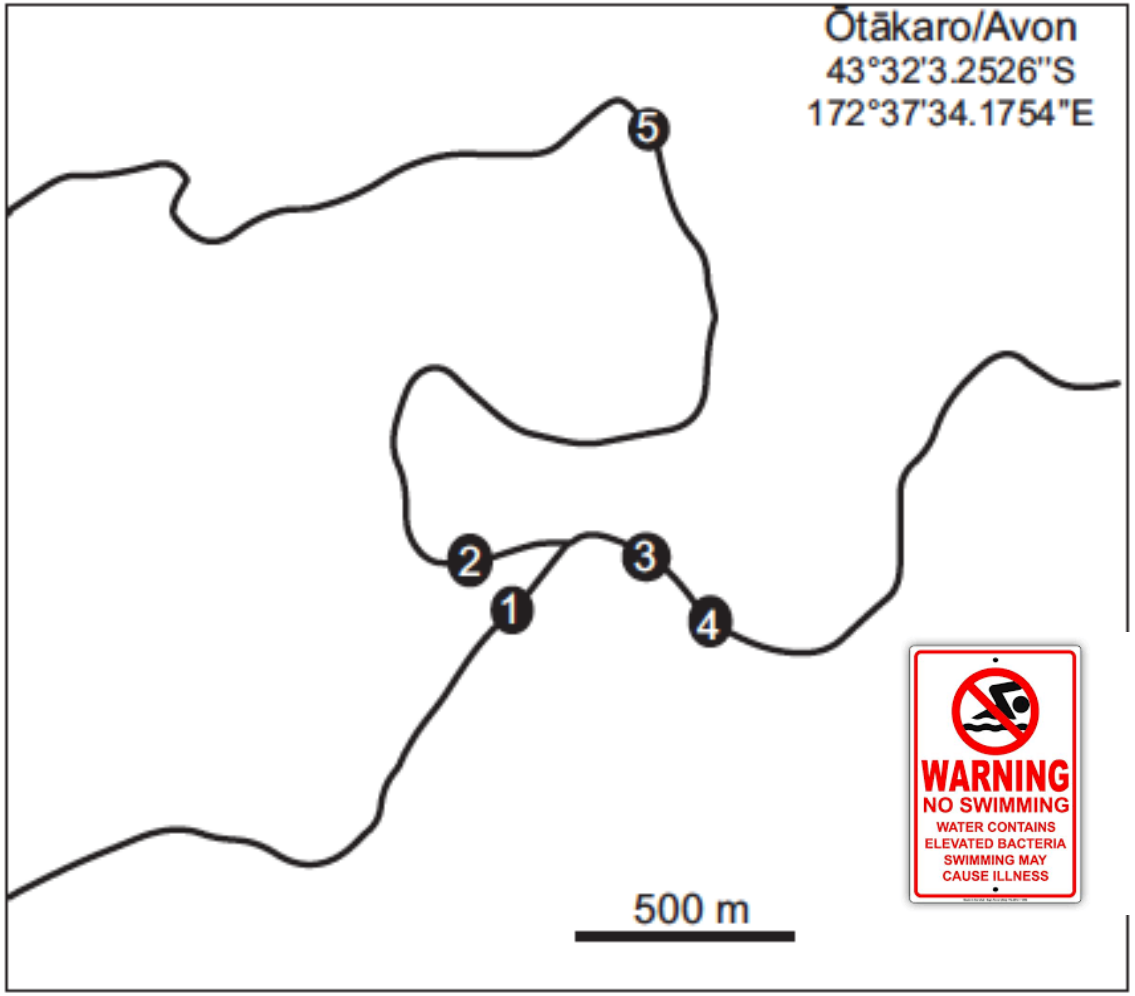
Unavoidable exposures

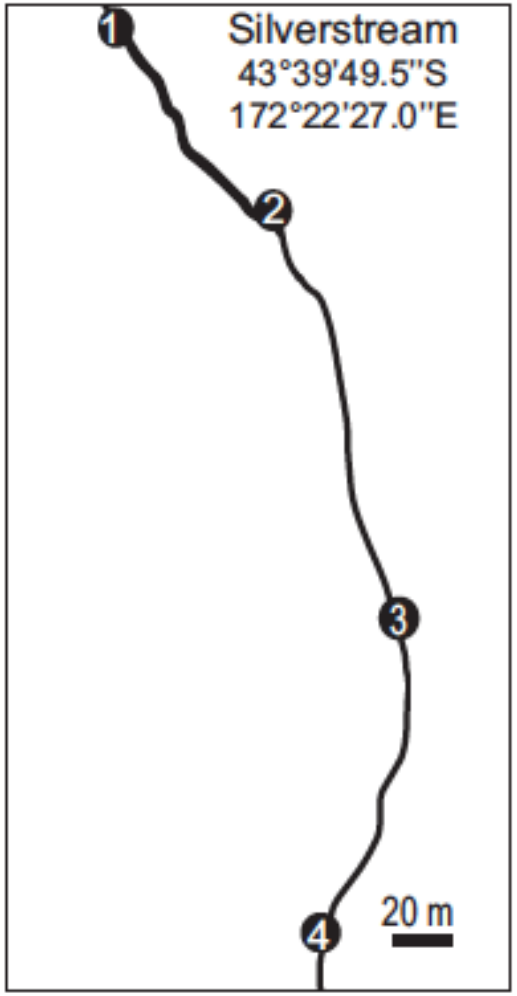
Havelock North Bore 1

Heathcote River Christchurch

Hurricane Ike storm surge

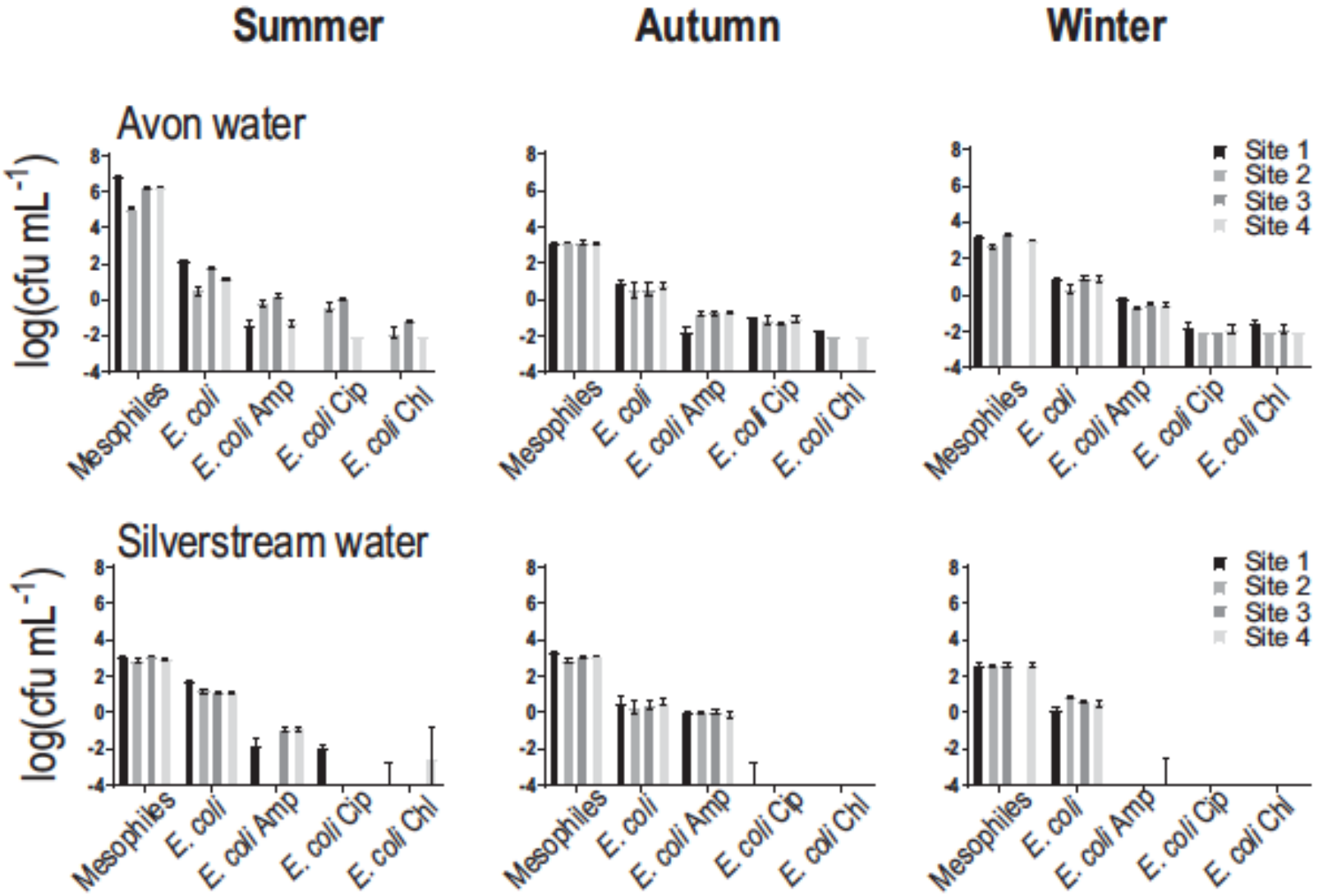
Canterbury rivers





FEMS Microbiology Letters, 366, 2019, fnz104
doi: 10.1093/femsle/fnz104

Microbiology of water



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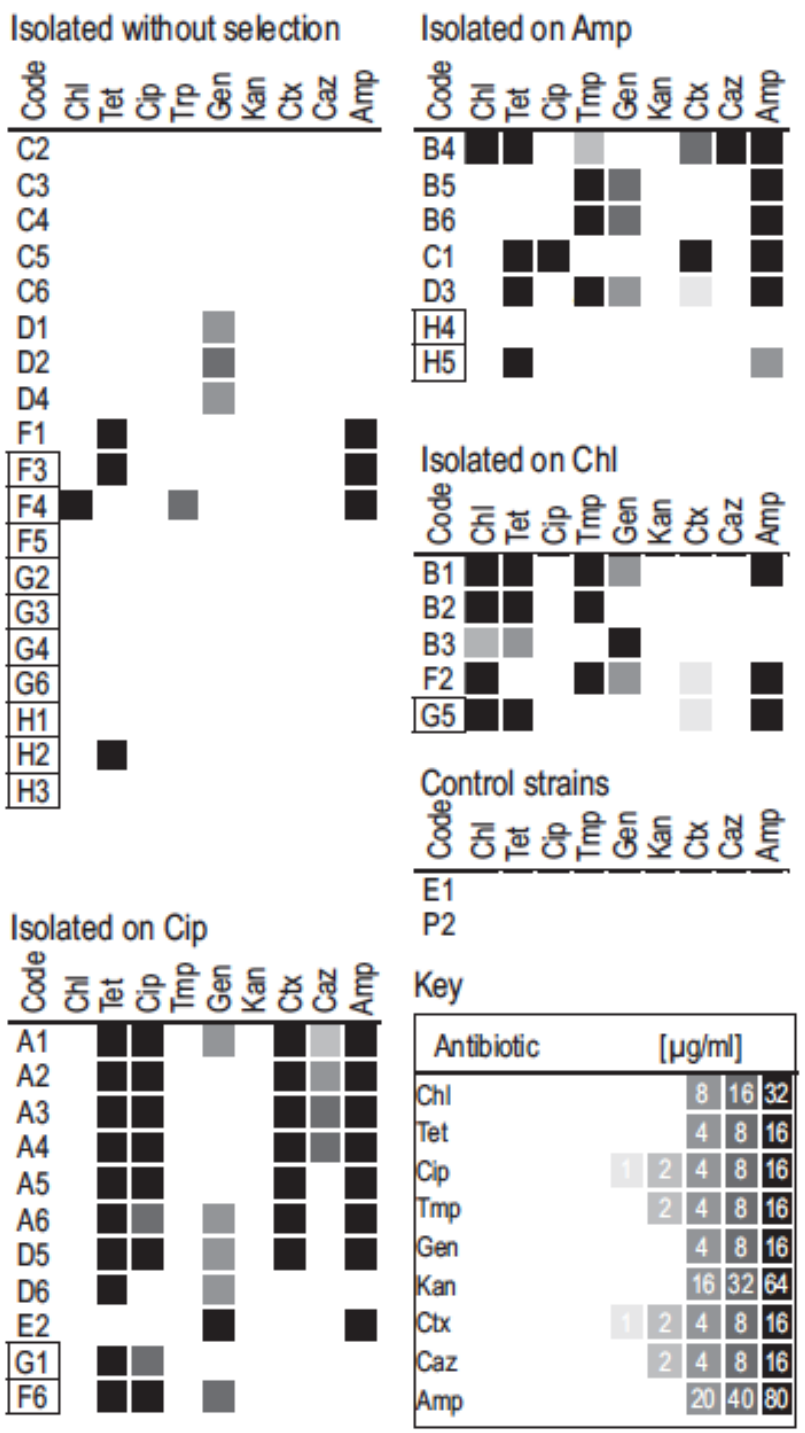


Frequency of multi-resistance

high frequencies of MDR

high MICs in MDR strains

MICs

FEMS Microbiology Letters, 366, 2019, fnz104
doi: 10.1093/femsle/fnz104

CIP MIC

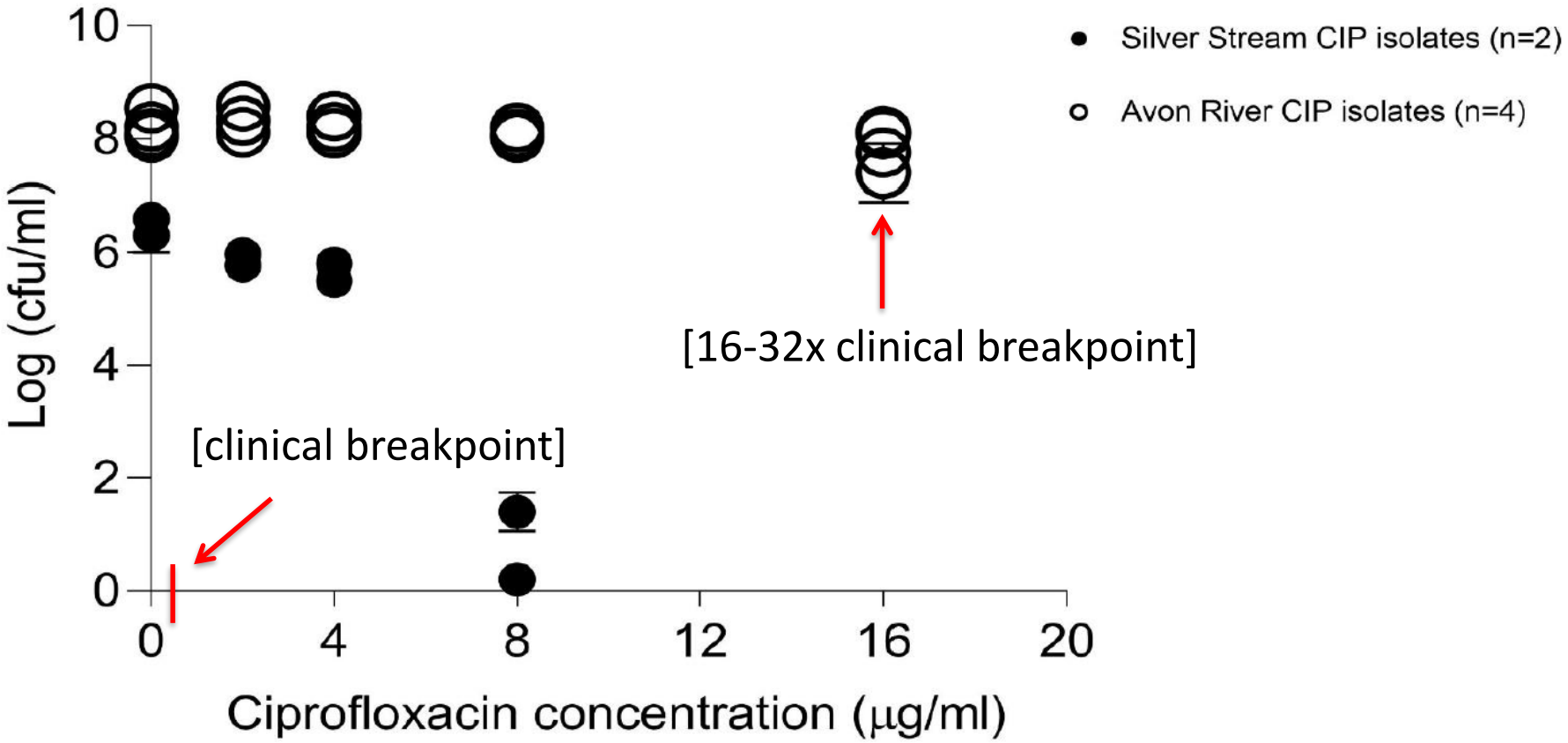


Figure 3.2. Dose response curve of ciprofloxacin resistant *E. coli* from Avon River (opened dot) and Silver Stream (closed dot). Dose curve is reported as the log-transformed CFU/mL count ± SEM (n = 4). This curve was used to determine the difference in the ciprofloxacin resistant *E. coli* from the two rivers.

Transmissible resistance

Table 2. ESBL and conjugation.

Strain Code	A1	A2	A3	A4	A5	A6	B4	C1	D5
ESBL (Ctx^R/Caz^R)	+/+	+/+	+/+	+/+	+/+	+/+	–/–	+/+	+/–
Conjugative transfer of Ctx^R/Caz^R	+/–	+/–	+/+	–/–	–/–	+/–	–/–	+/–	+/–
Conjugative transfer of other AB^R	–	–	Nal	–	–	–	–	–	–

Antibiotic concentrations were Cip (4 μg mL^{-1}), tetracycline (16 μg mL^{-1}), Amp (80 μg mL^{-1}), Chl (32 μg mL^{-1}), gentamicin (4 μg mL^{-1}), trimethoprim (2 μg mL^{-1}), Caz (8 μg mL^{-1}), Ctx (8 μg mL^{-1}), Nal (20 μg mL^{-1}). +: ESBL or conjugation detected; –: no ESBL or conjugation observed; Nal: nalidixic acid; AB: antibiotic.

FEMS Microbiology Letters, 366, 2019, fnz104
doi: 10.1093/femsle/fnz104

Why antibiotic resistance?

Because we use them: agriculture.

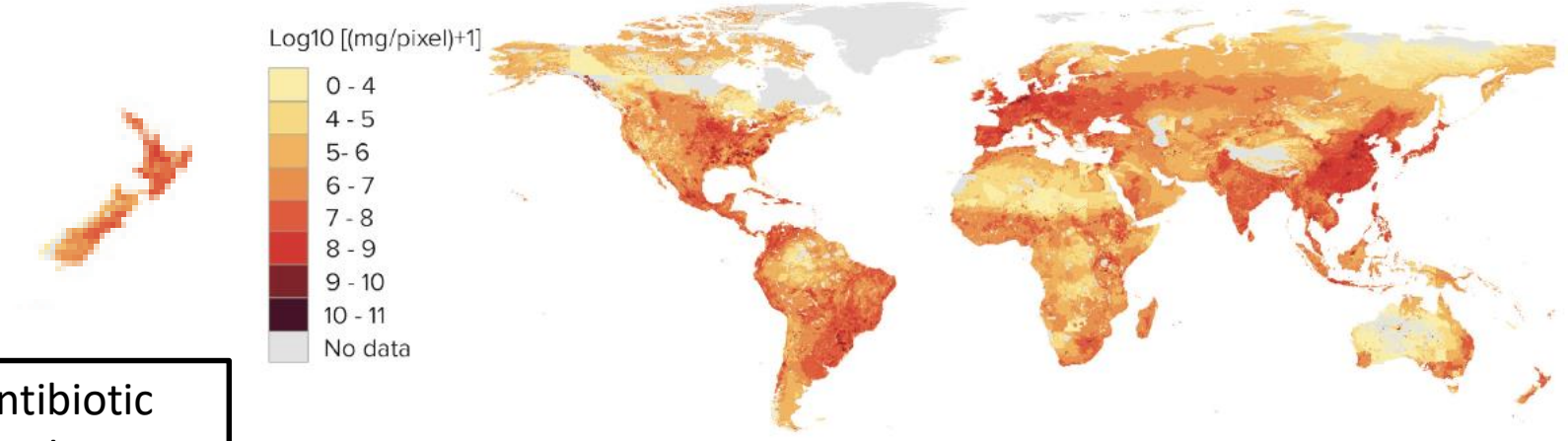


FIGURE 3-1: Global antibiotic consumption in livestock (milligrams per 10 km² pixels) 2010

Source: Van Boeckel et al. 2015

- >80% of antibiotic administered is excreted
- >MIC concentrations found in manure
- unintended antibiotic use in horticulture greater than intended because of manure fertilizers

Why antibiotic resistance?

Because we use them: medicine.

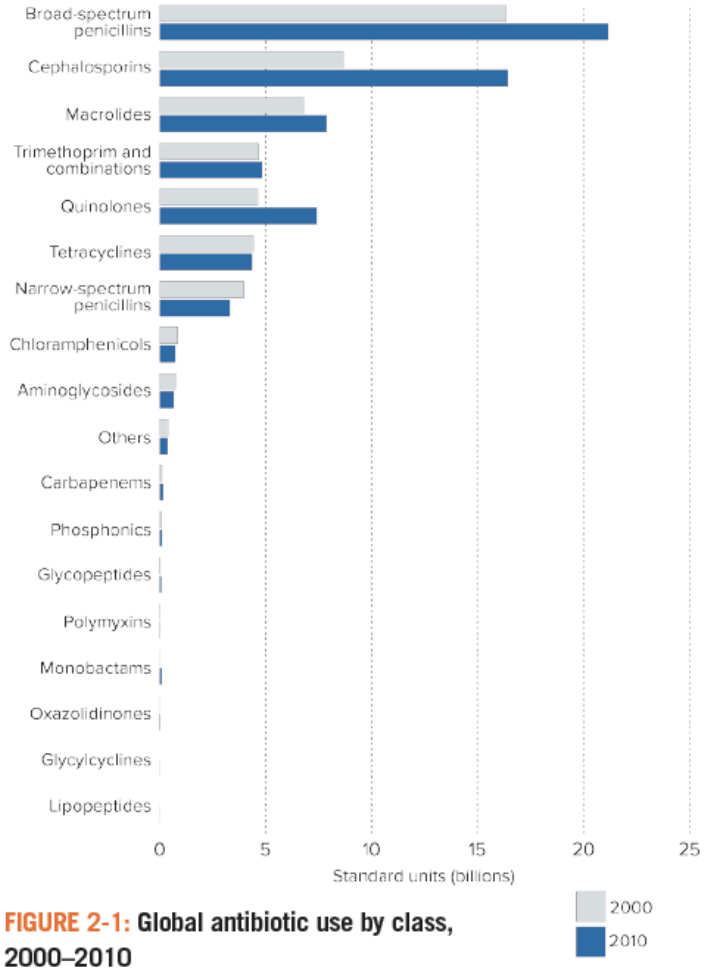


FIGURE 2-1: Global antibiotic use by class, 2000–2010

Van Boeckel et al. 2014 (adapted; based on IMS MIDAS)

10 ppb or less of antibacterial drugs, pesticides and veterinary drugs could increase antibacterial resistance in bacteria.
Kleiner et al 2007

Example of scale of pesticide use

635,029,318 kg of glyphosate was used worldwide

Table 1. Herbicide use by sector in millions of kilograms* of active ingredient.

Active ingredient	United States	
	Agriculture	Other**
glyphosate	127	6
2,4-D	16	6
atrazine	31	not reported
pendimethalin	5	3
dicamba	2	1

* Based on mid range of estimates for 2012.

**Home and garden combined with government and industry.

Source: (24) Swanson et al., 2014; US Geological Survey, 2012

A chemically intensive world

The Guardian
8 April 2019

Pesticides and antibiotics polluting streams across Europe

Wildlife and human health are threatened say scientists as Syngenta accepts 'undeniable demand' for change

▲ Jorge Casado collects a water sample from a stream. Photograph: Jonathan Findalen/Greenpeace

Pesticides and antibiotics are polluting streams across Europe, a study has found. Scientists say the contamination is dangerous for wildlife and may increase the development of drug-resistant microbes.

Urban

antibiotics

pesticide

Golden Bay residents "livid" over glyphosate sprayed on beachfront and rec park during school holidays – Stuff.co.nz

Table 1. Drugs Used in the Treatment of Bordetellosis[3,6–10]

Drug	*Canine Dosage (mg/kg)[a]*	*Feline Dosage (mg/kg)[a]*
Antibiotics		
Amikacin	15–20 q24h IV, IM, SC	15–20 q24h IV, IM, SC
Amoxicillin–clavulanate	12.5–25 q12h	12.5 q12h
Azithromycin	3.3 q24h for 3 days	5–10 q24–48h
Chloramphenicol	25–50 q8h	10–20 q12h
Doxycycline	5–10 q12–24h	5–10 q12–24h
Enrofloxacin	5–20 q24h	2.5–5 q24h
Gentamicin	4–8 q24h IV, IM, SC	4–8 q24h IV, IM, SC
Marbofloxacin	2.75–5.5 q24h	2.75–5.5 q24h
Tetracycline	15–20 q8h	15–20 q8h
Trimethoprim–sulfadiazine	15–30 q12–24h	15–30 q12–24h
Supportive Medications		
Aminophylline	5–11 q8–12h	4–6.6 q8–12h
Butorphanol	0.05 SC or 0.5–1 PO q6–12h	Not used
Codeine	0.1–0.3 q4–6h	Not used
Hydrocodone	0.25 q6–12h	Not used
Prednisone	0.5–1 q24h	1–2 q24h
Theophylline	5–11 q6–8h	4 q8–12h
Theophylline extended release	10 q24h	12 q24h

[a]Unless indicated otherwise, route of administration is PO.

Impact Evidence

Pesticides

ecure | https://www.radionz.co.nz/news/country/342401/study-finds-500-percent-rise-in-weedkiller-in-human-urine

| Center for... AVNavigator Learn RIng Activity Arlo Smart Home S... Mobile Wi-Fi AnswerGarden » ....

COUNTRY / RURAL

Study finds 500% rise in weedkiller in human urine*

12:50 pm on 26 October 2017

Share this

Alexa Cook, Rural Reporter
@alexacook_ alexa.cook@radionz.co.nz

A study showing a 500 percent rise in human exposure to glyphosate proves people ingest it when eating Roundup-sprayed crops, the lead researcher says.

Photo: 123RF

*[low]

Link to pesticides

We have found a link between pesticides and antibiotic resistance.

Common pesticides linked to antibiotic resistance

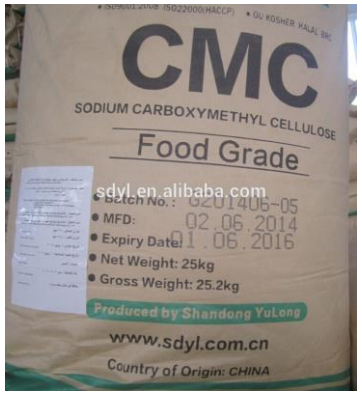
People exposed to herbicides require more antibiotics to kill bacteria, according to new research published in mBio

▲ Exposure to both herbicides and antibiotics at the same time has been linked to antibiotic resistance. Photograph: BSIP SA/Alamy

Antibiotics and herbicides, as it turns out, don't mix. At least that's the conclusion of a study published today in mBio, the peer-reviewed journal of

One of our studies as reported by the Guardian

Exposures to common ingredients in herbicide formulations and food induce antibiotic resistance



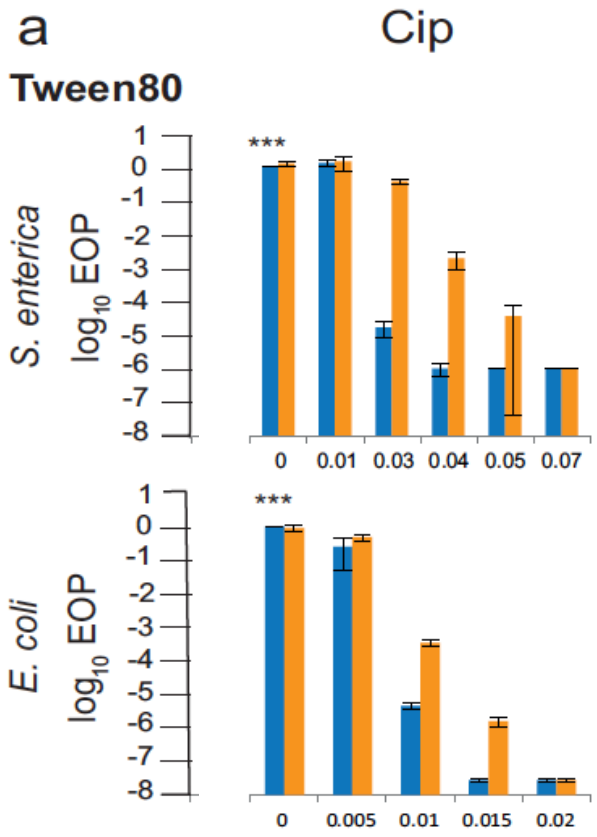
Δ MIC: 0-300%

Table 2. Fold-change shift in antibiotic effectiveness following exposure to herbicide ingredients

	Amp	Cam	Cip	Kan	Tet
S. enterica					
Active ingredients					
Dicamba	1.3 (1500)	7 (1500)	3.5 (1500)	0 (1500)*	2.7 (1500)
2,4-D	NS	2.5 (600)	1.8 (5000)	4 (6000)*	2.2 (500)
Glyphosate	1.8 (3000)	1.5 (3000)*	2 (200)	5 (200)	1.4 (3000)*
Surfactants					
Tween80	NS	2.3	1.2	1.8	1.8
CMC	1.7	NS	NS	1.5	1.4
E. coli					
Surfactants					
Tween80	NS	1.6	0	1.5*	NS
CMC	1.25*	NS	NS	4	NS

Microbiology. 2017 Nov 17. doi: 10.1099/mic.0.000573.

Tween80 used in ciprofloxacin formulations



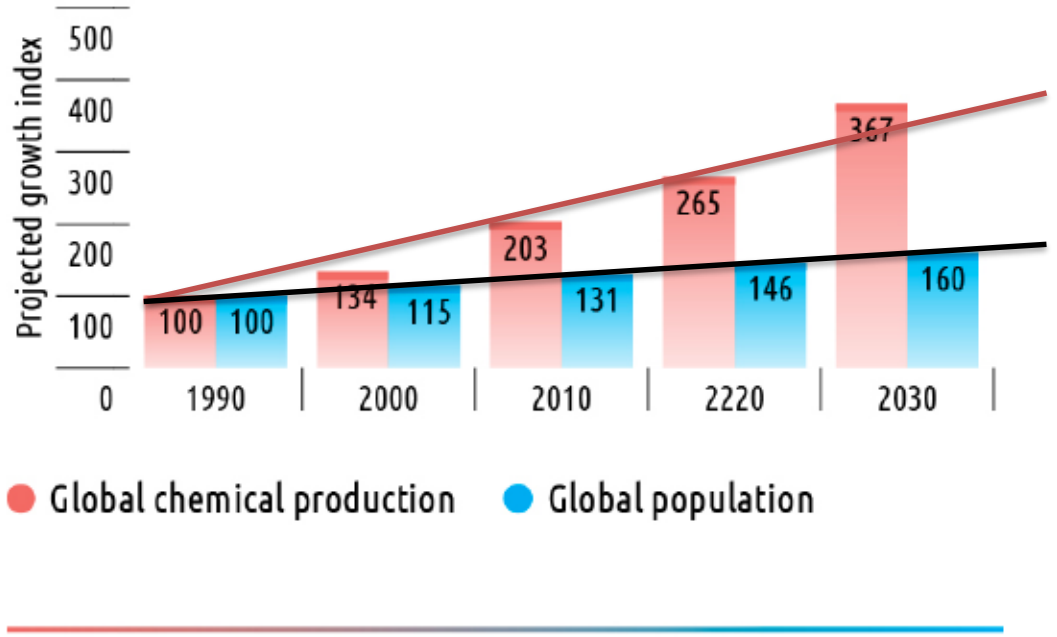
MIC: increases 250%

MIC: increases 75%

Microbiology. 2017 Nov 17. doi: 10.1099/mic.0.000573.

New exposures expected to increase

Figure 2: Growth of basic chemical production capacity vs. population growth (based on Cayuela and Hagan 2019 and UN Department of Economic and Social Affairs 2018)



UNEP/EA.4/21

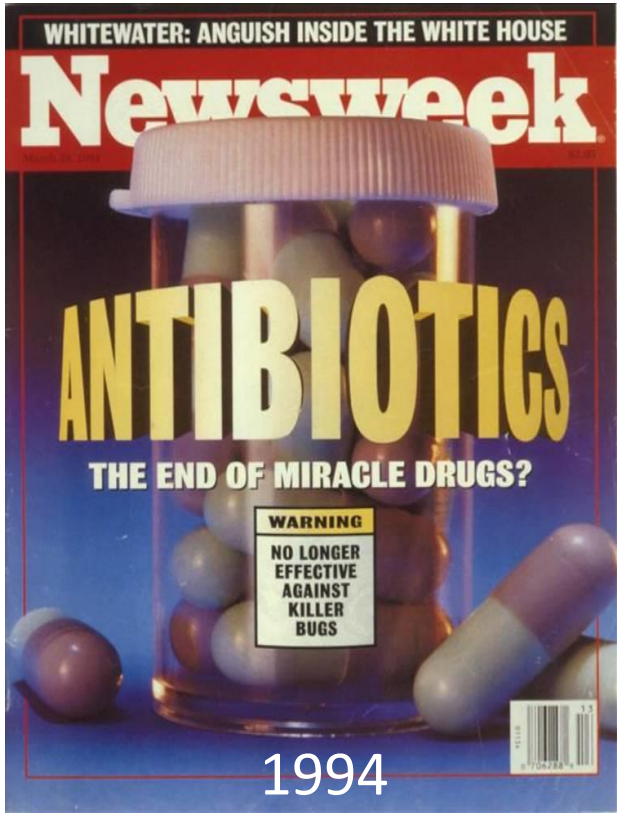
Take home messages

Environment a place where antibiotic resistance thrives

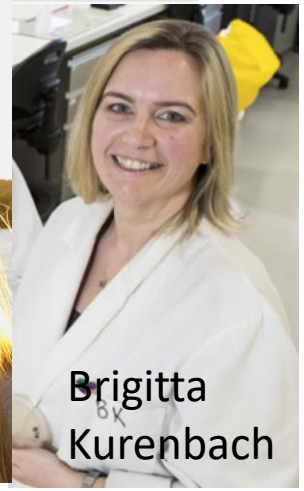
Combating resistance requires more than moderating use of antibiotics in medicine

Factors leading to resistance include chemical exposures to non-antibiotics too

Water safety assessments based on coliform counts may not be adequate



Acknowledgements



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William Godsoe, Lincoln U
Brent Gilpin, ESR Ltd.

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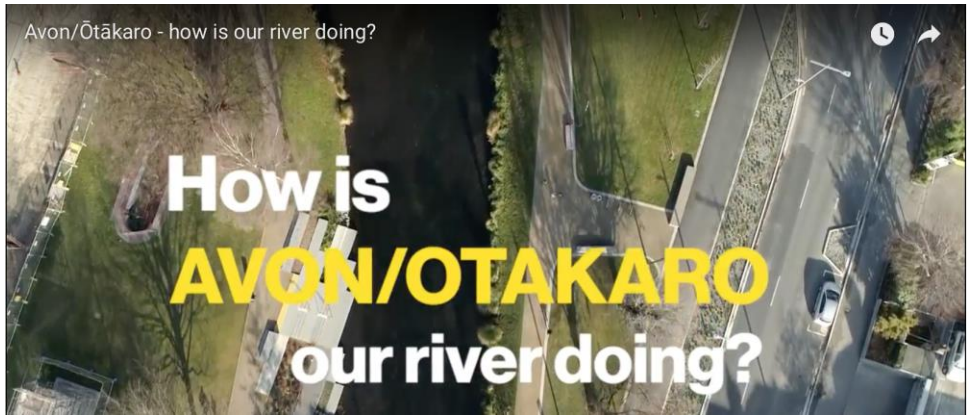
University of Canterbury

Future work



Continue sampling over time, over longer range of Avon River.

Test potential link between agrichemical use and resistance.

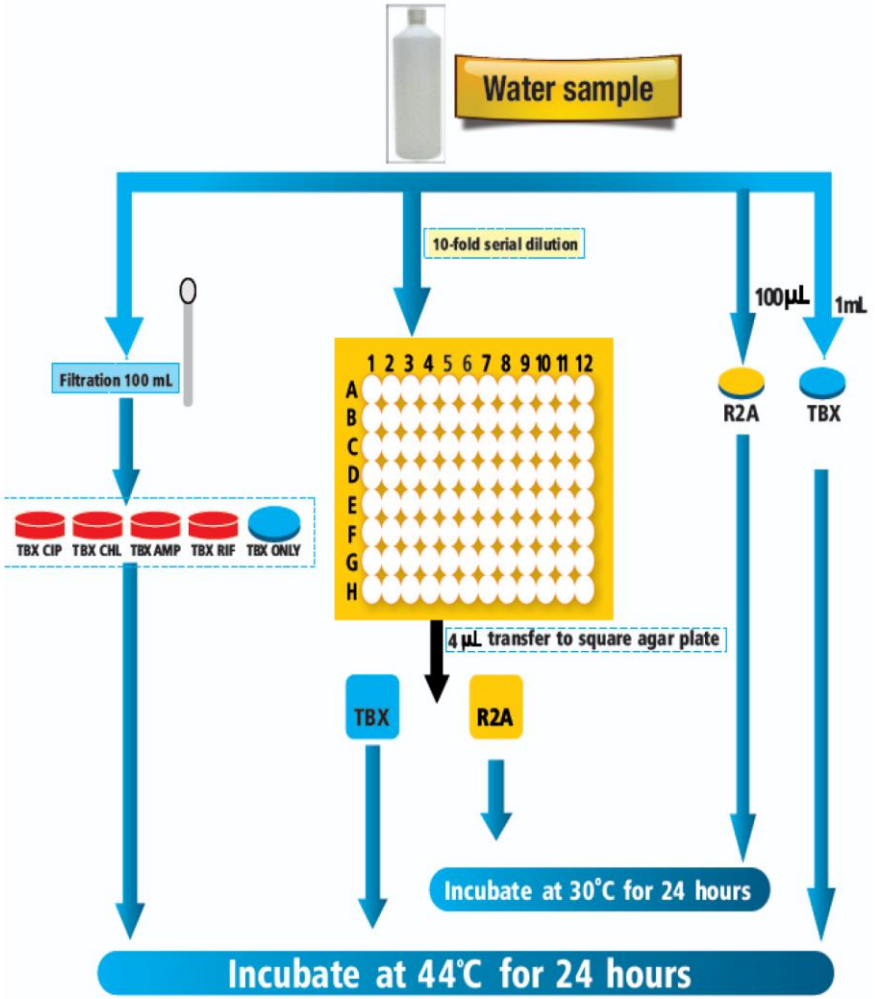
In collaboration with Brent Gilpin (ESR Christchurch) and Amy Osborne (UC), complete WGS genotyping.

Characterise potential for resistance HGT.

Along with Matt Stott (UC), expand coverage region to nation wide.

Continue to work with ecologists to look for remediation strategies.

Methods


Water sample
10-fold serial dilution
100µL
1mL
Filtration 100 mL
1 2 3 4 5 6 7 8 9 10 11 12
A
B
C
D
E
F
G
H
R2A
TBX
TBX CIP
TBX CHL
TBX AMP
TBX RIF
TBX ONLY
4 µL transfer to square agar plate
TBX
R2A
Incubate at 30°C for 24 hours
Incubate at 44°C for 24 hours

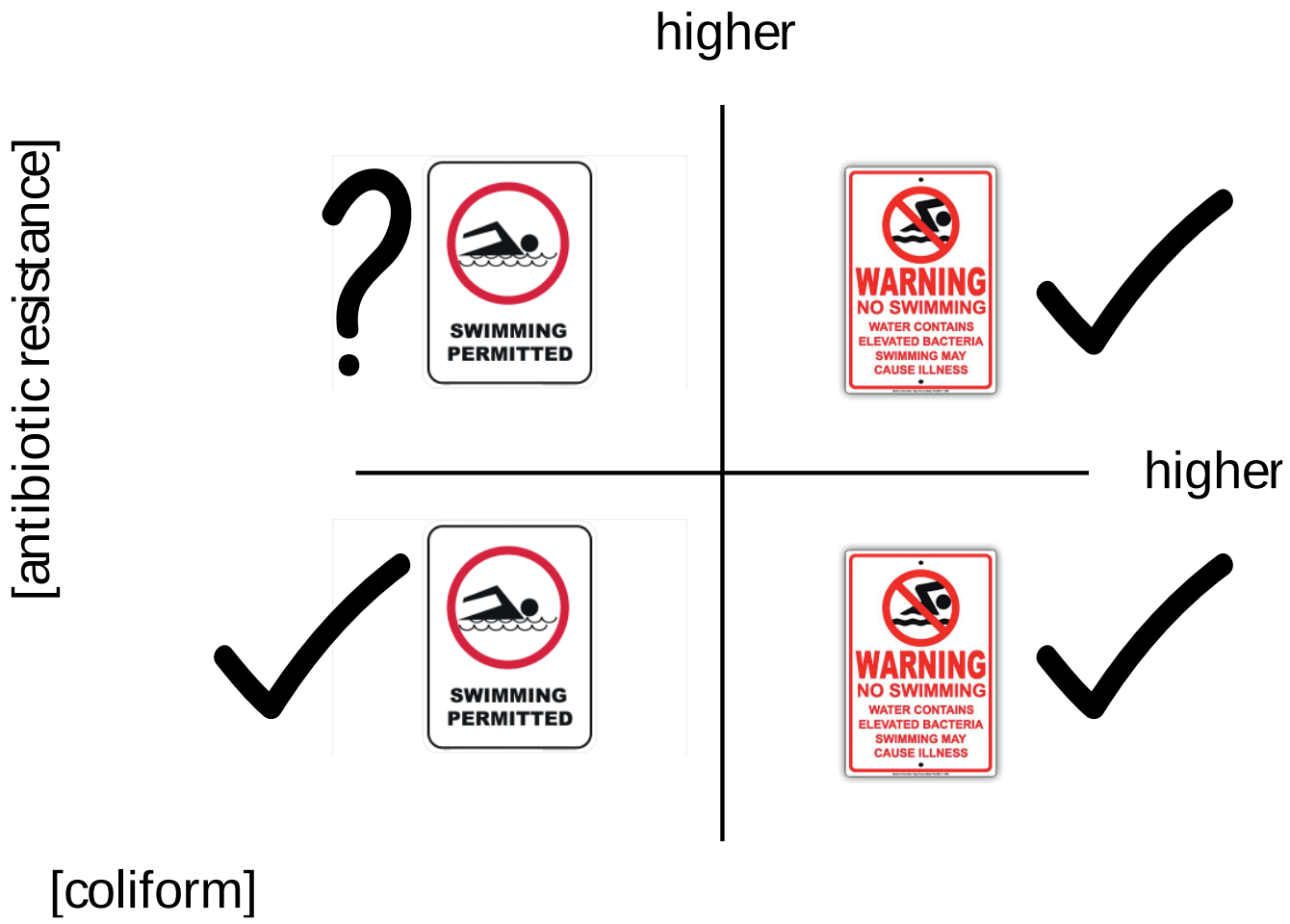
A chemically intensive world

- 140,000 new chemicals and pesticides are <70 years old
- universal human exposure to the 5,000 produced in greatest volume

Exposure analysis is limited because of eg,:

1. trade secrets hiding ingredients
2. unknown contaminants in products
3. accumulation of degradation/synthesis (eg, from cooking, microbial conversion) products
4. residues from packaging

Current Regulations



What is antibiotic resistance?

The rise in concentration of antibiotic required to kill target bacteria.

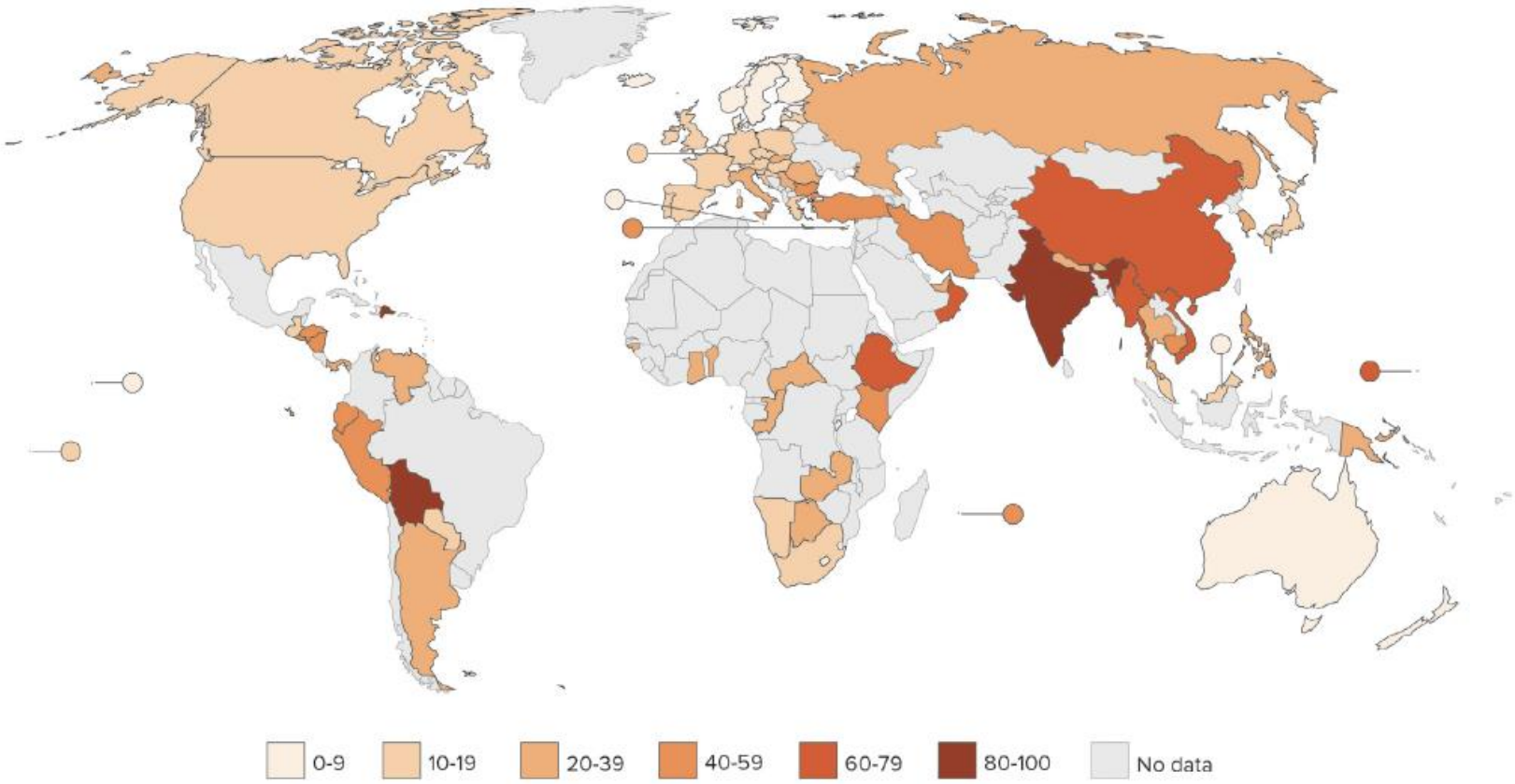
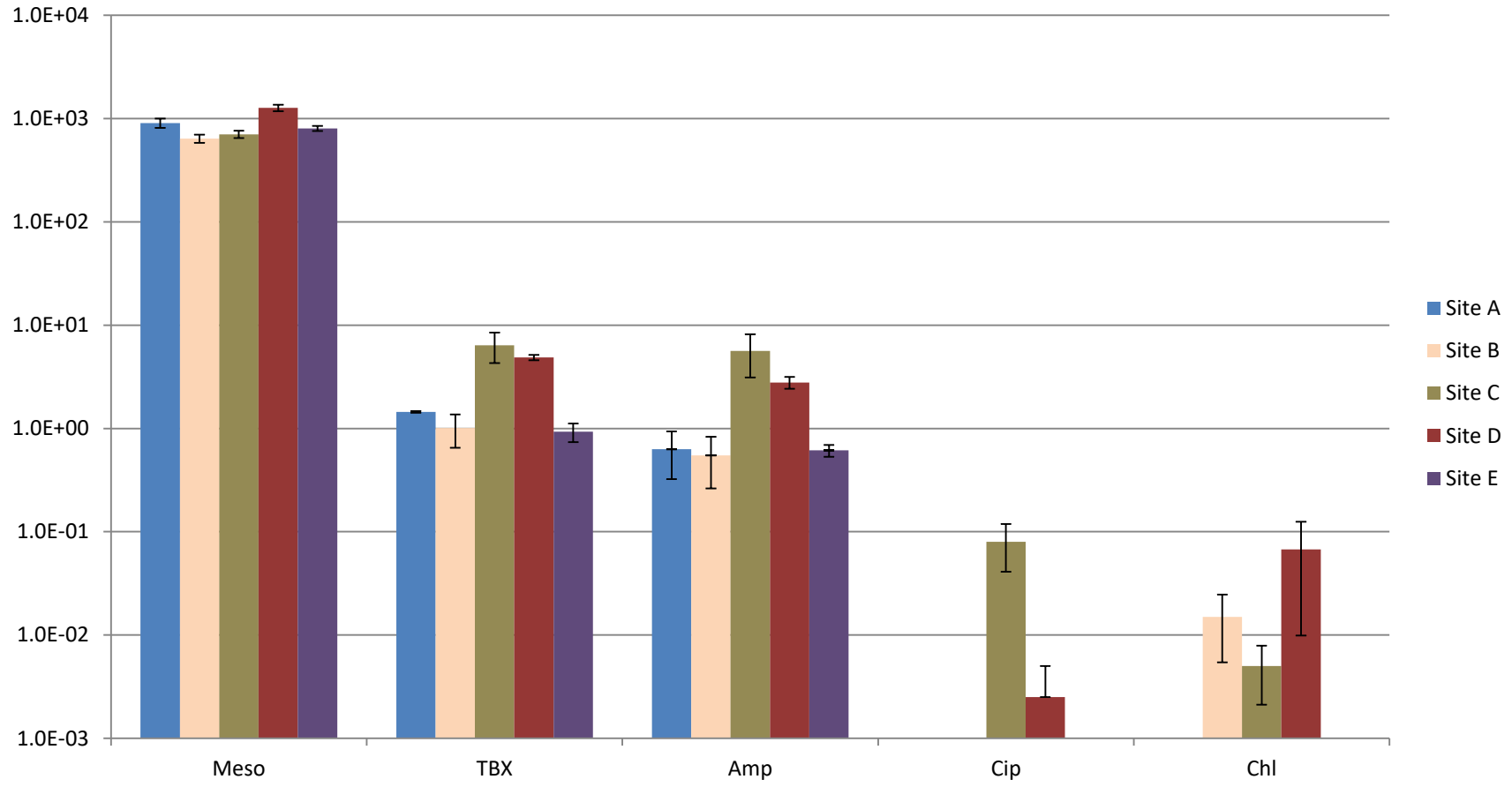


FIGURE 1-2: Percentage of extended-spectrum beta-lactamase producing *Escherichia coli, by country (most recent year, 2011–2014)**

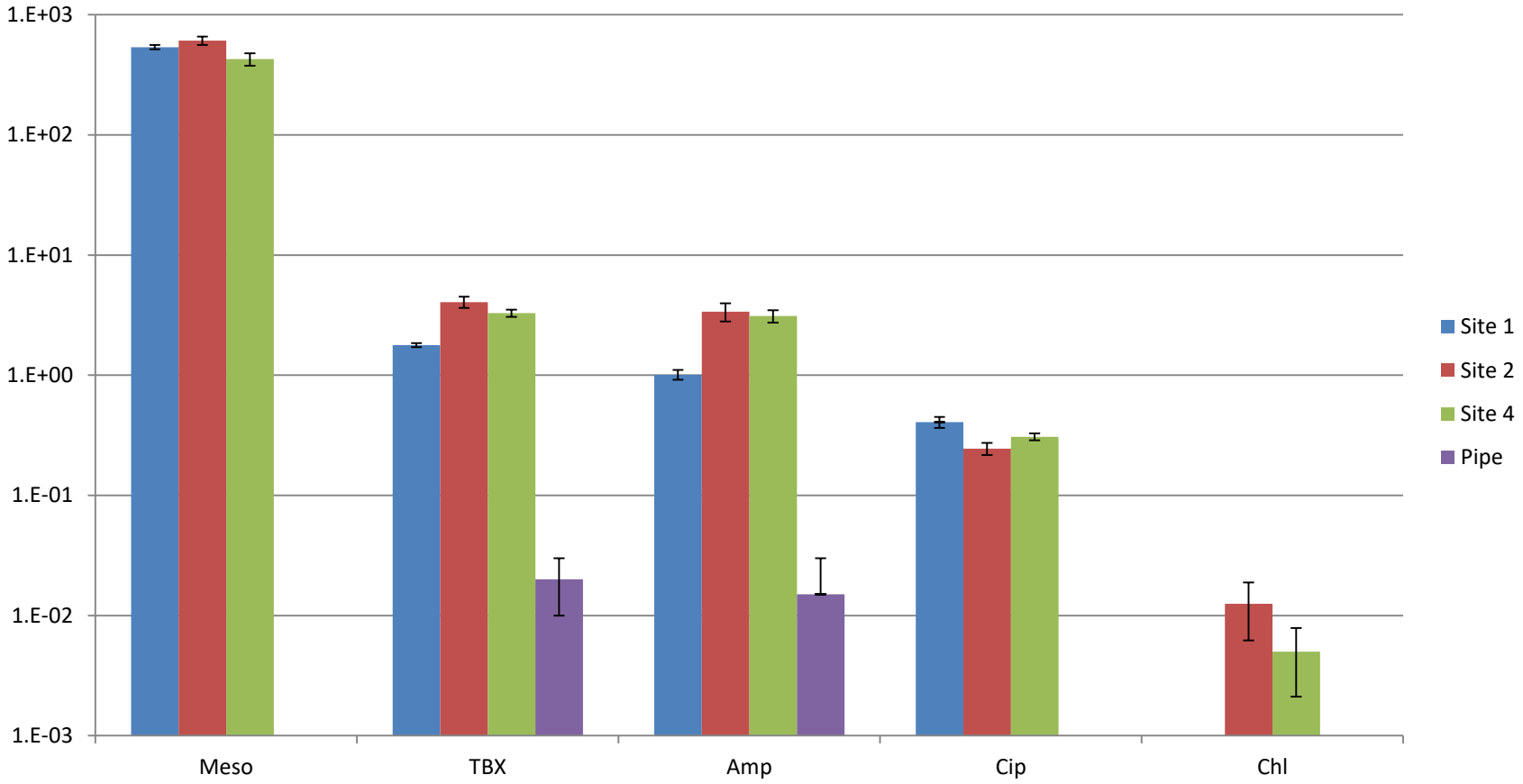
Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Avon @ Harper Ave



Site A: harper Ave = Site 0
Site B: behind golf club house
Site C: Ricc Stream by the bridge on Riccarton Ave
Site D: Addington Brook close to Riccarton Ave
Site E: Boat Shed

Riccarton stream above Hagely



Site 1: Picton Reserve Entry

Site 2: Hagley South bridge

Site 4: Ricc Stream by the bridge on Riccarton Ave Hagley north

Pipe: drainage pipe in Picton Reserve by site 1