Otago Spotlight Series

Infectious Disease Research

Opportunities for Infectious Disease Research in New Zealand: a Biomedical Perspective

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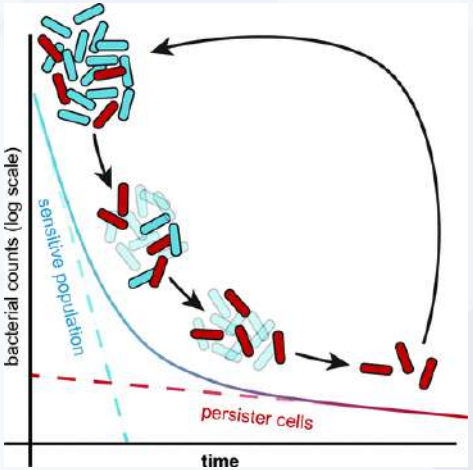
https://micro.otago.ac.nz/our-people/teaching-research-and-support/greg-cook/

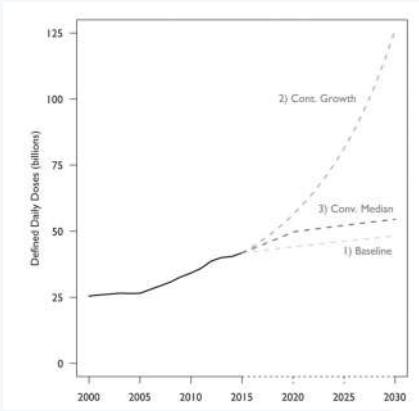
To keep pace with AMR

1. We need to discover and develop new antimicrobials – fast acting drugs with a new MOA

2. Deeper scientific understanding of how antimicrobials actually work – make our old drugs more effective. What about drug combinations?



3. We need to reduce antimicrobial consumption – humans or animals?




Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

Eili Y. Klein, Thomas P. Van Boeckel, Elena M. Martinez, Suraj Pant, Sumanth Gandra, Simon A. Levin, Herman Goossens, and Ramanan Laxminarayan

PNAS

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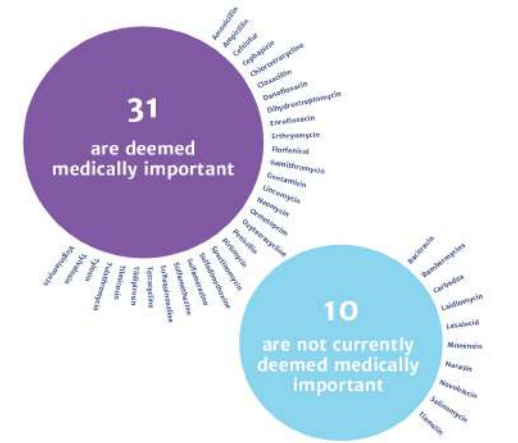
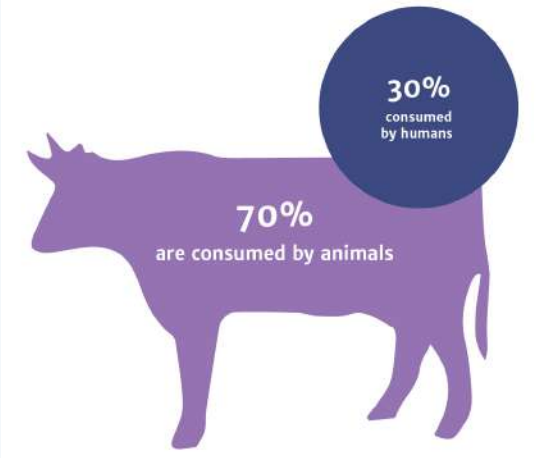
How can we reduce antimicrobial consumption?



Most antibiotics used in animals are medically important for humans

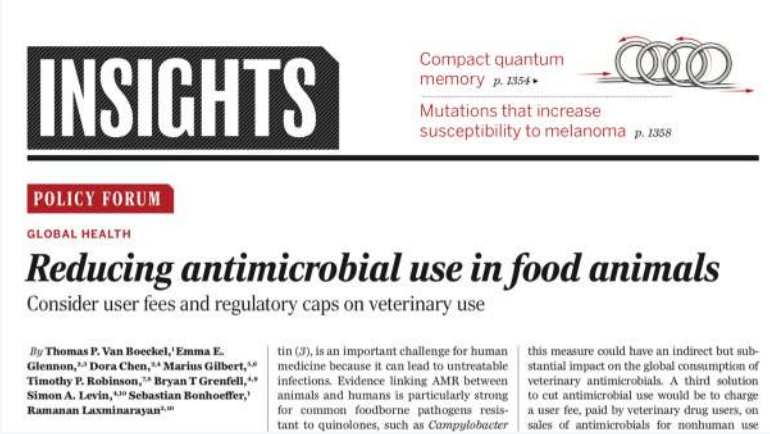


Animals (118 mg/kg) versus humans (130 mg/kg)

Table 4. Estimated antimicrobial use (mg active ingredient per kg biomass) in food-producing animals (including horses) compared with use for humans in 30 countries during 2012.

Country	Antimicrobial use for animals	Antimicrobial use for humans	Ratio of human: animal use
Australia	43.7 [a]	~148 [b]	3.39
Austria	54.9	70.2	1.28
Belgium	161.1	162.6	1.01
Bulgaria	98.9	109.4	1.11
Canada	~250	127.6	0.51
Cyprus	396.5	144.4	0.36
Czech Republic	79.8	84.1	1.05
Denmark	44.1	136.2	3.09
Estonia	56.0	70.1	1.25
Finland	23.8	140.1	5.89
France	99.1	175.8	1.77
Germany	204.8	66.9	0.33
Hungary	245.5	67.5	0.27
Iceland	5.9	125.9	21.34
Ireland	58.0	144.9	2.50
Italy	341.0	167.5	0.49
Latvia	44.1	88.8	2.01
Lithuania	39.4	102.0	2.59
Luxemburg	43.6	153.1	3.51
Netherlands	74.9	56.7	0.76
New Zealand	9.4	120.9	12.86
Norway	3.8	141.6	37.26
Poland	132.2	99.0	0.75
Portugal	157.1	133.1	0.85
Slovakia	43.2	115.9	2.68
Slovenia	37.0	108.3	2.93
Spain	242.0	108.6	0.45
Sweden	13.5	126.2	9.35
United States of America	266.2	166.3	0.62
United Kingdom	66.3	104.2	1.57

[a] 2010 data is the most recent published (Anonymous 2014e).
[b] Extrapolated from OECD Heath Statistics (Anonymous 2015e).



INSIGHTS

Compact quantum memory p. 1354 ▸

Mutations that increase susceptibility to melanoma p. 1358

POLICY FORUM

GLOBAL HEALTH

Reducing antimicrobial use in food animals

Consider user fees and regulatory caps on veterinary use

By Thomas P. Van Boeckel,[1] Emma E. Glennon,[2,3] Dora Chen,[3,4] Marius Gilbert,[5,6] Timothy P. Robinson,[7,8] Bryan T Grenfell,[4,9] Simon A. Levin,[3,10] Sebastian Bonhoeffer,[1] Ramanan Laxminarayan[4,10]

tin (3), is an important challenge for human medicine because it can lead to untreatable infections. Evidence linking AMR between animals and humans is particularly strong for common foodborne pathogens resistant to quinolones, such as *Campylobacter*

this measure could have an indirect but substantial impact on the global consumption of veterinary antimicrobials. A third solution to cut antimicrobial use would be to charge a user fee, paid by veterinary drug users, on sales of antimicrobials for nonhuman use

- Cap antimicrobial use (8-318 mg/kg – 50 mg/kg)
- Reduce meat intake 260g/day to 40g/day = reduce antimicrobial use by 66%
- Global user fee 50% increase in cost = 31% reduction in use

1350 29 SEPTEMBER 2017 • VOL 357 ISSUE 6358

Global trends in antimicrobial use in food animals

Thomas P. Van Boeckel[a,1], Charles Brower[b], Marius Gilbert[c,d], Bryan T. Grenfell[a,e,f], Simon A. Levin[a,g,h,1], Timothy P. Robinson[i], Aude Teillant[a,e], and Ramanan Laxminarayan[b,e,j,1]

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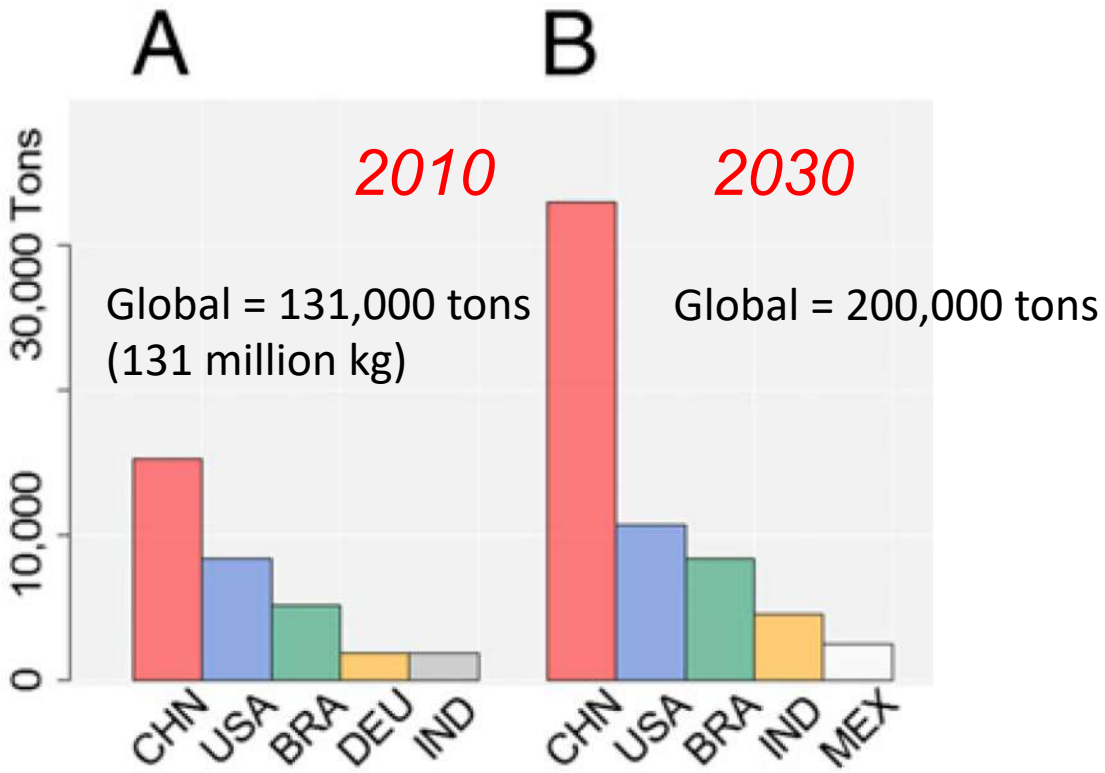
antimicrobial consumption in food animal production



Antimicrobial consumption will rise by 67% by 2030, and nearly double in Brazil, Russia, India, China, and South Africa.

Antimicrobial use in animals plays a role in the emergence, amplification, persistence and transfer of resistance determinants to other ecosystems

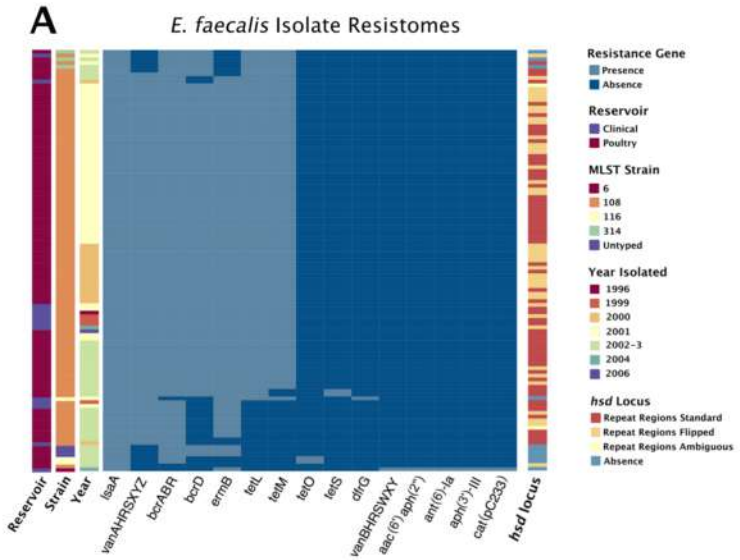
147 individual poultry farms

TABLE 1. Antimicrobial resistance profiles in enterococci isolated from broiler fecal samples

Supplier[a]	No. of isolates tested[a]	Number (%) resistant			
		Vancomycin	Avilamycin[c]	Erythromycin	Bacitracin[c]
A	185	12 (6.5)	34 (18.4)	145 (78.4)	183 (98.9)
A[b]	104	4 (3.9)	19 (18.3)	77 (74)	103 (99)
B	56	1 (1.8)	2 (3.6)	10 (17.9)	55 (98.2)
C	37	5 (13.5)	2 (5.4)	15 (40.5)	36 (97.3)
Total	382	22 (5.8)	57 (14.9)	247 (64.7)	377 (98.7)

[a] Enterococci were isolated using m-*Enterococcus* agar lacking antimicrobials.
[b] Samples taken from supplier A, with broilers currently on an antimicrobial-free feeding regime.
[c] See Materials and Methods for breakpoints used.

Rachel Darnell



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0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.1.204–210.2003

A Clonal Lineage of VanA-Type *Enterococcus faecalis* Predominates in Vancomycin-Resistant Enterococci Isolated in New Zealand

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Received 25 July 2002/Returned for modification 13 September 2002/Accepted 24 October 2002

JOURNAL OF CLINICAL MICROBIOLOGY, July 2003, p. 3331–3333 Vol. 41, No. 7
0095-1137/03/$08.00+0 DOI: 10.1128/JCM.41.7.3331–3333.2003

Characterization of a Vancomycin-Resistant *Enterococcus faecalis* (VREF) Isolate from a Dog with Mastitis: Further Evidence of a Clonal Lineage of VREF in New Zealand

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Department of Microbiology, Otago School of Medical Sciences, University of Otago, Dunedin, New Zealand

Received 5 February 2003/Returned for modification 23 March 2003/Accepted 26 April 2003

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0099-2240/04/$08.00+0 DOI: 10.1128/AEM.70.10.5764–5768.2004

Persistence of Vancomycin-Resistant Enterococci in New Zealand Broilers after Discontinuation of Avoparcin Use

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Received 25 February 2004/Accepted 7 June 2004

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0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.10.3743–3748.2004

Acquired Bacitracin Resistance in *Enterococcus faecalis* Is Mediated by an ABC Transporter and a Novel Regulatory Protein, BcrR

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Received 26 January 2004/Returned for modification 19 April 2004/Accepted 24 May 2004

frontiers in Microbiology

REVIEW
published: 03 August 2016
doi: 10.3389/fmicb.2016.01196

CrossMark

Veterinary Medicine Needs New Green Antimicrobial Drugs

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[1] Ecole Nationale Vétérinaire de Toulouse, Institut National de la Recherche Agronomique, TOXALIM, Université de Toulouse, Toulouse, France, [2] Comparative Biomedical Sciences, The Royal Veterinary College, Hatfield, UK

1. Break the *link* between human and veterinary medicine (one resistome)

2. Safeguard against the exchange of AMR determinants between animals-plants and humans – narrow spectrum agents

Green antimicrobials needed to fight environmental pathogens

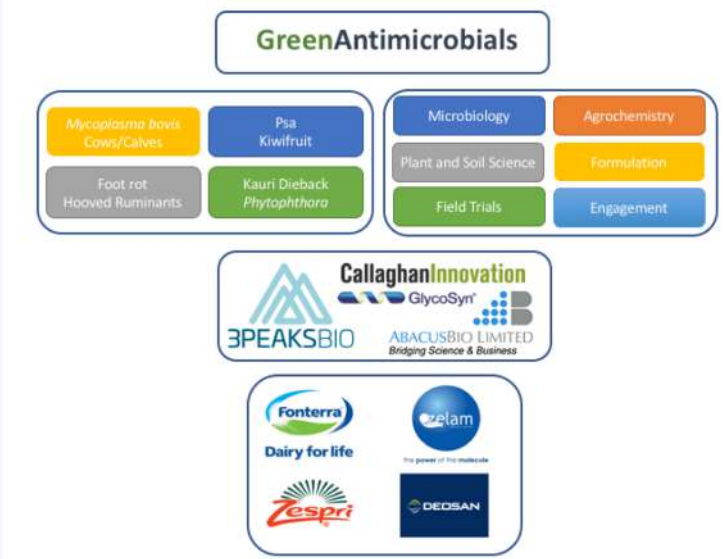
Kauri dieback

PSA Kiwifruit

MASTITIS
Mycoplasma bovis
Streptococcus uberis
Staphylococcus aureus
Escherichia coli

FOOT ROT
Fusobacterium necrophorum

Liver abscesses



Greenhouse gas emissions

NO_2^-
NO
N_2O
CH_4

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DSM

BRIGHT SCIENCE. BRIGHTER LIVING.

2015

PNAS

An inhibitor persistently decreased enteric methane emission from dairy cows with no negative effect on milk production

Alexander N. Hristov[a,1], Joonpyo Oh[b], Fabio Giallongo[a], Tyler W. Frederick[a], Michael T. Harper[a], Holley L. Weeks[a], Antonio F. Branco[b], Peter J. Moate[c], Matthew H. Deighton[c], S. Richard O. Williams[c], Maik Kindermann[d], and Stephane Duval[e]

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2016

PNAS

Mode of action uncovered for the specific reduction of methane emissions from ruminants by the small molecule 3-nitrooxypropanol

Evert C. Duin[a], Tristan Wagner[b], Seigo Shima[b], Divya Prakash[a,1], Bryan Cronin[a], David R. Yáñez-Ruiz[c], Stephane Duval[d], Robert Rümbeli[e], René T. Stemmler[e], Rudolf Kurt Thauer[b,2], and Maik Kindermann[e,2]

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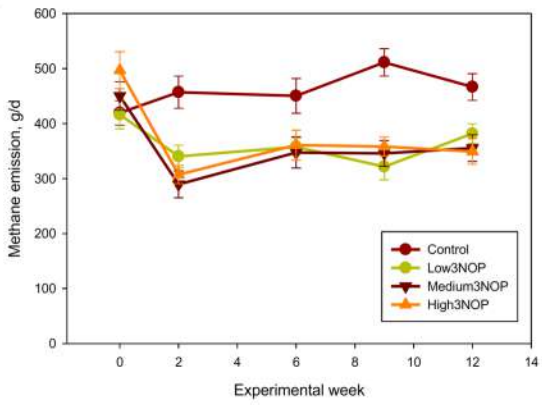
3-nitrooxypropanol methyl coenzyme-M (CoM) reductase

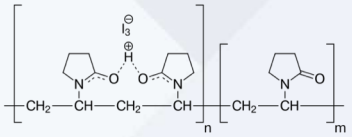
60 mg/kg dry matter (daily): 30% inhibition

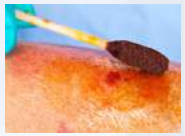


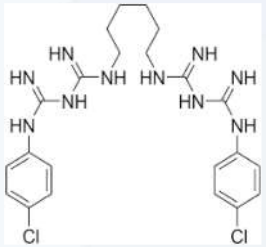
Development of next-generation sanitisers for the control of bovine mastitis in the dairy industry

- Inflammation of the mammary gland in dairy cows
- Significant economic burden – estimated $280 million/year
- Negatively impacts animal welfare, global issue, **$US35B problem**
- Topical santisers (teat sprays-dips) are vital tools in preventing bovine mastitis, applied post milking – global AMR Controlled using teat sprays (active ingredients are chlorhexidine and iodine) – very cheap

Mastitis: the need for new sanitisers – prevention rather than cure







- Chlorhexidine (CHX) and iodine (povidone-iodine) are on WHO list of essential medicines
- Both used in hospitals as skin/surgical sanitisers
- CHX identified by MPI as a strategic risk to NZ exports – residues in milk products, not on CODEX *Alimentarius*
- Rising tolerance to chlorhexidine in *Staphylococcus aureus* hospital isolates
- Co-selection of other antimicrobial resistances

Overall goals:

1. Develop a new active/sanitiser that is able to synergise with chlorhexidine

Reduces the amount of chlorhexidine in existing teat sprays, thereby reducing the residue risk in milk

2. Develop a stand alone product, with a new active (sanitizer) that negates the use of the essential medicine chlorhexidine/iodine agricultural settings

Our Team

AGMARDT
ENABLING TRANSFORMATIONAL INNOVATION

(2015-16)

DEOSAN

MINISTRY OF BUSINESS, INNOVATION & EMPLOYMENT
HIKINA WHAKATUTUKI

(2016-19)

DEOSAN




Microbiology


Chemistry


Formulation


Innovation


Essie Van Zuylen
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Nichaela Harbison-Price
PhD student

Research Students

UiO : Universitetet i Oslo

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Passion | Innovation | Evolution

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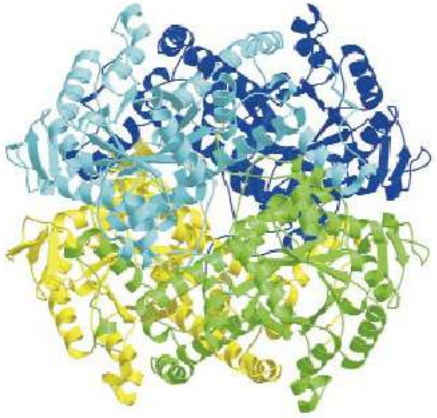
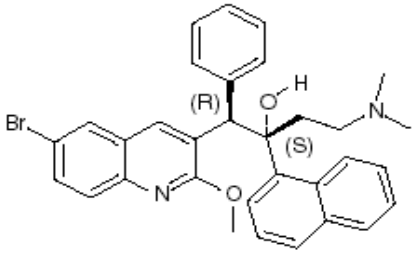
How do we drug metabolic targets: *phenotypic screen* or *target identification/validation* or both?



Chemogenomics

Metabolic Target → **Drug**

Only a valid target when a drug has been found against it



Compound library

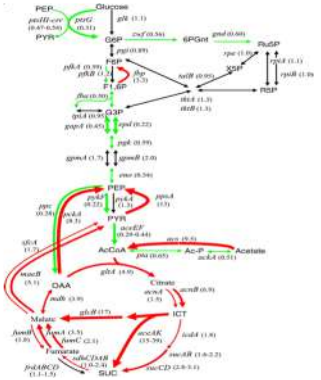
Phenotypic screening

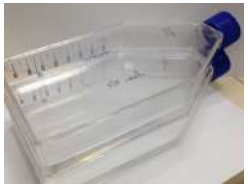
Drug → **Metabolic Target**

Drug identifies the target

- **Time to test 100,000 compounds against all targets (614 essential genes) = 1-2 years**
- **61 million drug-target interactions assessed**

Phenotypic screening repurposed to hit metabolic targets

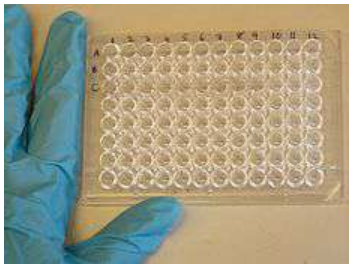




Pathogen grown
37°C for 4 days

Cells washed extensively to remove metabolites

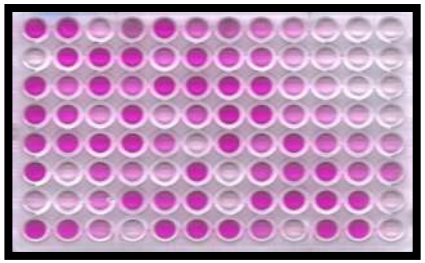
Prepare cell suspension
Targeting metabolism not growth



Compound library added to cell suspension (20 µM)

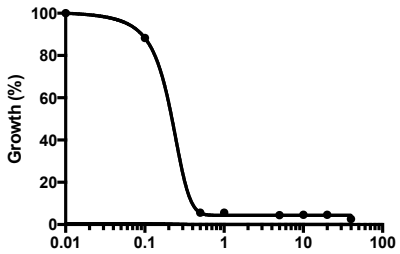
FDA-approved drugs
Natural products

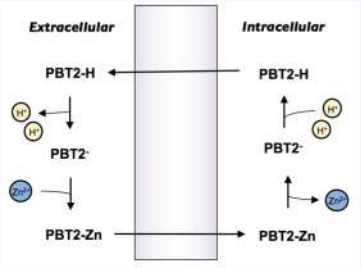
Assay to measure metabolite production
Aerobic/anaerobic



Determine OD_{520}(nm) in plate reader

MIC performed on positive hits (if compound is available)



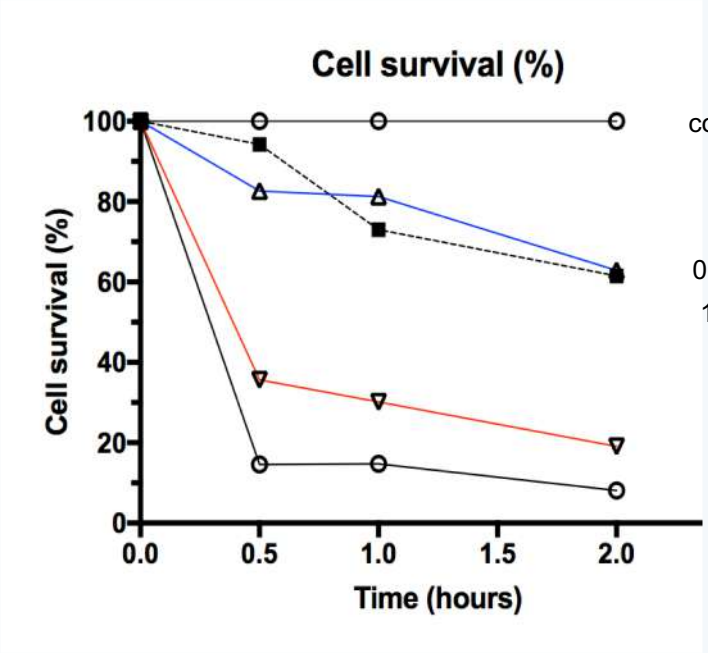


Examples of zincaphore leads with activity against mastitis-causing microorganisms

Compound	M (g/mol)	*S. uberis* ATCC 19436 MIC (μg/ml)		*S. aureus* ATCC 6538 MIC (μg/ml)		*E. coli* ATCC 10536 MIC (μg/ml)	
		No Zinc	Zinc (50 μM)	No Zinc	Zinc (50 μM)	No Zinc	Zinc (50 μM)
PBT2	271.14	64	0.125	8	4	8	4
ZDR22-HCL	388	256	0.125	64	4	>256	>256
ZDR24	395.4	64	0.25	16	8	128-256	≥256
ZDR27	423.45	64	0.125	16	16	>256	>256
ZDR35	472.49	2	1	4	4	32	>256
ZDR46	453.46	4	1	4	4	>256	>256
ZDR090	466.5	4	0.5	16	16	16	16
ZDR115	506.5	4	2	16	16	16	16

2017: Quinoline sulfonamide compounds and their use as antibacterial agents. United States Provisional Patent Application No. 62/608,141.

Bactericidal activity against mastitis-causing bacteria

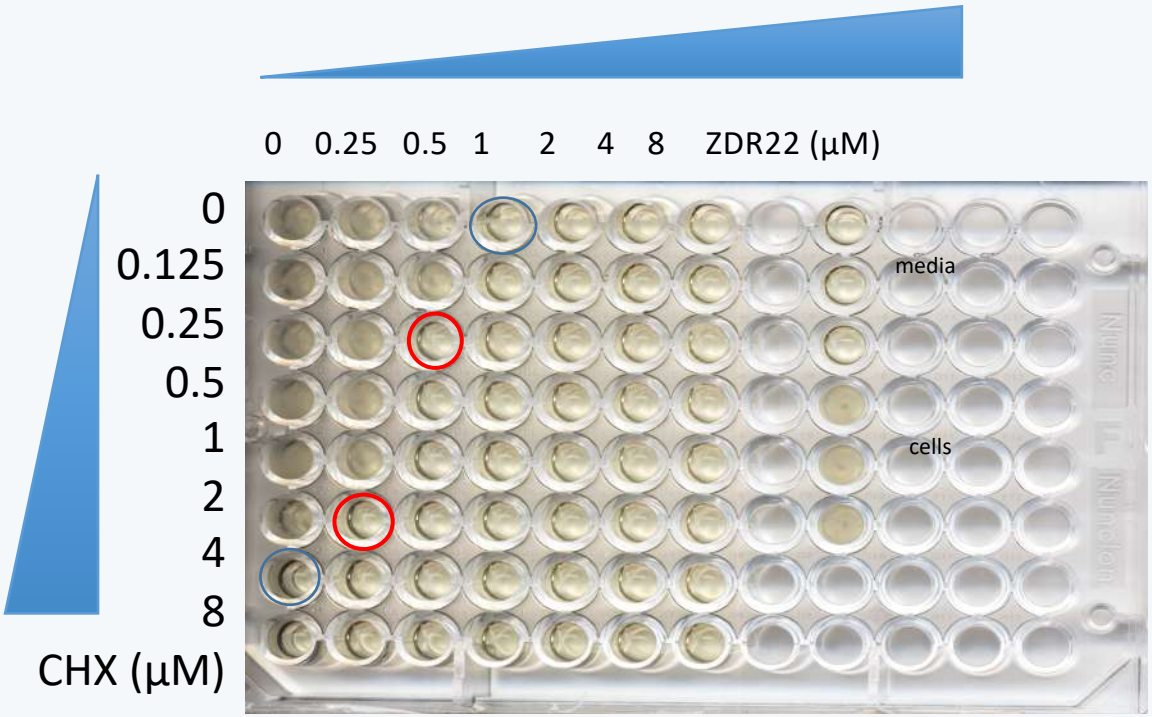


Bactericidal – sterilizing activity
No resistance mechanism
Works against *S. uberis* biofilms
Very low cytotoxicity
Cheap to make

Not used in humans – first green antimicrobial

13,067,100 kilograms of antimicrobials were sold for use in food production animals; **28% percent consisted of ionophores (compounds not used in human medicine)**

ZDR22 synergises with chlorhexidine against *S. uberis*



ZDR22 can reduce the chlorhexidine concentration required to inhibit *S. uberis* 16-fold.

- ZDR22 MIC: 1 µM, ZDR22 CIC: 0.25µM
- CHX MIC: 4 µM, CHX CIC: 0.25µM
- FICI= 0.3125 (synergistic)

Zincaphores as sanitisers

- Zincaphores, a product developed **specifically** for the animal market: SAR (chemistry) developed against mastitis-causing bacteria.

- **Zincaphores unlikely to contribute to AMR due to the multi-targeting MOA:**
  - Bacterial intracellular zinc toxicity
  - Displacement of intracellular metal ions from proteins
  - Disruption of metal ion transport
  - Hypersensitivity to oxidative stress, production of reactive oxygen species
  - Disruption of glycolysis and glucose metabolism

European Standard EN1656 chemical disinfectants and antiseptics test: 5 log reduction in 5 min (1% skim milk)

Acknowledgements

CEO Kip Bodle

Margaret Brimble
David Rennison

Mark Walker
Australian Infectious Disease Research Centre

Debbie Williamson
Glen Carter
Ian Monk

Health Research Council of New Zealand

Otago Bacterial Energetics and Antimicrobial Resistance Group

MAURICE WILKINS CENTRE FOR MOLECULAR BIODISCOVERY

the ROYAL SOCIETY of NEW ZEALAND TE APĀRANGI

MARSDEN FUND TE PŪTEA RANGAHAU A MARSDEN

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