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AMR in Aquaculture, recent developments

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Centre for Environment Fisheries & Aquaculture Science

Cefas Aquatic Animal Health OIE

Cefas

FAO Reference Centre for AMR (UK)

Established 2018

Cefas – aquatic animals and the environment

APHA – terrestrial animals, the environment and food stuffs

VMD – monitoring antimicrobial use AMU and development of policy surrounding AMR and AMU

Centre for Environment Fisheries & Aquaculture Science

Veterinary Medicines Directorate

Animal & Plant Health Agency

The Fleming Fund

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Veterinary Medicines Directorate

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Food and Agriculture Organization of the United Nations

Year one in review

Supports National action plan implementation

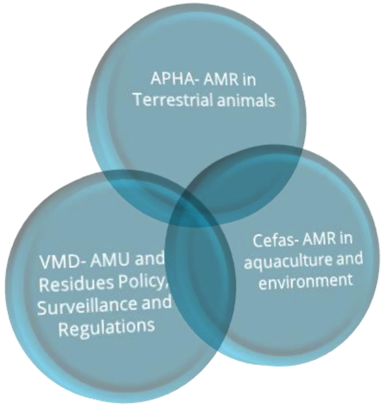
Build capacity for veterinary AMR, AMU and Residues surveillance

Active surveillance in Bangladesh with local farmers and FAO Officials.

Antimicrobial use surveillance and medicines authorizations Ghana Food and Drug Administration.

Residues surveillance workshop in Laos

FAO Reference Centre for AMR



Ghana

Meetings with key stakeholders

Training: AST and disease diagnostics

Projects looking at AMU and at AMR in aquaculture and livestock sectors

Cefas: involved in Lake Volta tilapia

Received: 19 April 2017 | Revised: 31 May 2017 | Accepted: 6 June 2017
DOI: 10.1111/jfd.12681

SHORT COMMUNICATION

WILEY Journal of Fish Diseases

Cold Spring Harbor Laboratory CSH bioRxiv THE PREPRINT SERVER FOR BIOLOGY

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New Results

Comment on this paper

First detection of Infectious Spleen and kidney Necrosis Virus (ISKNV) associated with massive mortalities in farmed tilapia in Africa

José Gustavo Ramírez-Paredes, Richard K. Paley, William Hunt, Stephen W. Feist, David M. Stone, Terry Field, David J. Haydon, Peter A. Ziddah, Samuel Duodu, Timothy S. Wallis, David W. Verner-Jeffreys

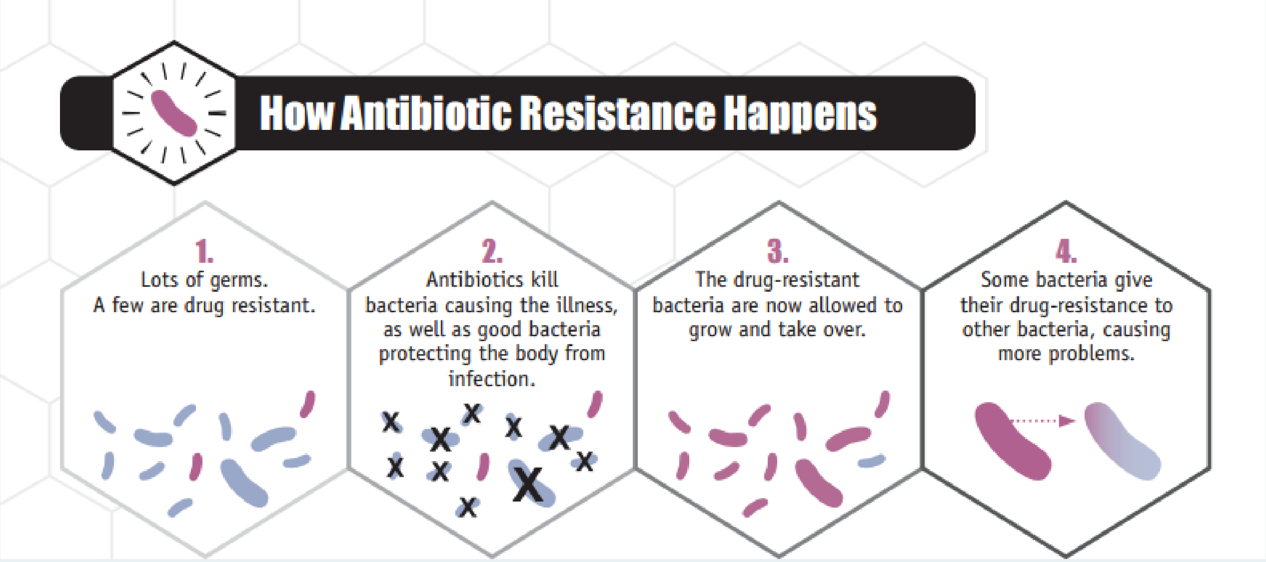
doi: https://doi.org/10.1101/680538

Use of antibiotics in Aquaculture

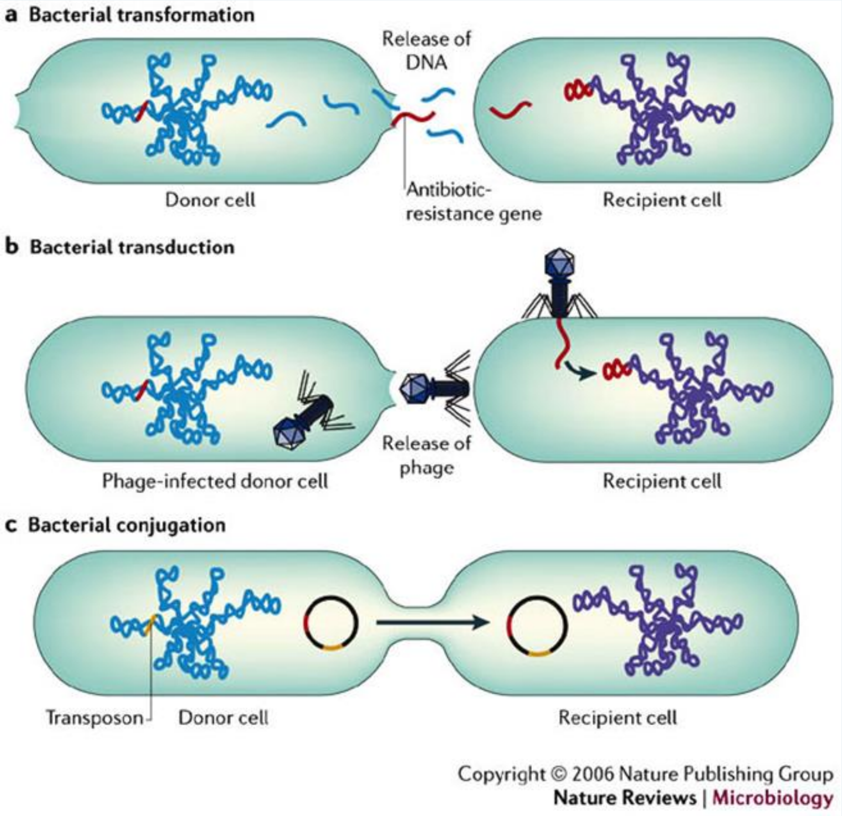
- Antimicrobials used to control bacterial diseases in farmed fish
- Vaccines: reduced use. e.g. 50 mt in Norway in 1991 to 649 kg in 2007
- Limited range of available licensed antibiotics

  UK: oxytetracycline, amoxicillin, (oxolinic acid), florfenicol

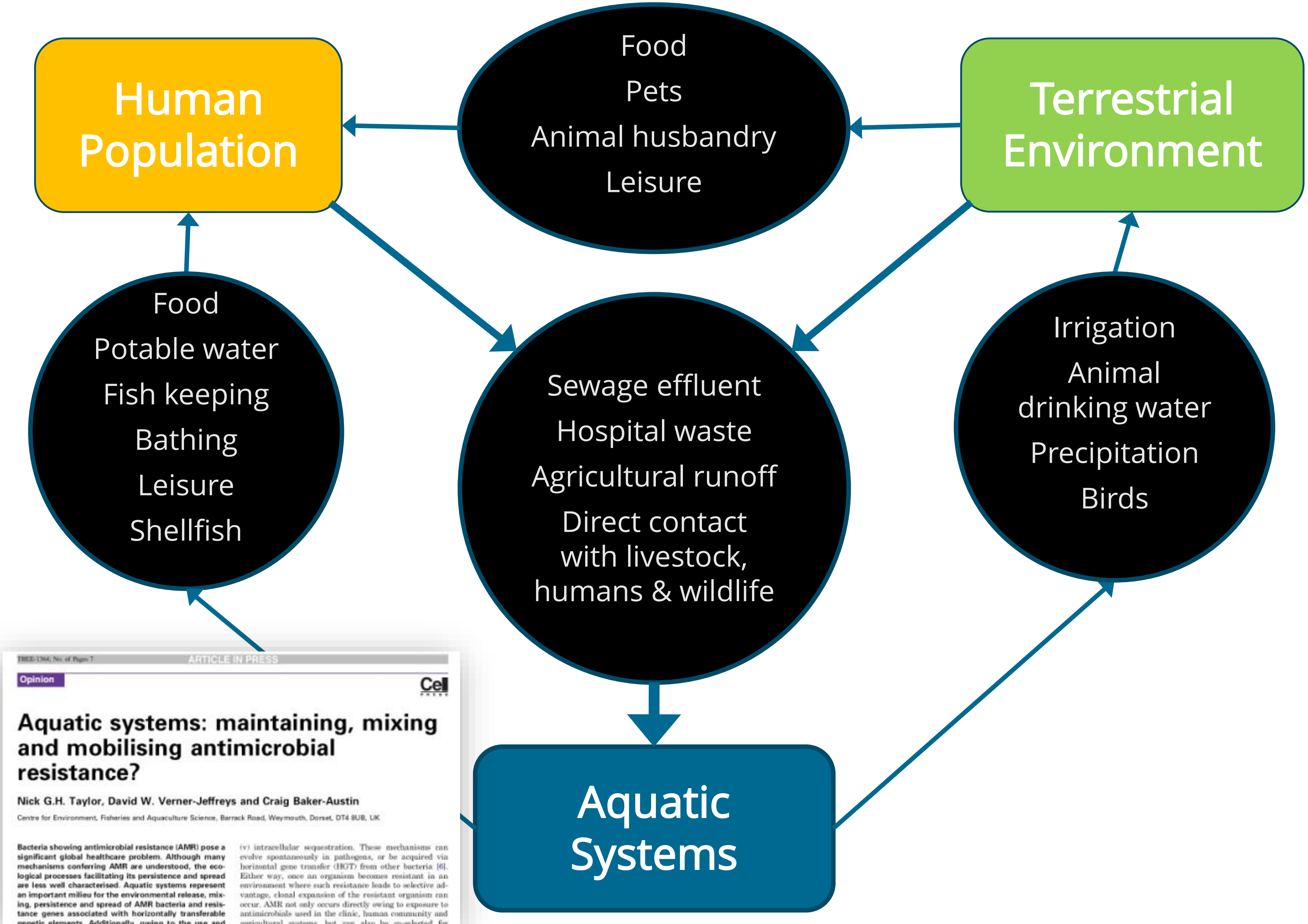
What is resistance



CDC, *Antibiotic resistance threats in the United States, 2013*. 2013, Centre for Disease Control and Prevention.



FROM THE FOLLOWING ARTICLE:
Antimicrobial-resistant bacteria in the community setting E. Yoko Furuya & Franklin D. Lowy *Nature Reviews Microbiology* **4**, 36-45 (January 2006) doi:10.1038/nrmicro1325



ARTICLE IN PRESS

Opinion

Aquatic systems: maintaining, mixing and mobilising antimicrobial resistance?

Nick G.H. Taylor, David W. Verner-Jeffreys and Craig Baker-Austin

Centre for Environment, Fisheries and Aquaculture Science, Barrack Road, Weymouth, Dorset, DT4 8UB, UK

Bacteria showing antimicrobial resistance (AMR) pose a significant global healthcare problem. Although many mechanisms conferring AMR are understood, the ecological processes facilitating its persistence and spread are less well characterised. Aquatic systems represent an important milieu for the environmental release, mixing, persistence and spread of AMR bacteria and resistance genes associated with horizontally transferable

(v) intracellular sequestration. These mechanisms can evolve spontaneously in pathogens, or be acquired via horizontal gene transfer (HGT) from other bacteria [6]. Either way, once an organism becomes resistant in an environment where such resistance leads to selective advantage, clonal expansion of the resistant organism can occur. AMR not only occurs directly owing to exposure to antimicrobials used in the clinic, human community and

AMR in Aquaculture

- Early reports of resistance:
  - N. America: SA and Tet resistant *A. salmonicida* strains 1950's and 1960s
  - Pentaresistant strains by early 1990's in N. European A. salmon culture
- Some resistance intrinsic
- Early recognition of role of conjugative plasmids in spreading AMR in aquaculture pathogens
  - R plasmids now found in almost all drug resistant fish pathogens (Aoki 1992)
  - Increasing evidence that these R plasmids, and associated AMR genes, integrons and transposons often very similar to those found in clinical isolates

Drivers of AMR in Aquaculture

- Direct selection pressure:
  - ➢Antibiotic use
- Gene transfer from the environment:
  - ➢Pond fertilization
  - ➢Agricultural run off
  - ➢Human effluent

Drivers of AM

- >90% of
  LMICs
- Majo
- Poo
- Risk
- In Eu
  antibi

Typical therapeutants used in Indian major carp feeds

Feed additive	Content (percent AI*)	Cost	Dosage and use
Branded antibiotics			
Oxytetracyclin	10		
Enrofloxacin	10	600 INR/kg (US$12.7/kg)	
Sulphamethoxisole + Trimethioprim	10+2		100 mg AI/kg fish weight (consecutively for 7 days)
Chlorotetracyclin	15		
Crustacean parasiticides			
Ivermectin	0.2	280 INR/kg (US$5.9/kg)	1 kg brand product/1 000 kg feed) (consecutively for 5 days)
Anthelminthics			
Albendazole	5	260 INR/kg (US$5.5/kg)	1 kg brand product/1 000 kg feed (consecutively for 5 days)

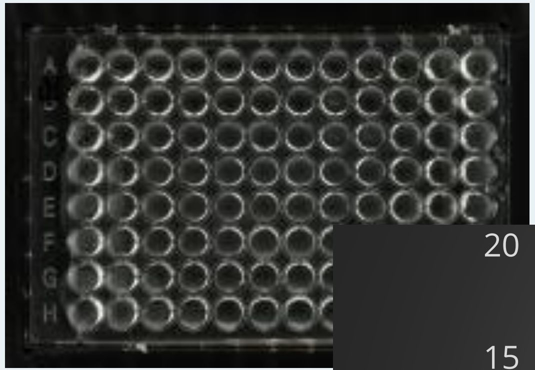
* AI = active ingredient.

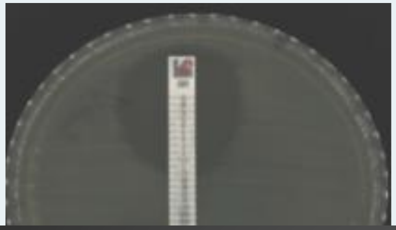
Source: Field Survey (2010).

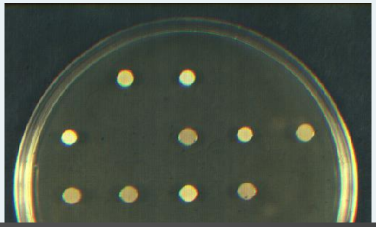
ai

Detection of resistance

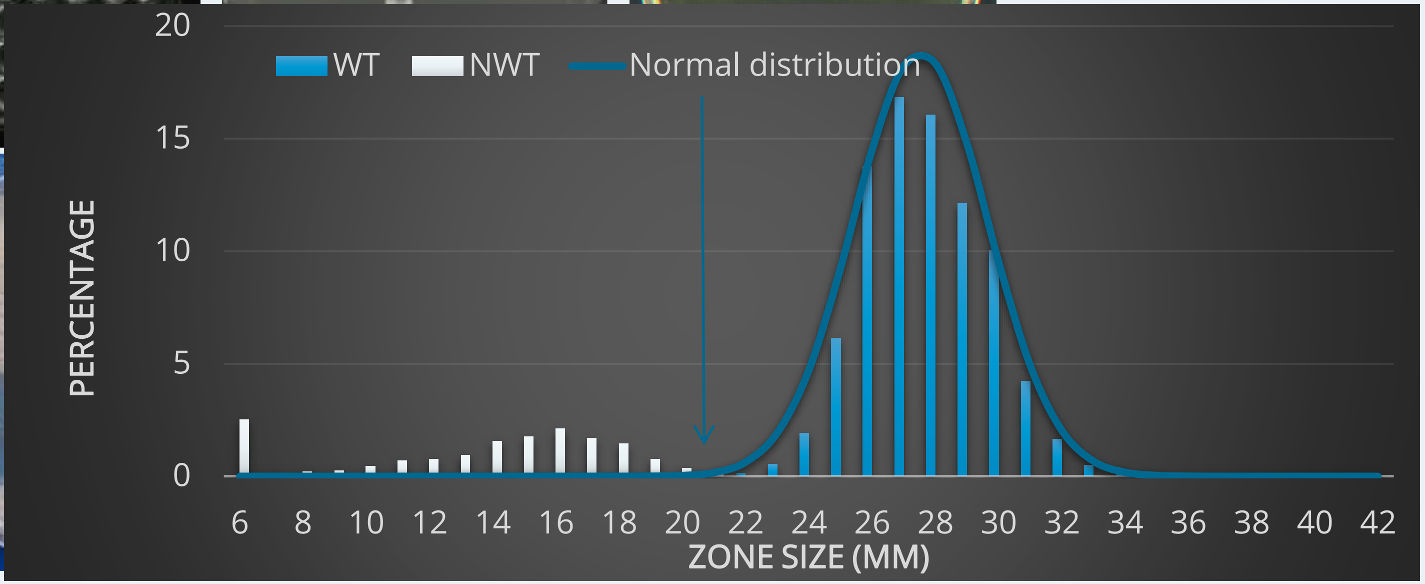
- Phenotypic
  Quantitative
  MIC







  Qualitative
  S/I/R or
  ECOFF: Wild Type
  versus non Wild Type

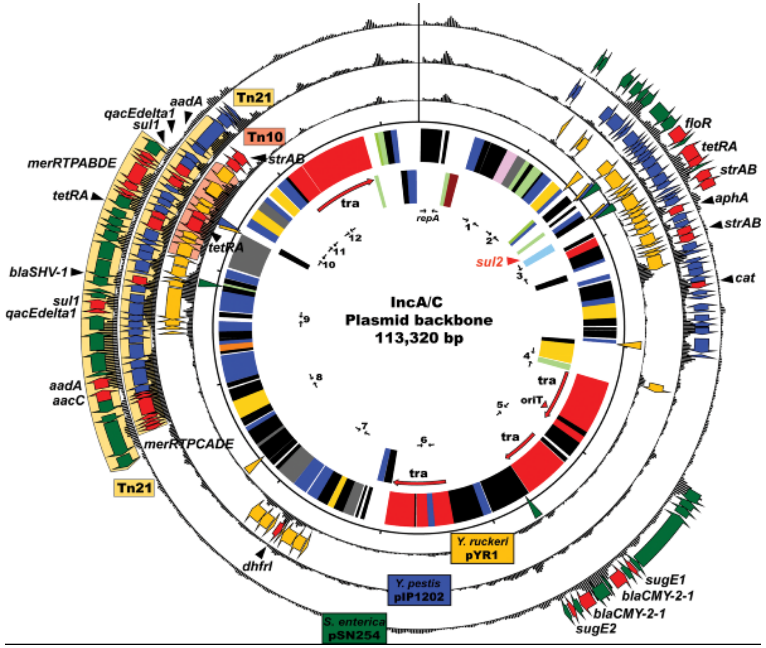


- Genotypic Next Generation Sequencing

IncA/C – an example

- IncA/C are a group of plasmids conferring resistance to a range of antibiotics, including florenphenicol, streptomycin and tetracycline. Now found in numerous distantly-related bacteria:
- *Yersinia pestis* (bubonic plague) in Madagascar.
- *Vibrio cholerae* in China.
- *Salmonella enterica* (humans and cattle) in USA and France.

- Furunculous in Atlantic salmon in Canada.
- *Photobacterium damselae* subsp. *damselae* in Japan.
- *Edwardsiela ictiluri* in catfish, USA.
- All linked to acquisition of incA/C plasmids via horizontal gene transfer



Welch et al. 2007
PLoS ONE 2(3): e309

Multidrug resistant *Edwardsiela ictiluri* from catfish in USA

- Resistance mediated by IncA/C plasmid.
- Transferrable resistance to :

Florfenicol, oxytetracycline, chloramphenicol, stretomycin, potentiated sulphonamides, ampicillin, and 2nd and 3rd generation cephalosposins (e.g. ceftiofur and cefoxin)

- R genes: *floR* and *bla*CMY-2 detected.

Welch et al. 2009 Antimicob Agents Chemother 53, 845-846

Example: *Flavobacterium psychrophilum*

- Rainbow trout fry syndrome (RTFS)/ bacterial cold water disease : one of common diseases constraining salmonid production worldwide
- No licensed vaccines
- Farmers use antibiotics
- Surveillance data gaps
  - Antimicrobial use to control RTFS/ BCWD
  - Resistance
    - Rates of resistance in Fp
    - Risks of resistance in Fp emerging?
  - Complication: differences in testing procedures and the interpretive criteria between laboratories.

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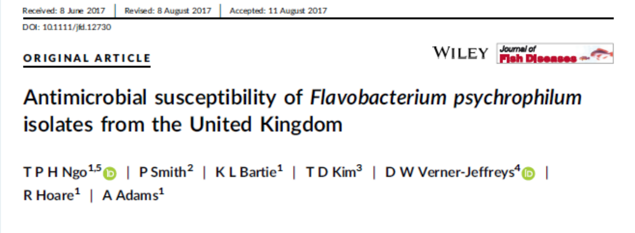


Received: 8 June 2017 | Revised: 8 August 2017 | Accepted: 11 August 2017
DOI: 10.1111/jfd.12730

ORIGINAL ARTICLE

WILEY Journal of Fish Diseases

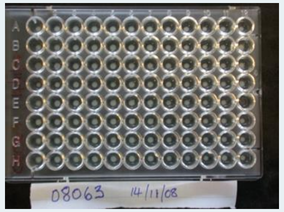
Antimicrobial susceptibility of *Flavobacterium psychrophilum* isolates from the United Kingdom

T P H Ngo[1,5] | P Smith[2] | K L Bartie[1] | T D Kim[3] | D W Verner-Jeffreys[4] | R Hoare[1] | A Adams[1]

Filling the data gaps...:

140 *F. psychrophilum* isolates tested , 125 from range UK farms 2005-2015

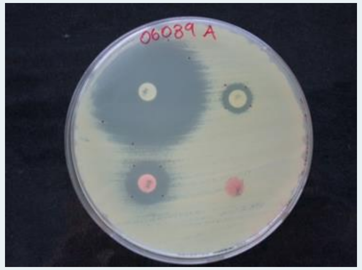
Broth Microdilution



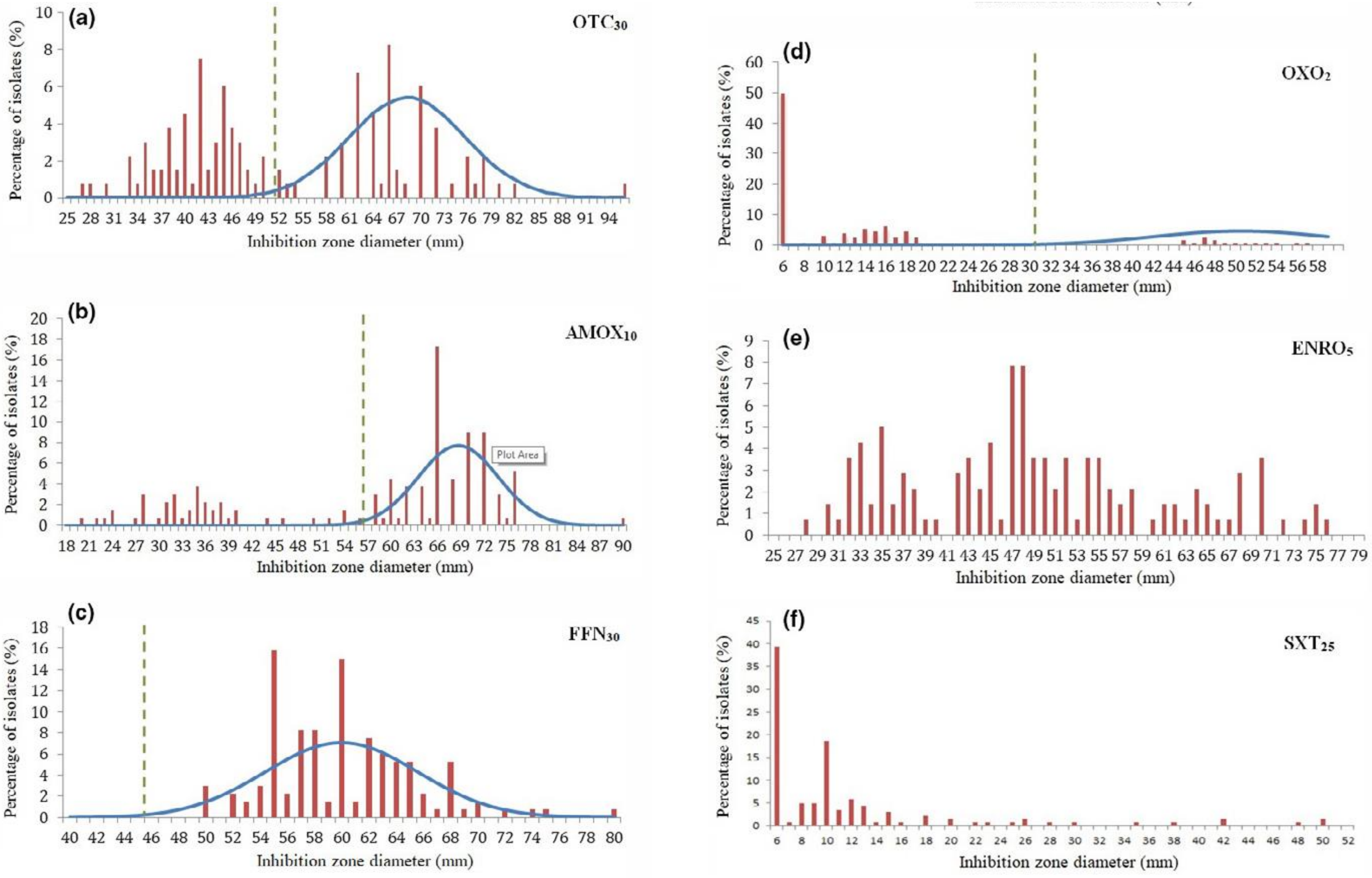
- VET04-A2 guideline (CLSI, 2014)
- Sensititre CMP1MSP plates

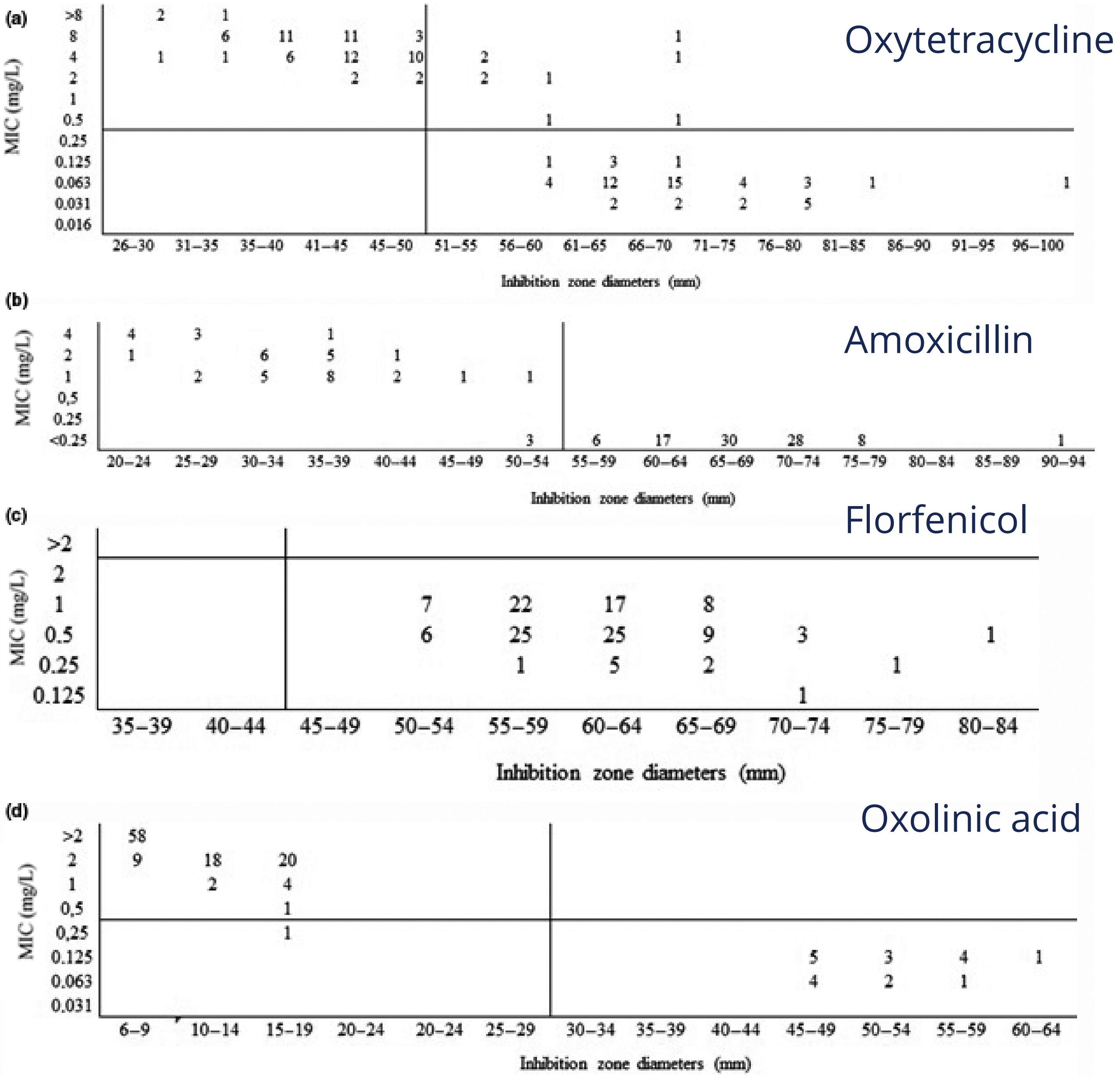
Disc Diffusion

- M42-P protocol (CLSI, 2006)
- AMOX, 10 µg; ENRO, 5 µg; FFN, 30 µg; OA, 2 µg; OTC, 30 µg; SXT, 25 µg



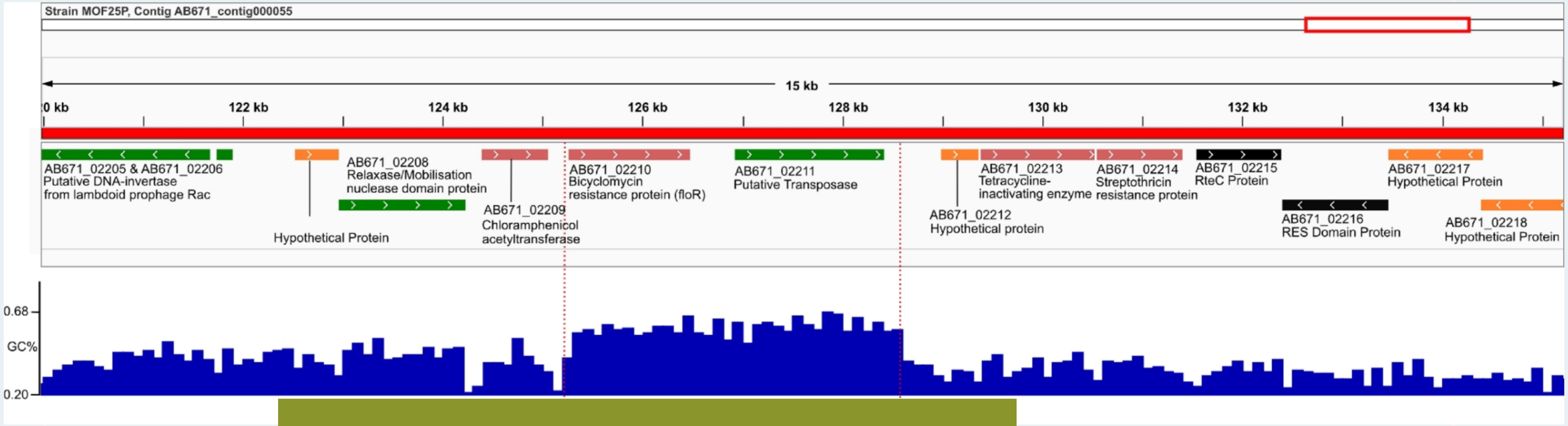
Normalized resistance interpretation(NRI) was used to: determine the epidemiological cut-off value (COWT). Identify wild type (full susceptibility, WT) and non-wild type (reduced susceptibility, NWT) isolates.


(a)
OTC30
Percentage of isolates (%)
Inhibition zone diameter (mm)
(b)
AMOX10
Plot Area
Percentage of isolates (%)
Inhibition zone diameter (mm)
(c)
FFN30
Percentage of isolates (%)
Inhibition zone diameter (mm)
(d)
OXO2
Percentage of isolates (%)
Inhibition zone diameter (mm)
(e)
ENRO5
Percentage of isolates (%)
Inhibition zone diameter (mm)
(f)
SXT25
Percentage of isolates (%)
Inhibition zone diameter (mm)


(a)
Oxytetracycline
MIC (mg/L)
Inhibition zone diameters (mm)
(b)
Amoxicillin
MIC (mg/L)
Inhibition zone diameters (mm)
(c)
Florfenicol
MIC (mg/L)
Inhibition zone diameters (mm)
(d)
Oxolinic acid
MIC (mg/L)
Inhibition zone diameters (mm)

Conclusions

- Florfenicol is still the most effective treatment for controlling RTFS outbreaks within the UK.
- Oxytetracycline and amoxicillin could be considered as alternative antimicrobials to FFN for RTFS management.
- It is important to perform routine susceptibility testing using standardised methods (e.g. VET04-A2 guideline) and CO_{WT} values (e.g. NRI).



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MICROBIOLOGY ECOLOGY FEMS

Volume 93, Issue 4
April 2017

Article Contents

Detection of the florfenicol resistance gene *floR* in *Chryseobacterium* isolates from rainbow trout. Exception to the general rule?

David W. Verner-Jeffreys ✉, Thomas Brazier, Ramon Y Perez, David Ryder, Roderick M. Card, Timothy J. Welch, Rowena Hoare, Thao Ngo, Nikki McLaren, Richard Ellis, ... Show more

FEMS Microbiol Ecol (2017) 93 (4): fix015.
DOI: https://doi.org/10.1093/femsec/fix015
Published: 11 February 2017 **Article history** ▾

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Abstract

Centre for Environment Fisheries & Aquaculture Science

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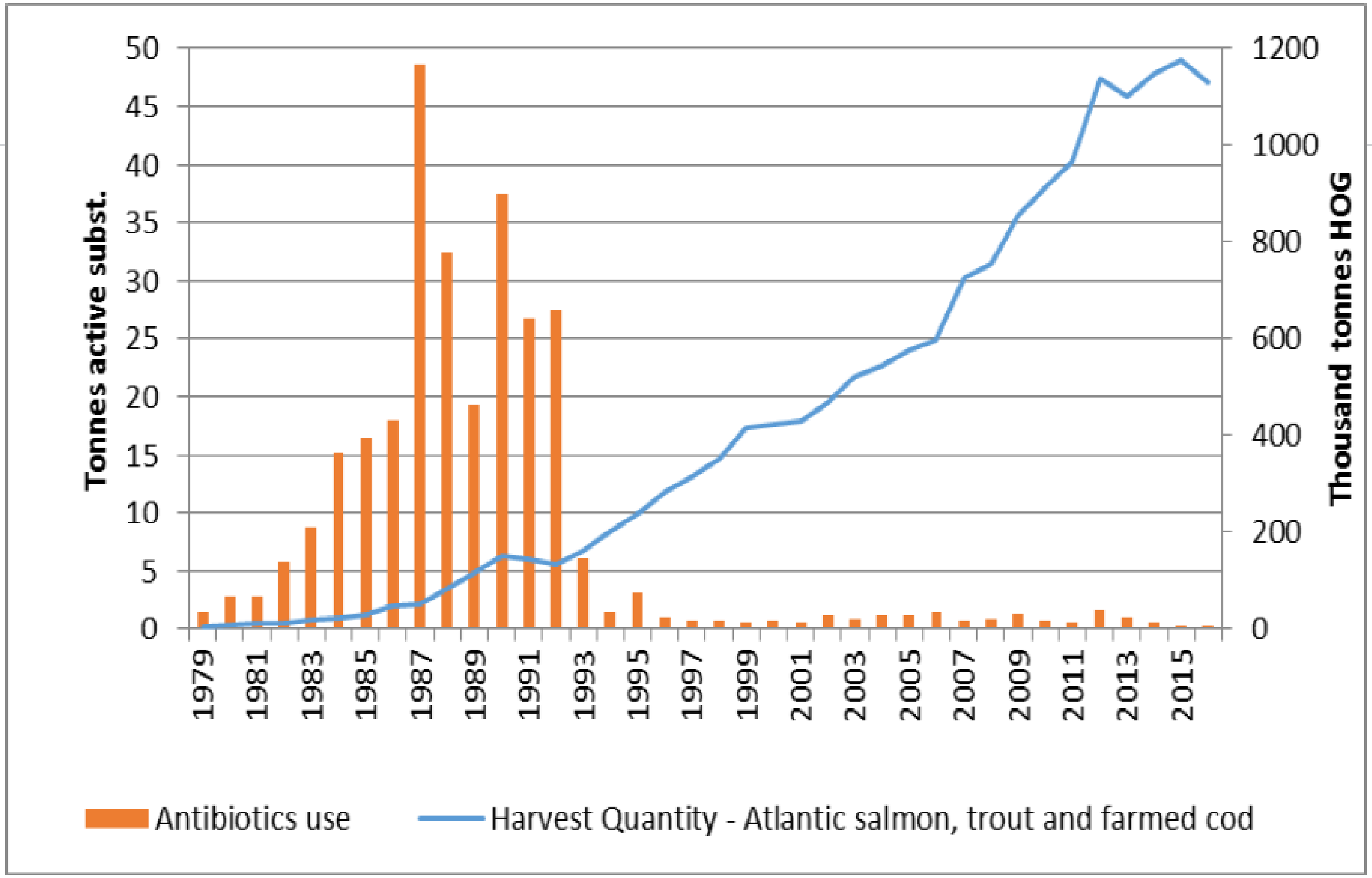

Norwegian data but similar trends in Scotland
The challenge domestication of new species
Emerging disease and escalating use of antibiotic through the 1980s
Rapid decline in antibiotic use in the early 1990s as vaccine technology advanced

Antibiotic Usage Data

Antibiotic usage by food-producing animal species,
2018 compared with 2015, 2016 and 2017

	Total coverage %*	2018 Total tonnage**	2018 Total per unit***	Compared with 2015 %	Compared with 2016 %	Compared with 2017 %
Gamebirds	90	9.7	—	—	↓ 52	↓ 25
Salmon	100	1.0	6.5 mg/kg	—	—	↓ 60
Trout	90	0.2	13 mg/kg	—	—	↓ 32
Dairy†	30	4.9	17 mg/kg	↓ 30	↓ 36	↑ 9
Beef † (¥)	5.5 (4.0)	1.1 (1.0)	21 mg/kg (25 mg/kg)	— 0	— ↓ (2)	— ↓ (6)

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Source: p. 8
VARSS REPORT 2018

Conclusions

- Use of antimicrobials in aquaculture has driven selection of resistant bacteria
- Strong evidence: transfer of R determinants and plasmids from human/terrestrial animal environments into aquaculture environments
- Transfer in opposite direction yet to be established
- Focus of future work:
  - Determine extent of use of antimicrobial agents in aquaculture
  - Assess development of resistance in key pathogens
  - Standard setting : methods and interpretative criteria. Generation of ECOFF values for key aquaculture pathogens. CLSI & EUCAST
  - Gain better understanding of factors promoting environmental persistence (e.g. co-selection for metals/ biocide resistance)
  - Assess real risks to humans, terrestrial animals and fish of antibiotic use in aquaculture
  - Recommend methods/practices to minimise identified risks
  - One Health Approaches needed!

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