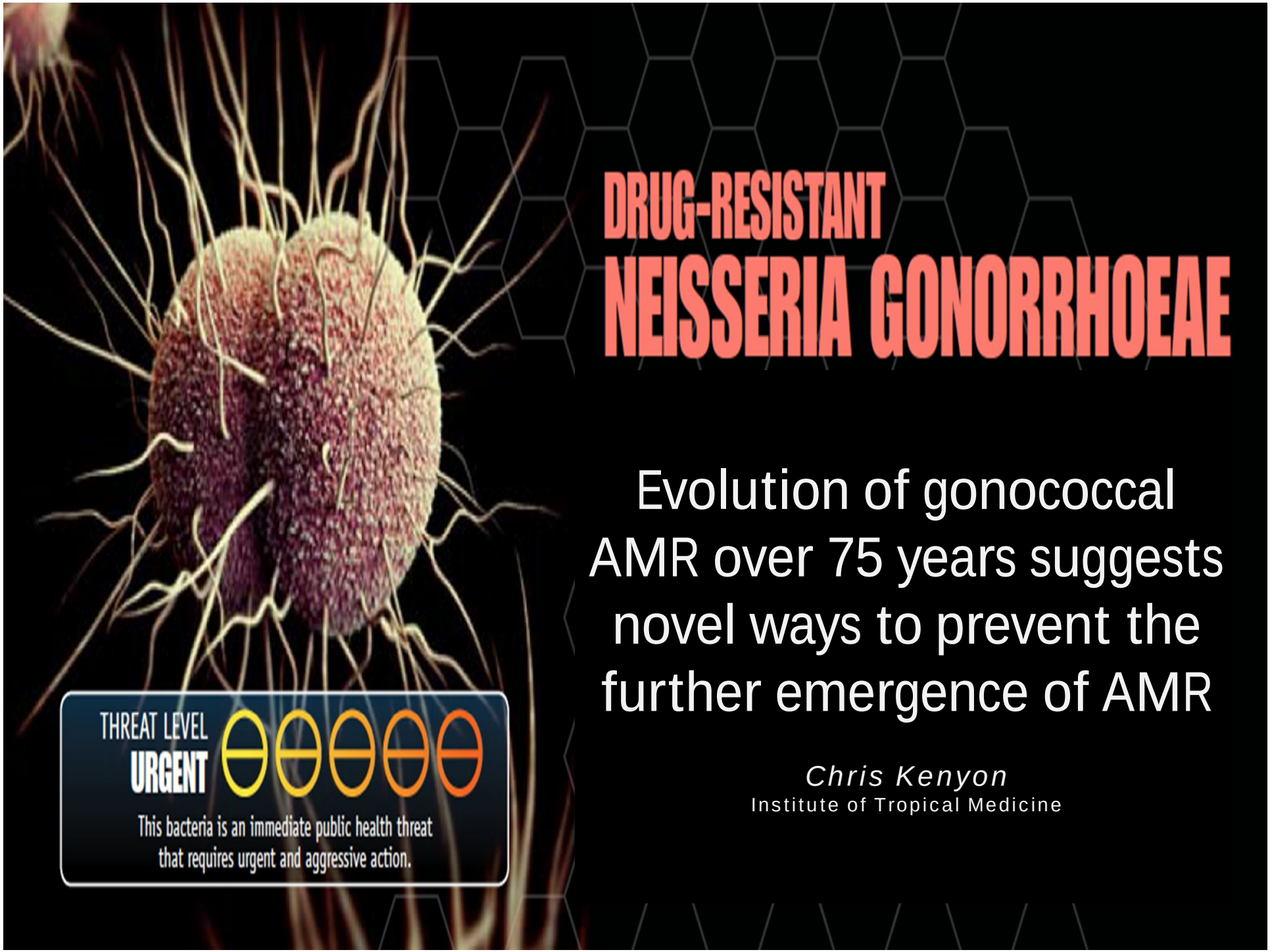
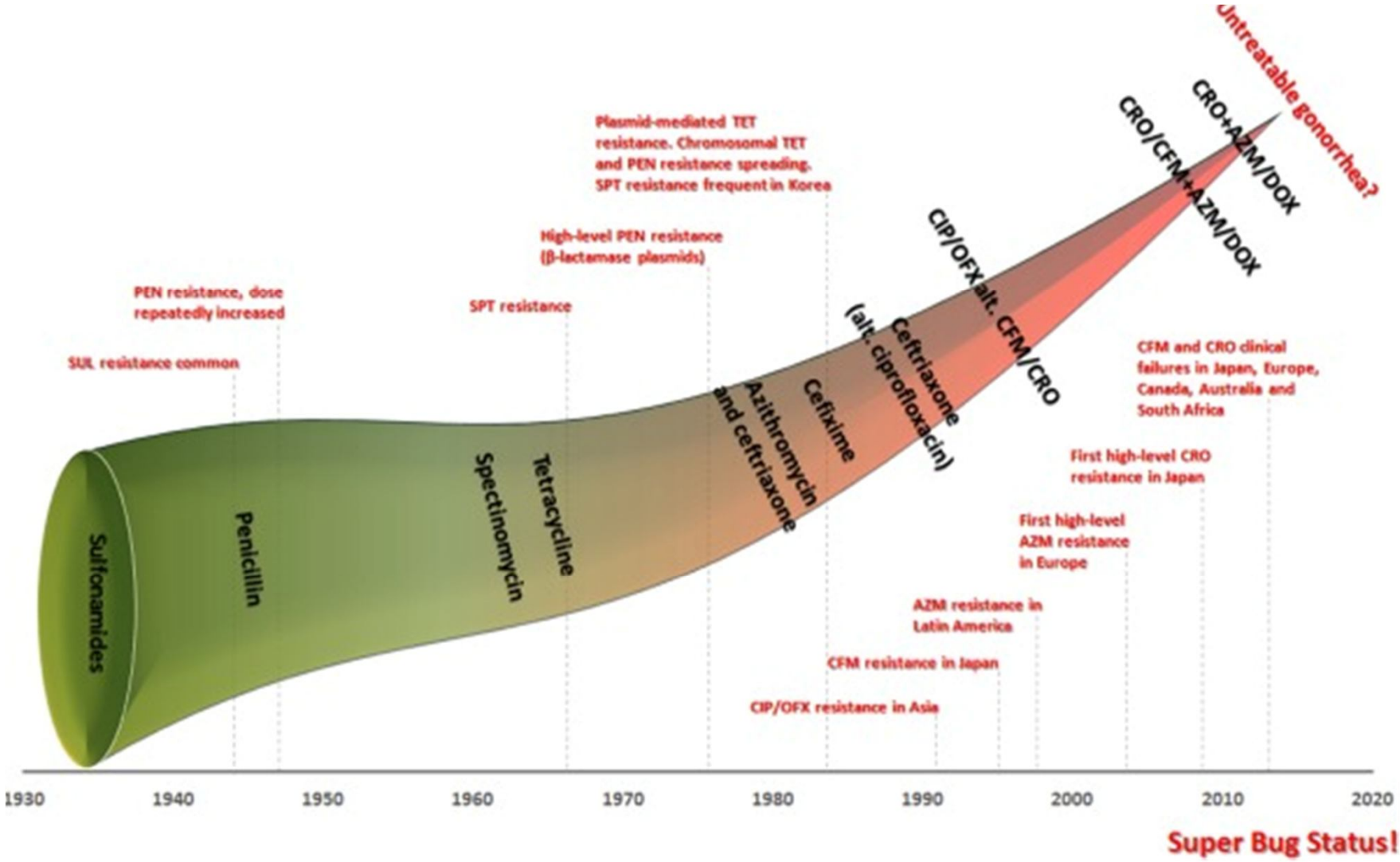

DRUG-RESISTANT
NEISSERIA GONORRHOEAE
THREAT LEVEL
URGENT
This bacteria is an immediate public health threat
that requires urgent and aggressive action.
Evolution of gonococcal AMR over 75 years suggests novel ways to prevent the further emergence of AMR
Chris Kenyon
Institute of Tropical Medicine

The ‘unstoppable’ emergence of AMR



Unemo Clin Micro Rev2014

Dealing with the threat of XDR Ng

Lancet ID Commission

Way forward?

- Improved dual therapy
- Repurposing old ABs
- New ABs
- Vaccine

Sexually transmitted infections: challenges ahead

Magnus Unemo, Catriona S Bradshaw*, Jane S Hocking, Henry J C de Vries, Suzanna C Francis, David Mabey, Jeanne M Marrazzo, Gerard J B Sonder, Jane R Schwebke, Elske Hoornenborg, Rosanna W Peeling, Susan S Philip, Nicola Low†, Christopher K Fairley†*

	Northern Territories (Australia) 2015*	Japan 2015*
Azithromycin	0% (≥1mg/L)	53% (≥0.5mg/L)
Ciprofloxacin (≥1mg/L)	2%	90%
Ceftriaxone (≥0.25mg/L)	0%	14%
Penicillin (≥1mg/L)	2%	?
	Whiley EID 2017	Yasuda STD 2017

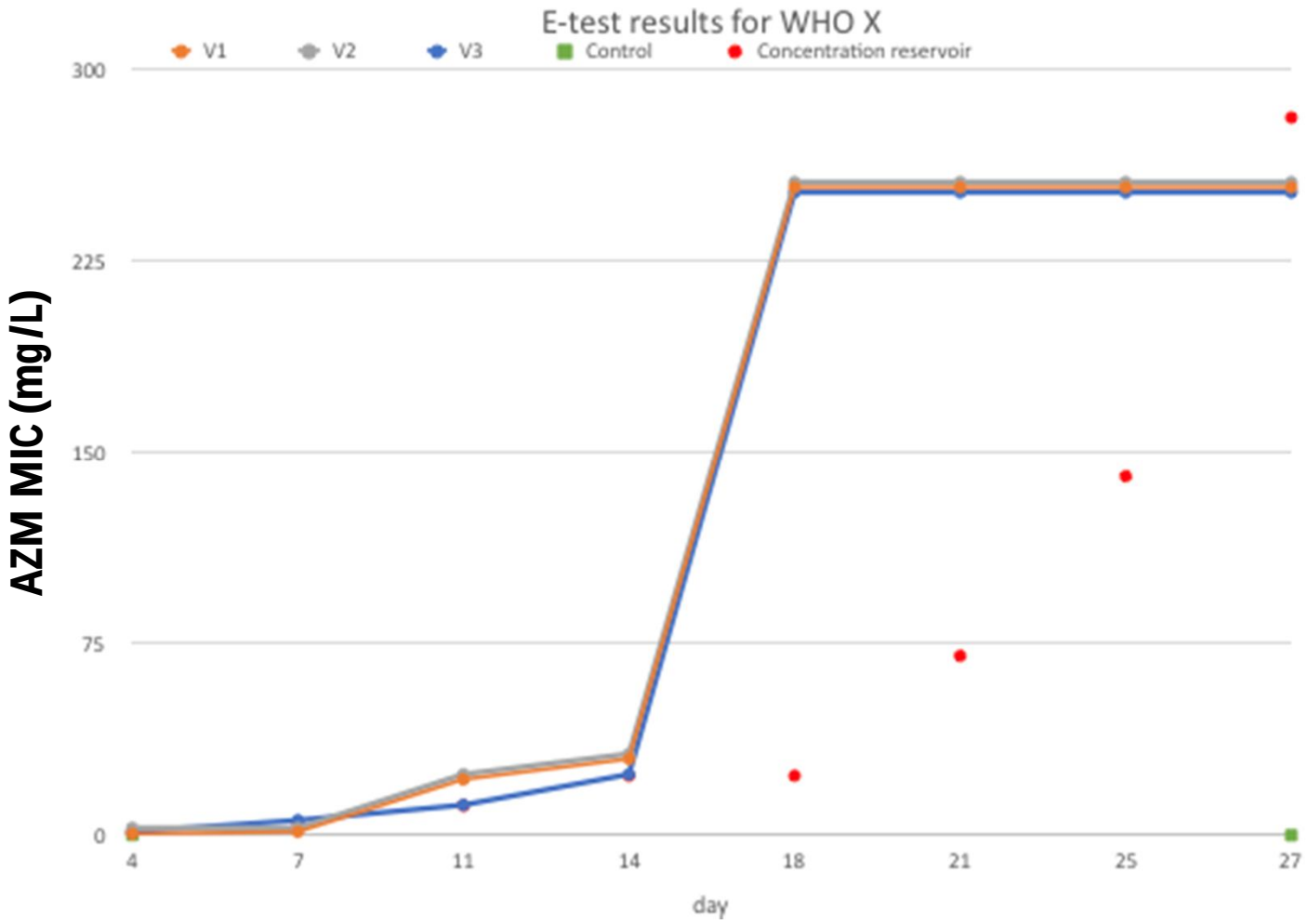
Why not me?

Why me?

* Agar dilution, same breakpoints excl AZM as shown

AB exposure -> AMR

e.g. from NG-morbidostat

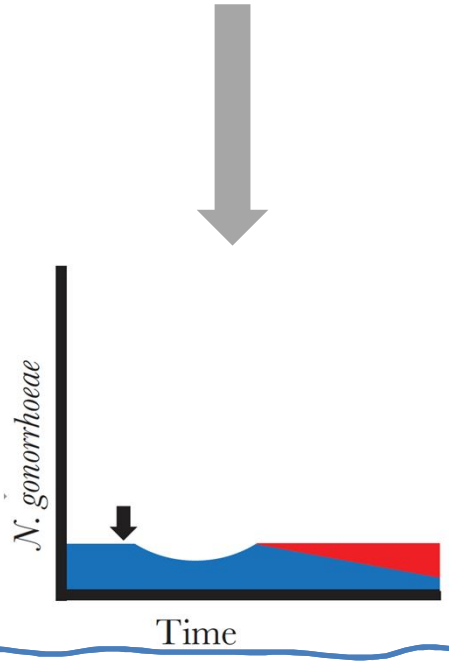


Laumen Unpublished

3 different types of AB exposure -> AMR

1. Direct selection

Penicillin used to treat Ng



2. Indirect bystander selection

3. Direct bystander selection

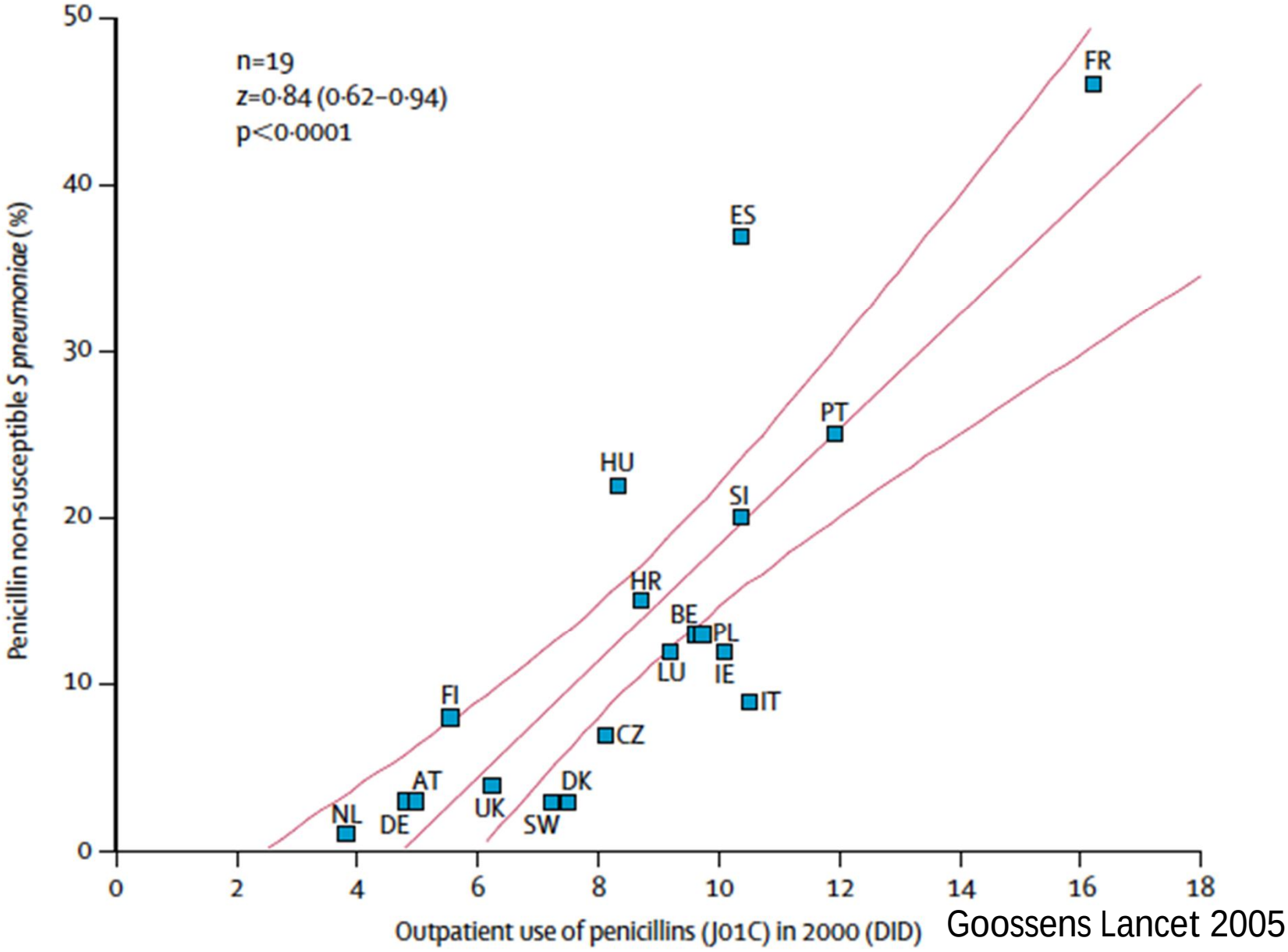
<u>Bystander selection for Ng in 2010 in USA:</u>

- Quinolones - 98%
- Cephalosporins - 15%

Tedijanto PNAS 2018

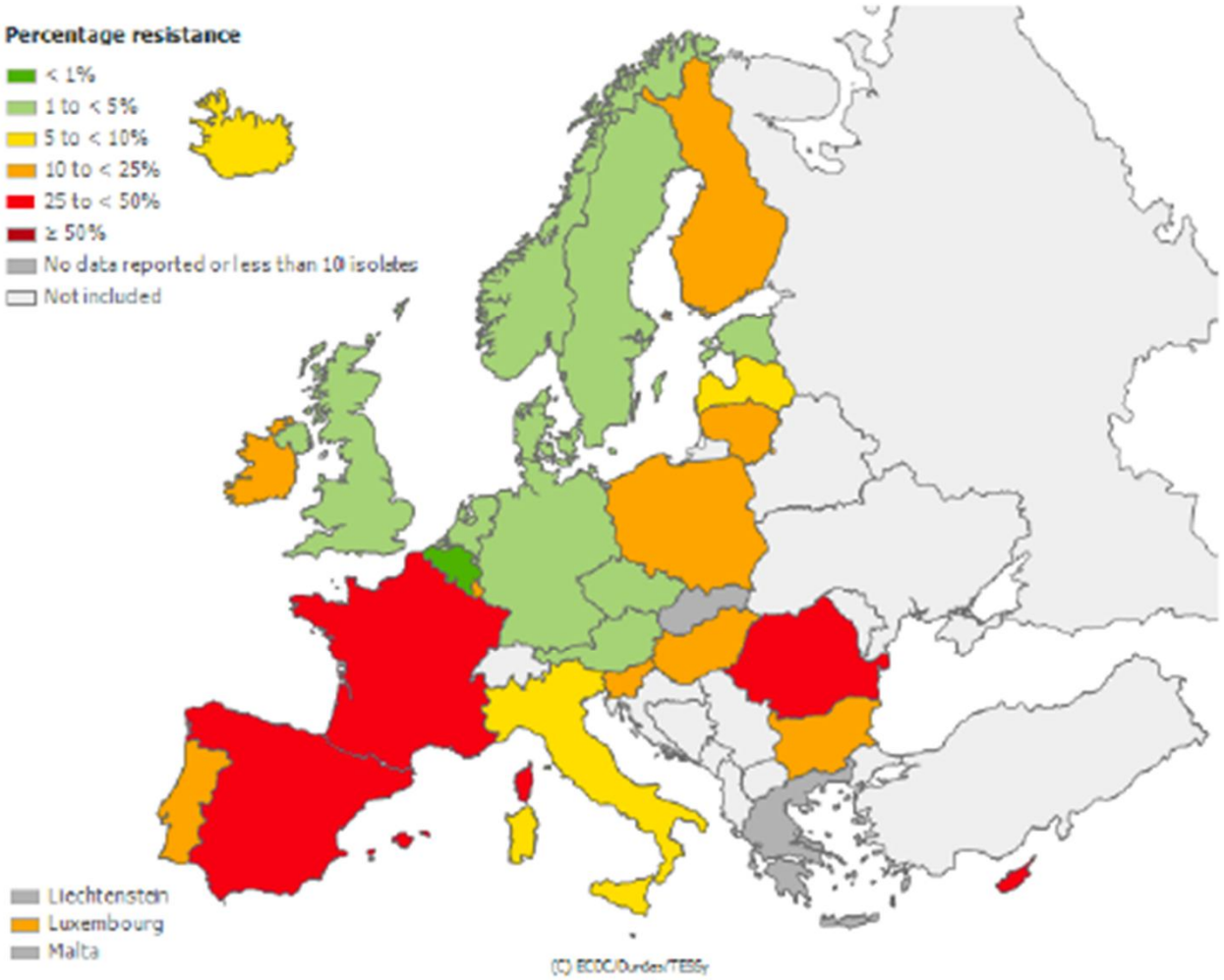
EVIDENCE FOR BYSTANDER SELECTION IN NG AT POPULATION LEVEL?

Pneumococcus



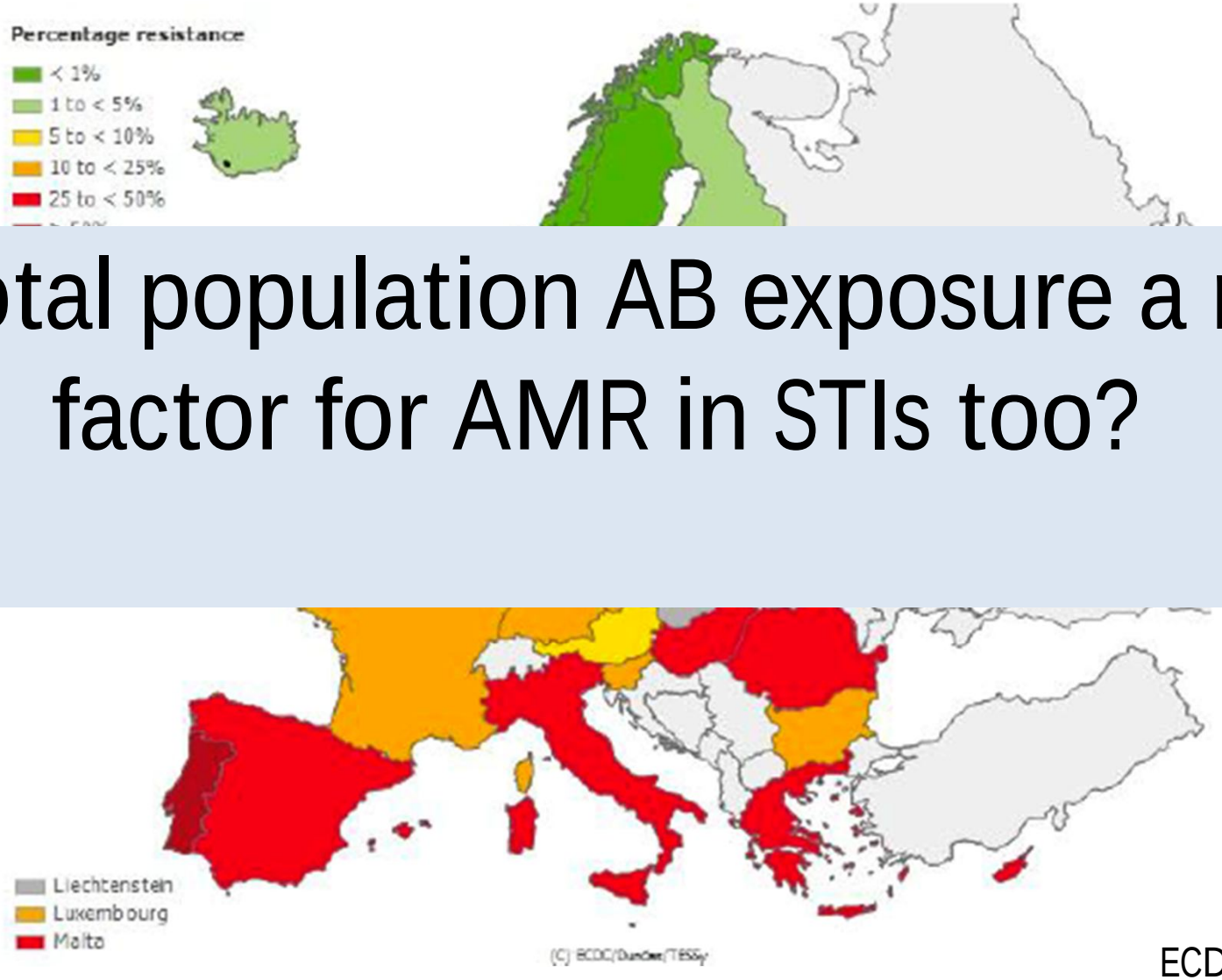
Goossens Lancet 2005

S. Pneumoniae penicillin R BSI, 2010



ECDC

MRSA BSI 2010

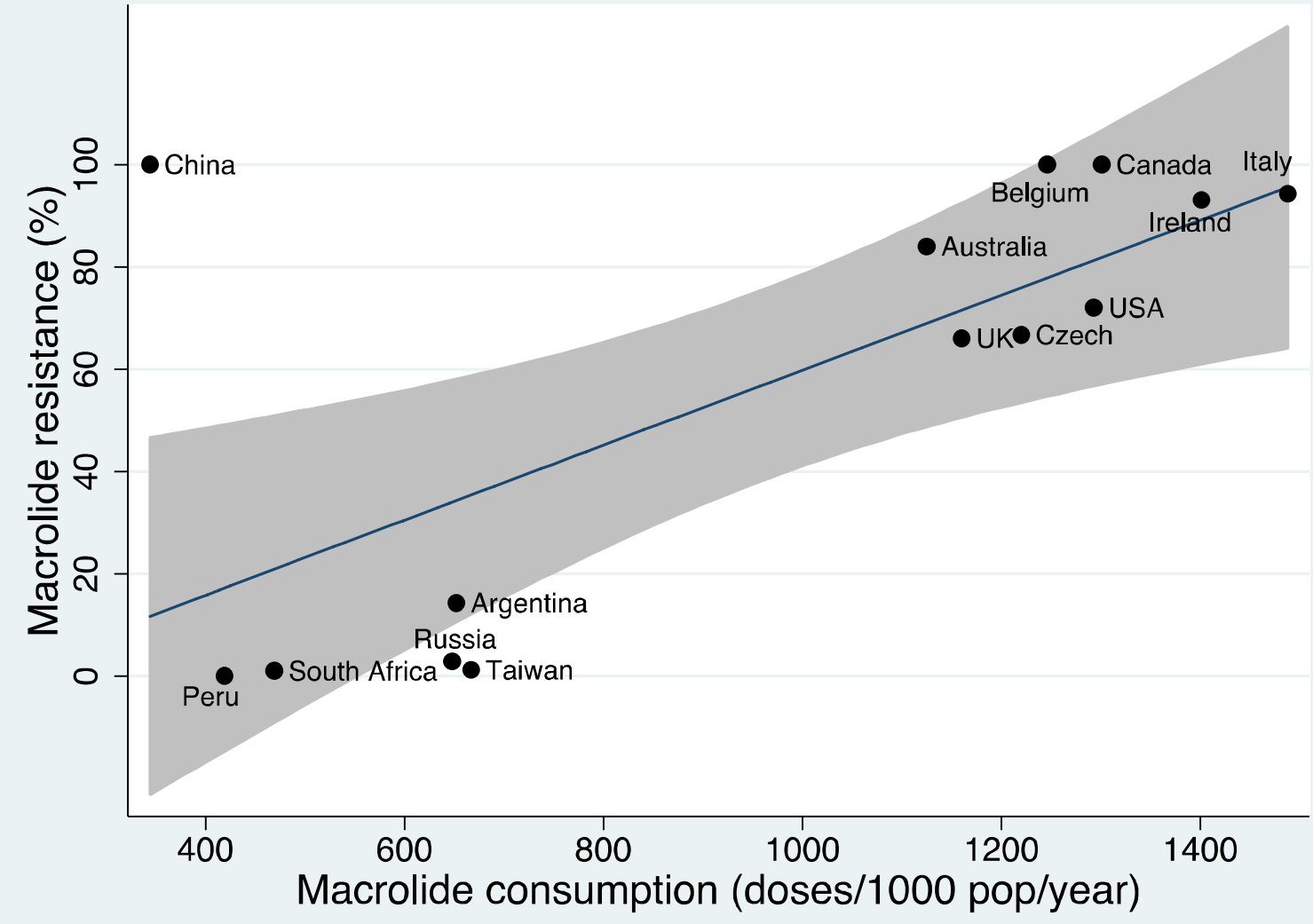


Is total population AB exposure a risk factor for AMR in STIs too?

ECDC

Treponema pallidum:

Macrolide AMR vs. consumption

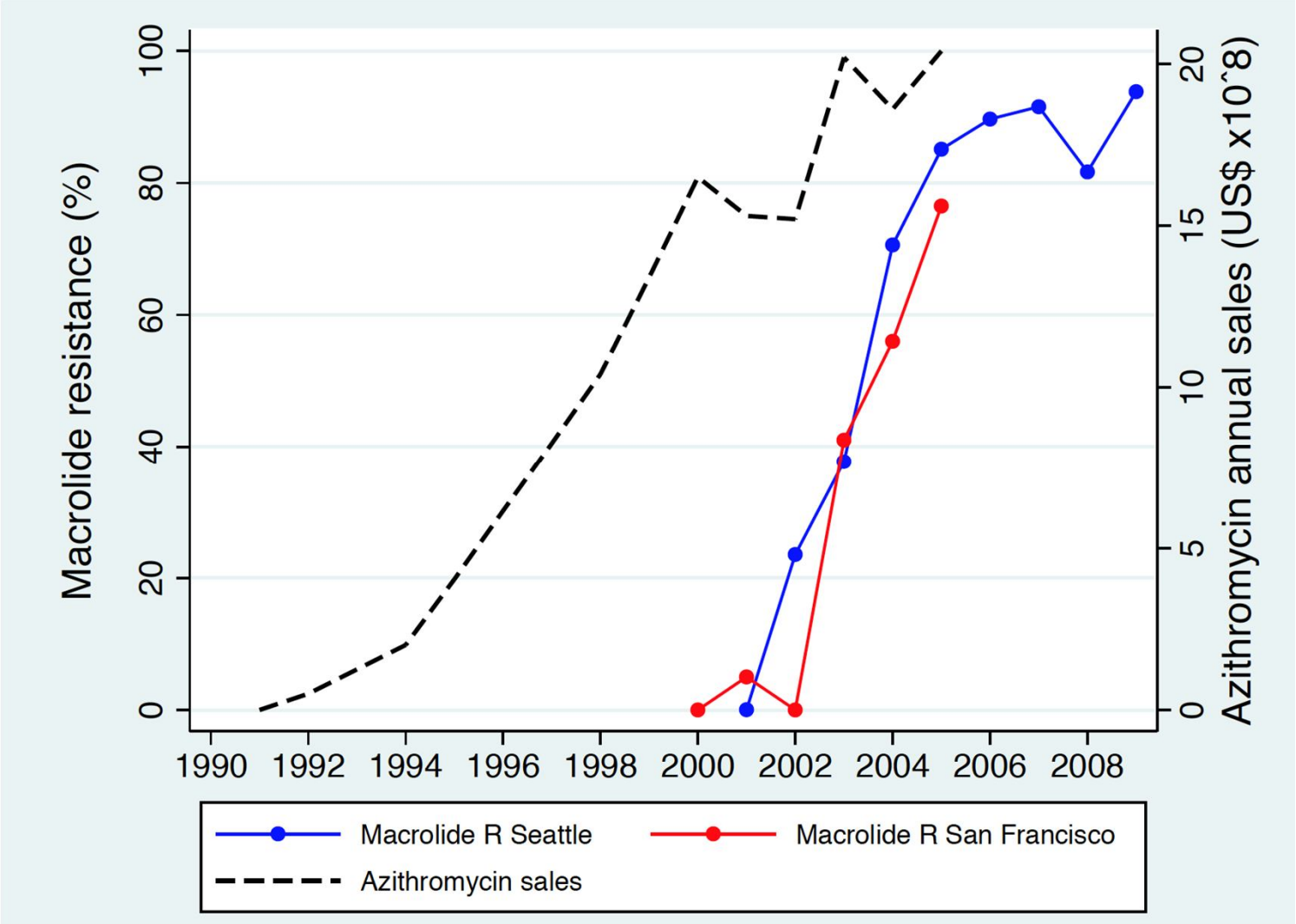


coeff. 0.7, P = 0.009

Kenyon J Med Micro 2018

Treponema pallidum:

Macrolide AMR vs. consumption



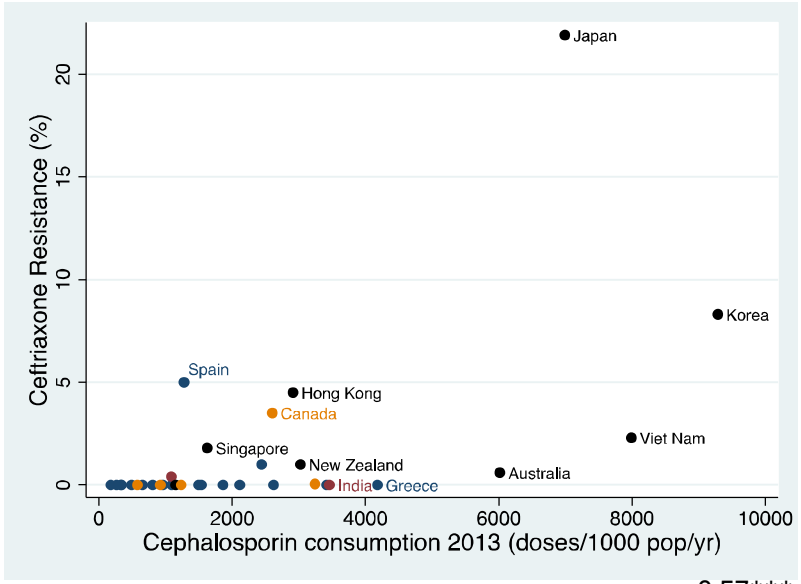
Kenyon J Med Micro 2018

AB consumption vs Ng AMR

Global study

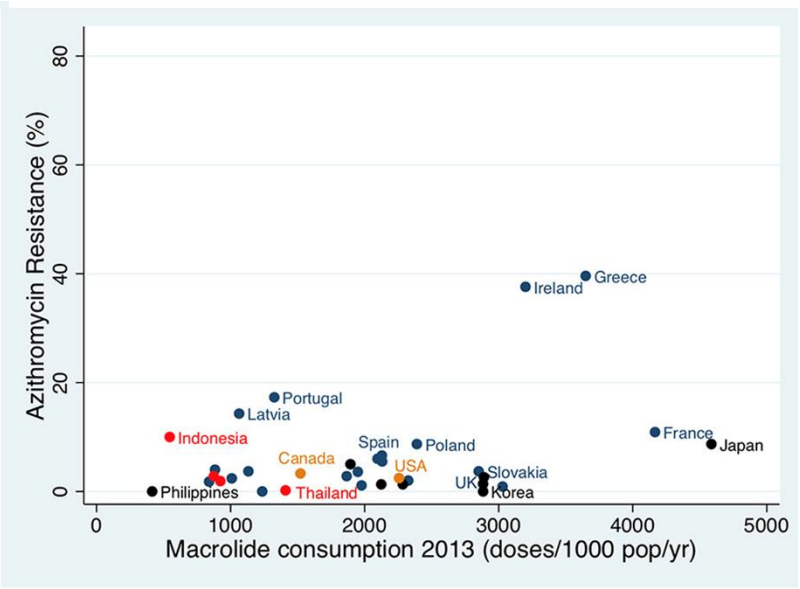
- AMR data: WHO GASP 2009-2014
- AB consumption data: CDDEP/IMS (doses 1000 pop/yr)

Cephalosporin



r=0.57***

Macrolide



r=0.38*

Kenyon et al Frontiers 2018

Consumption vs. Ng AMR in Europe

(2009-2016)

Consumption

	Maximum (country)	Minimum (country)	Fold difference
Cephalosporins	3376 (EL)	76 (NL)	44
Fluoroquinolones	1501 (IT)	266 (UK)	6
Macrolides	3300 (Greece)	296 (Sweden)	11

AMR

	% AMR Maximum	% AMR Minimum	Fold difference
Cefixime	12.7 (DK)	0 (EE)	>12
Ceftriaxone	5.0 (ES)	0	>5
Ciprofloxacin	70.0 (LU)	20.7 (EE)	3.4
Azithromycin	13.5 (EL)	0	>13

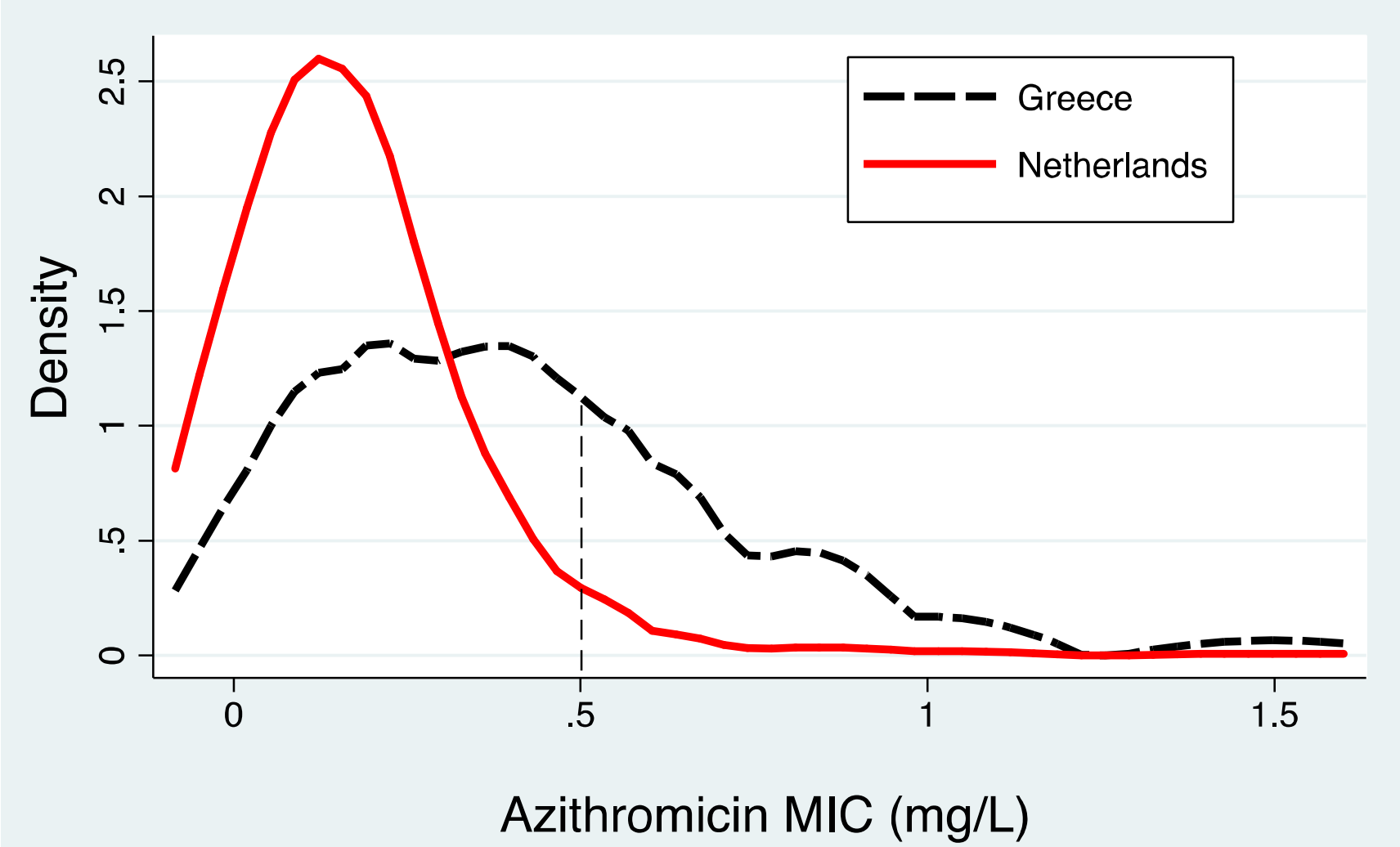
Kenyon JID 2019

Mixed effects linear regression analyses of relationship between AB consumption and AMR

Exposure var	Outcome var	Antimicrobial resistance		Geometric mean MIC	
		Coef.	P-value	Coef.	P-value
Cephalosporin	Ceftriaxone	0.2	0.073	0.003	0.003
Cephalosporin	Cefixime	1.6	0.062	0.004	0.017
Macrolide	Azithromycin	3.0	0.086	0.01	0.497
Quinolone	Ciprofloxacin	16.8	0.006	0.49	0.063

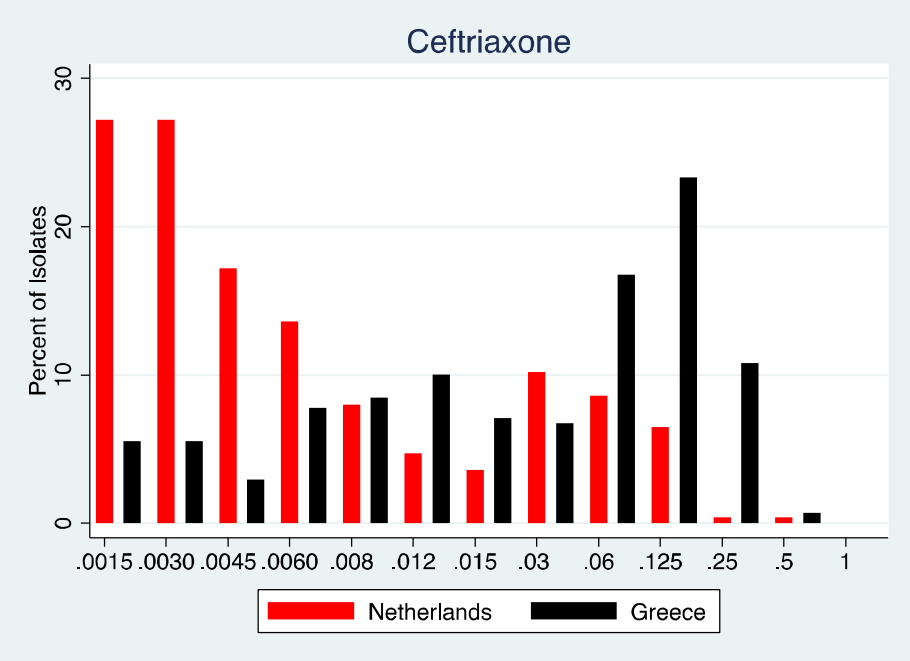
Kenyon JID 2019

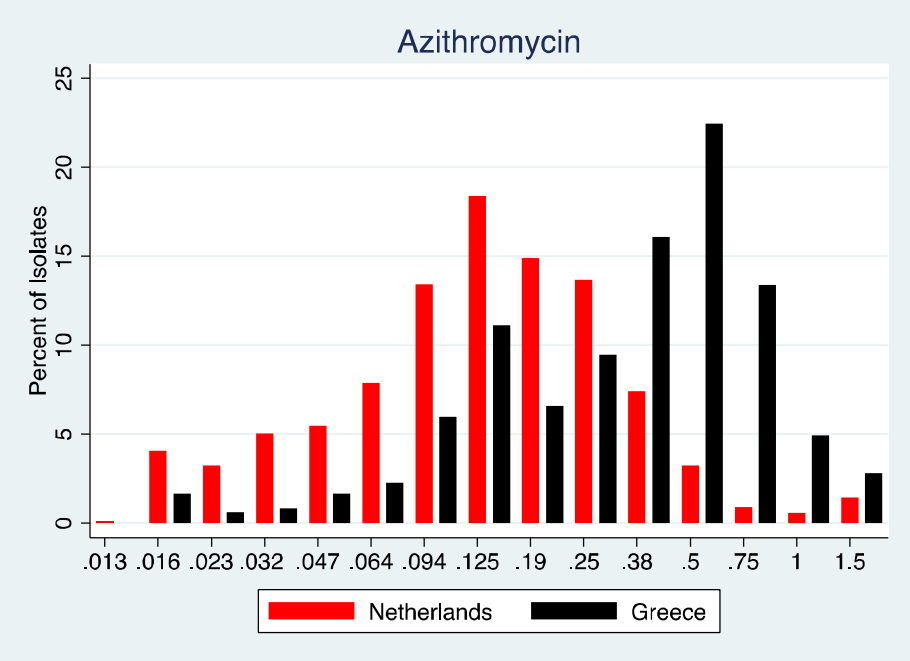
AB consumption predicts geometric mean MIC for susceptible isolates



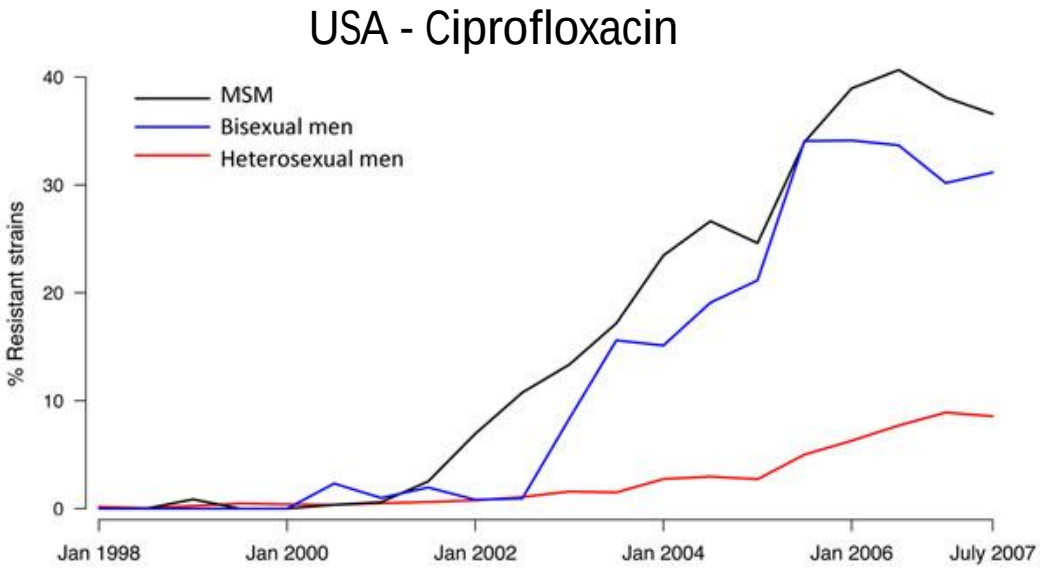
Kenyon JID 2019

High consumption -> right shifted MIC





Kenyon JID 2019



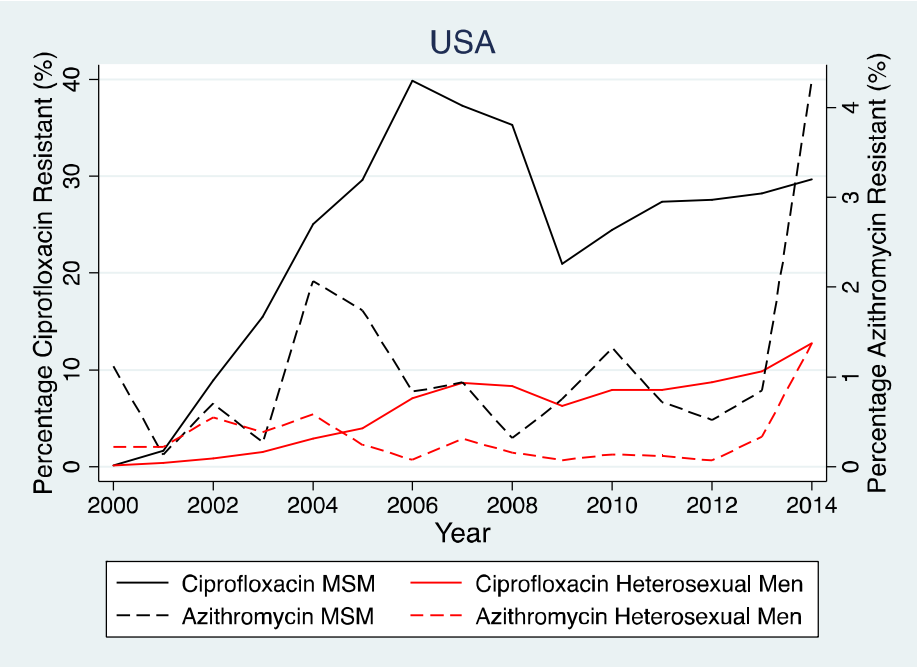
Part 2

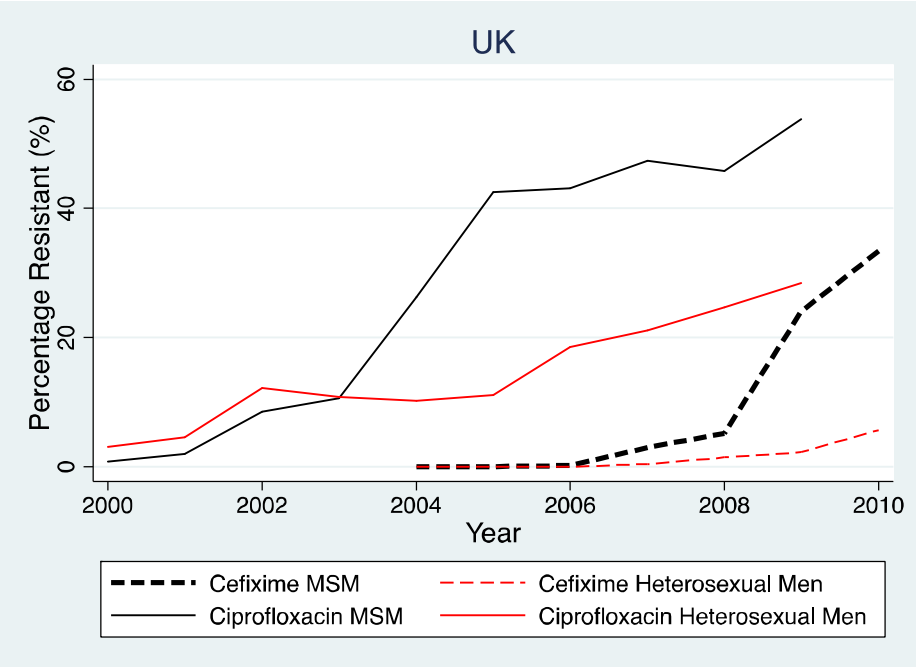
THE ROLE OF AB CONSUMPTION IN CORE GROUPS IN AMR

Emerg Infect Dis 18: 1290-1297

The role of core groups in the emergence and dissemination of antimicrobial-resistant *N gonorrhoeae*

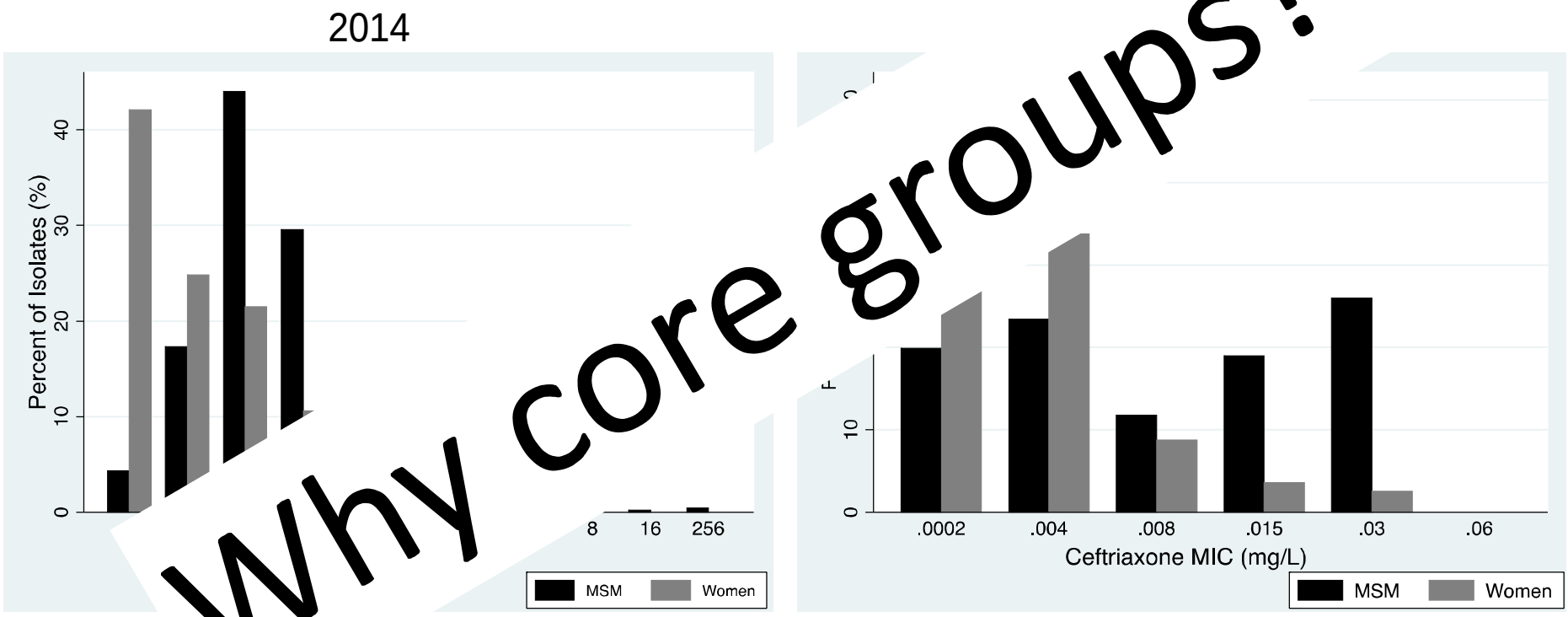
D A Lewis[1,2,3]





Lewis STI 2013; Emerg Infect Dis 18: 1290-1297

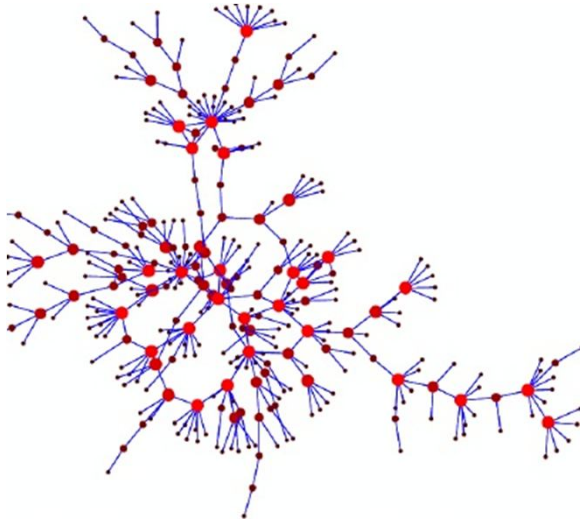
MSM Ng MICs right shifted



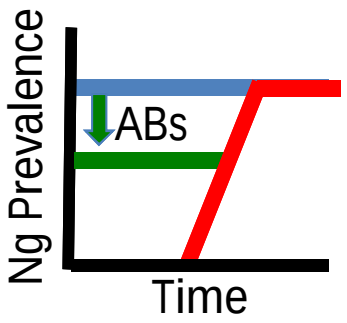
Why core groups?

Kenyon Emerg Infec Dis 2018

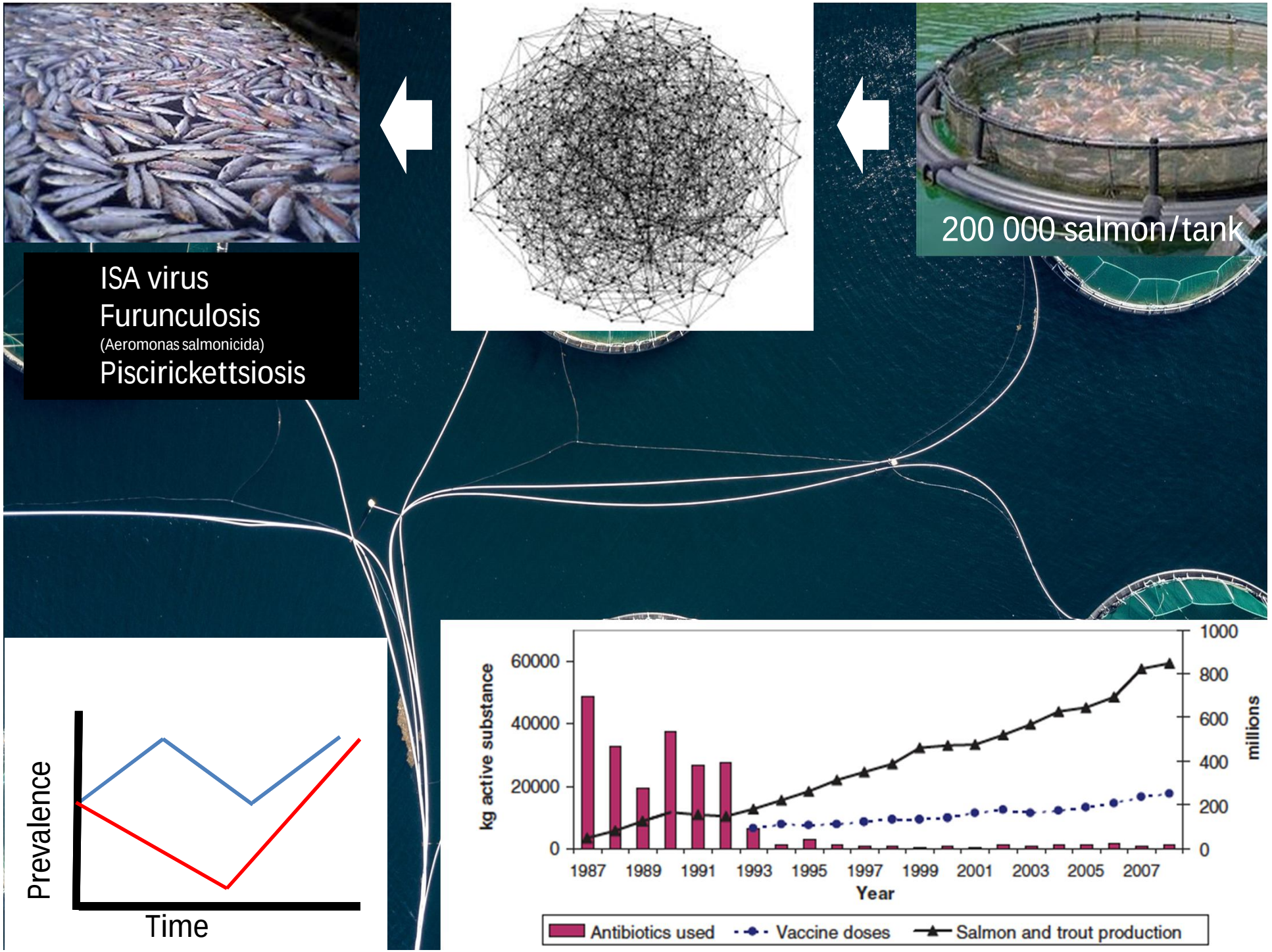
Pharmacoecologic theory of Ng AMR



+

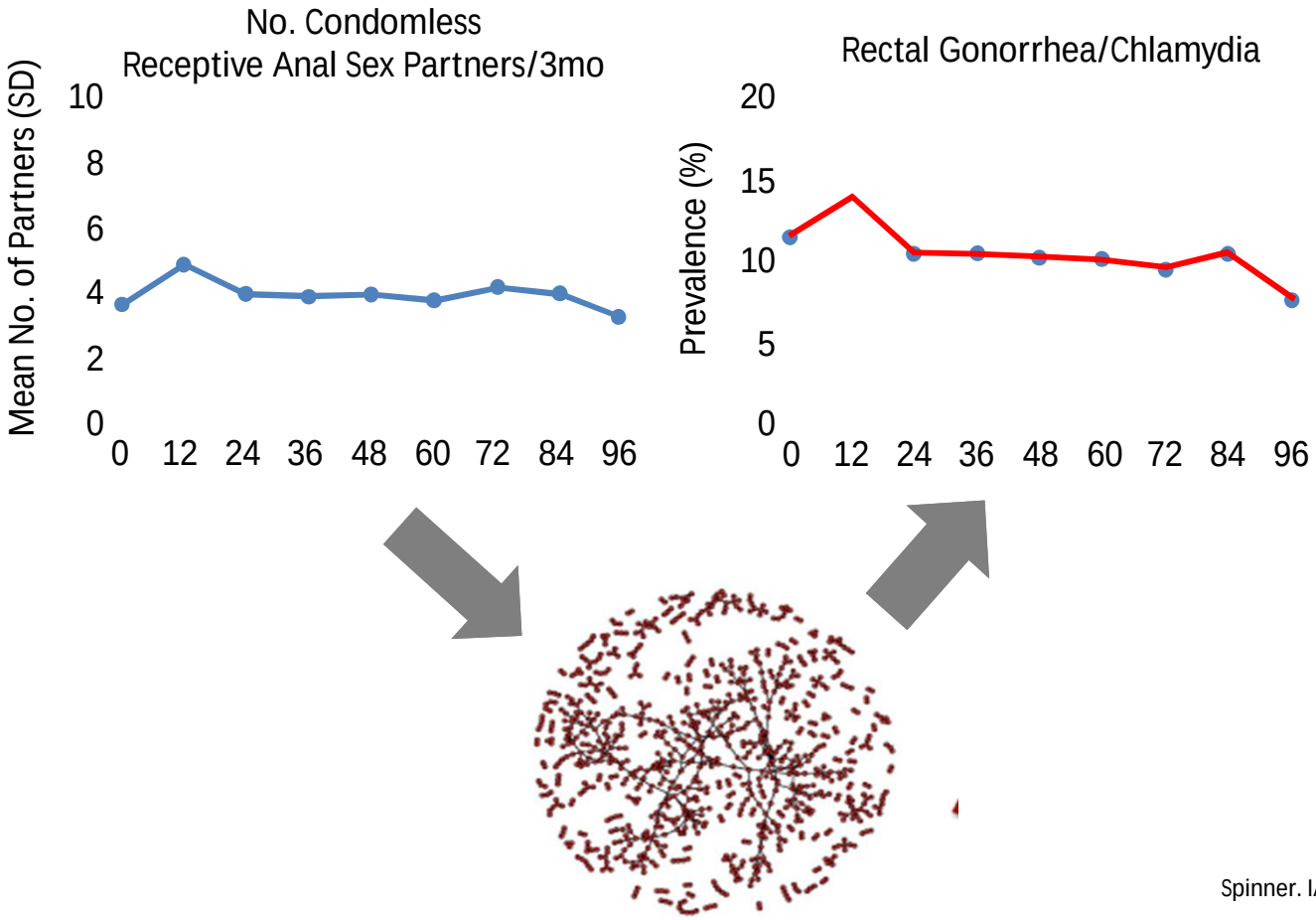


Kenyon et al Emerg Infect Dis 2018; Network: Potterat STI 2002


200 000 salmon/tank
ISA virus
Furunculosis
(Aeromonas salmonicida)
Piscirickettsiosis
Prevalence
Time
kg active substance
millions
Year
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
0
20000
40000
60000
200
400
600
800
1000
Antibiotics used
Vaccine doses
Salmon and trout production

PrEP cohorts: Network connectivity -> high equilibrium prev. NG

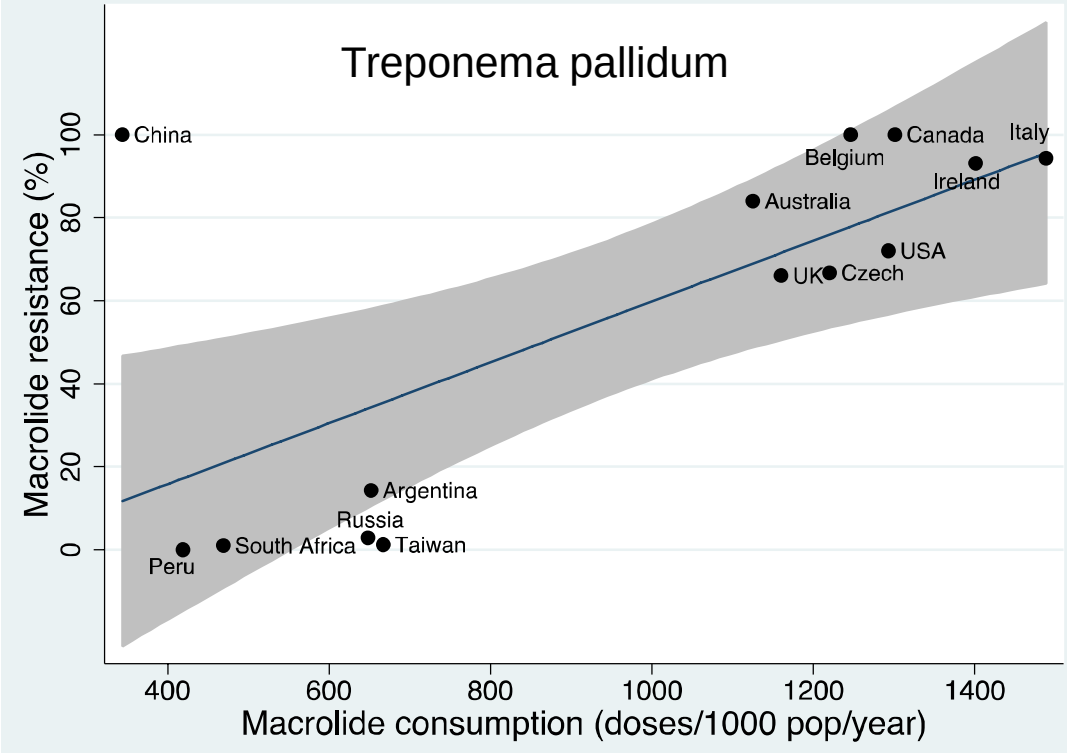
e.g. DISCOVER PrEP RCT



Spinner. IAS 2019. Abstr TUAC0403LB.

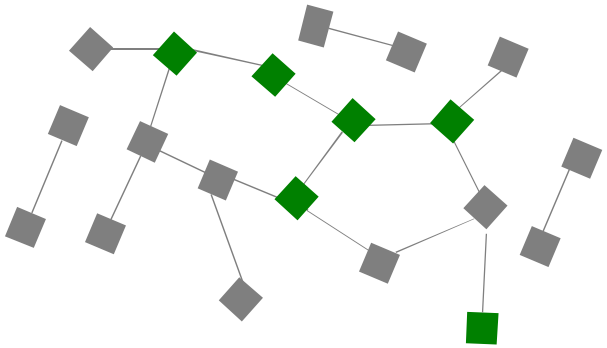
3mo 3 site Ng/Ct screening in PrEP cohorts -> ++ AB consumption

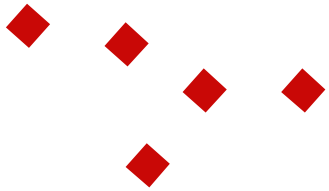
- Macrolides: 4400 dose/ 1000 pop/yr (11-fold higher than NL)
- Cephalosporins: 256 dose/ 1000 pop/yr (3-fold higher NL)



Kenyon AIDS 2018; Kenyon J Med Micro 2018

Network connectivity + **Intensive screening**





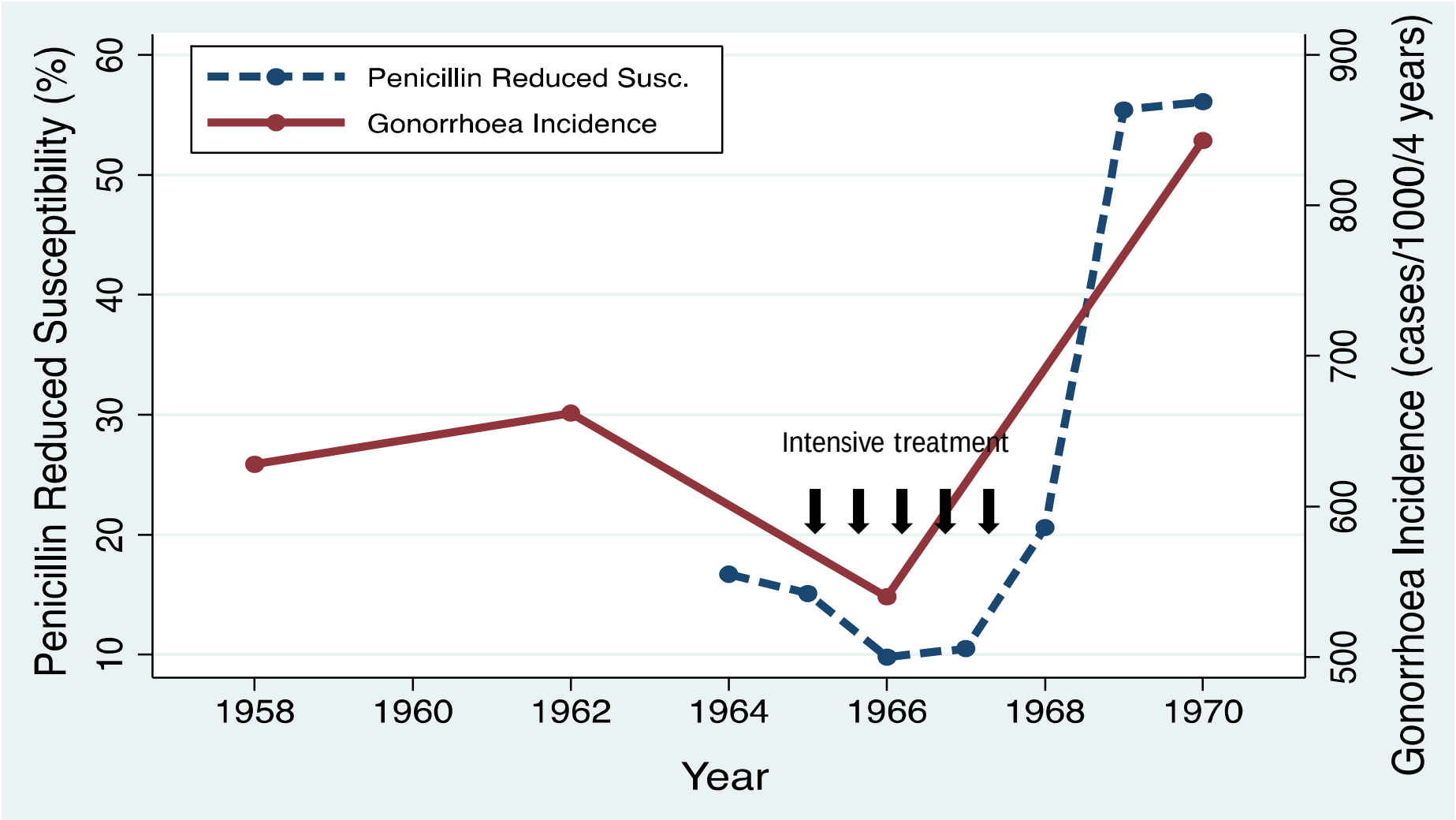
High MICs in commensal *Neisseriae* in Belgian MSM

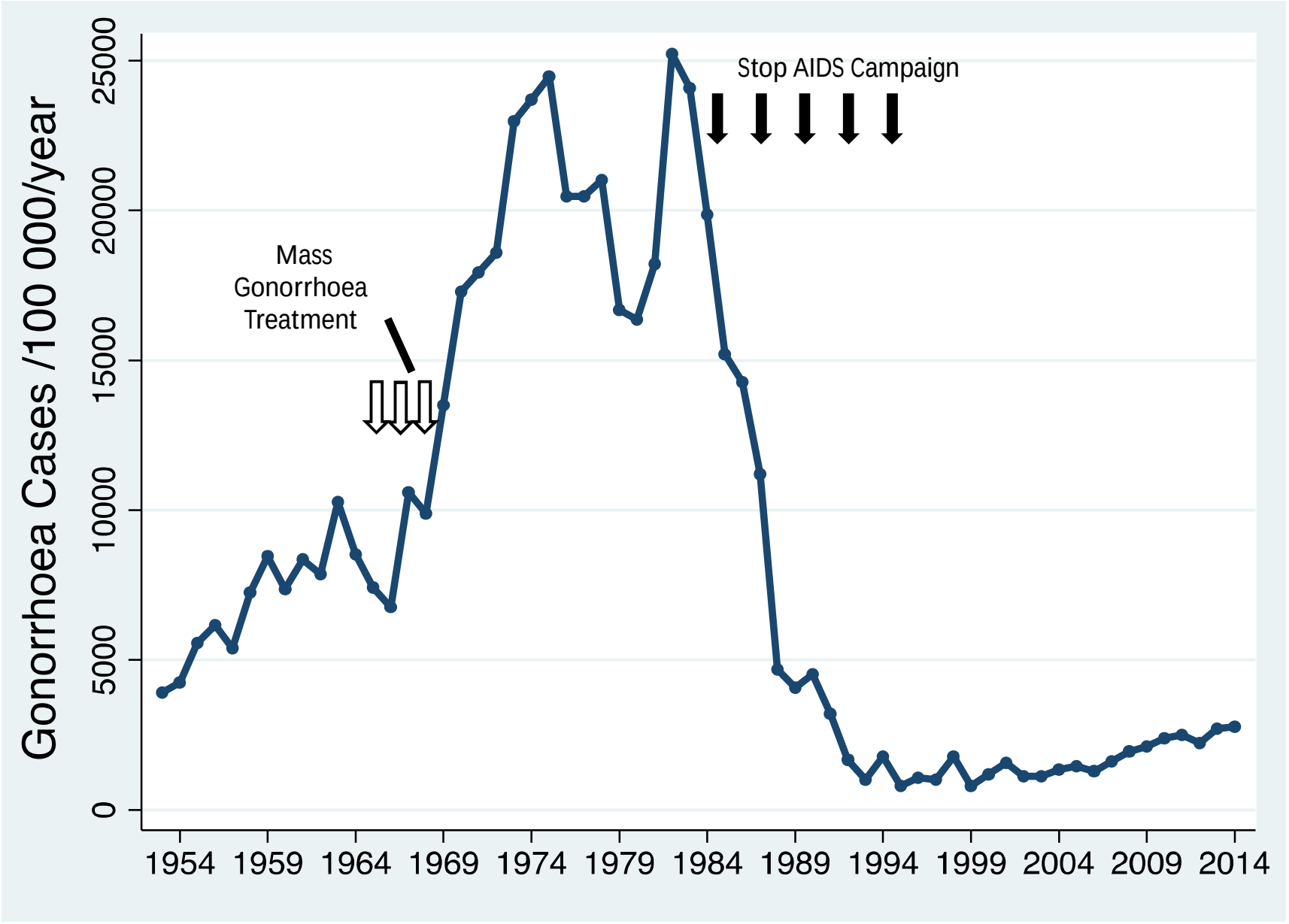
Neisseria subflava	**Belgium 2019 - Median MIC (Range) n=11** mg/L	**Japan 2005 - Median MIC (Range) n=45** mg/L	**ITM Collection (1983-2013) n=6** mg/L
Azithromycin	256 (0.047- >256)	-	1 (0.5-4)
Ceftriaxone	0.38 (0.023-2.0)	0.03 (0.001-0.12)	0.03 (0.015-0.06)
Method	E-test	Agar dilution	E-test
Reference	Unpublished	Furuya JIC 2017	Unpublished

Commensal *Neisseriae* as early warning system?

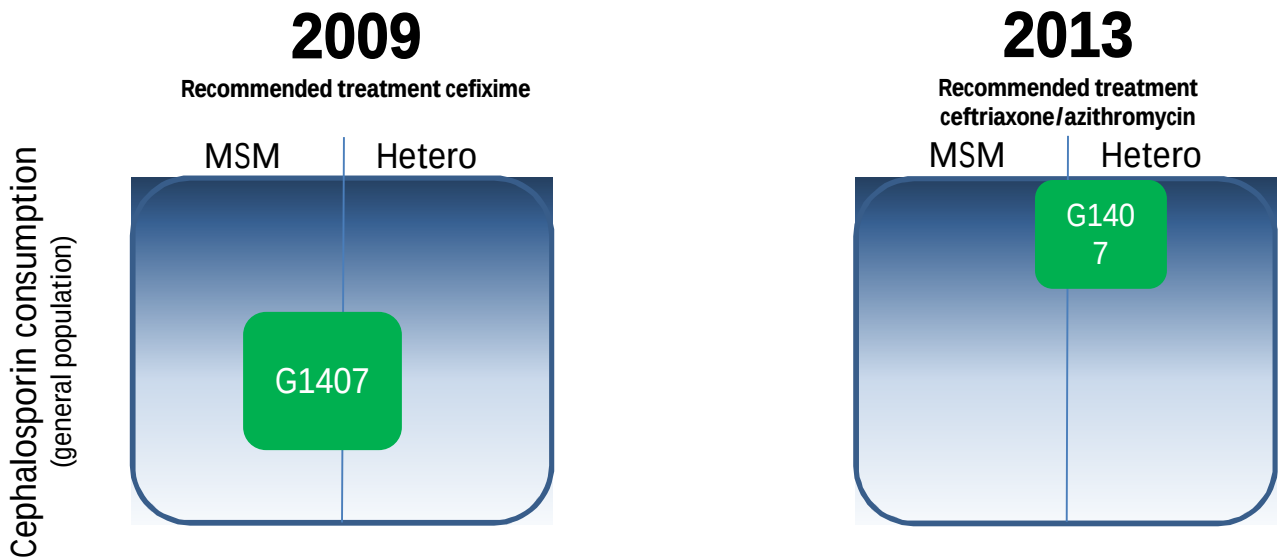
Mass treatment/screening -> AMR

e.g. Greenland





Kenyon STDs 2019

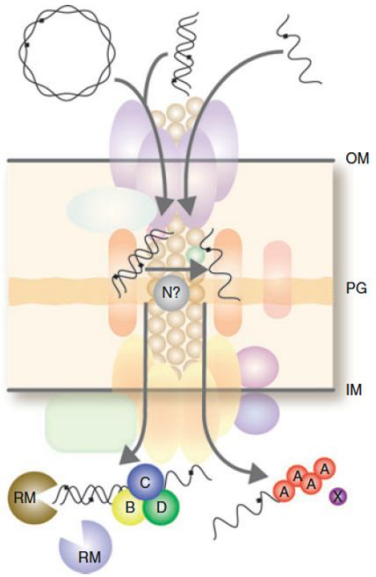


Part 3

COMBINING POPULATION & CORE GROUP PERSPECTIVES

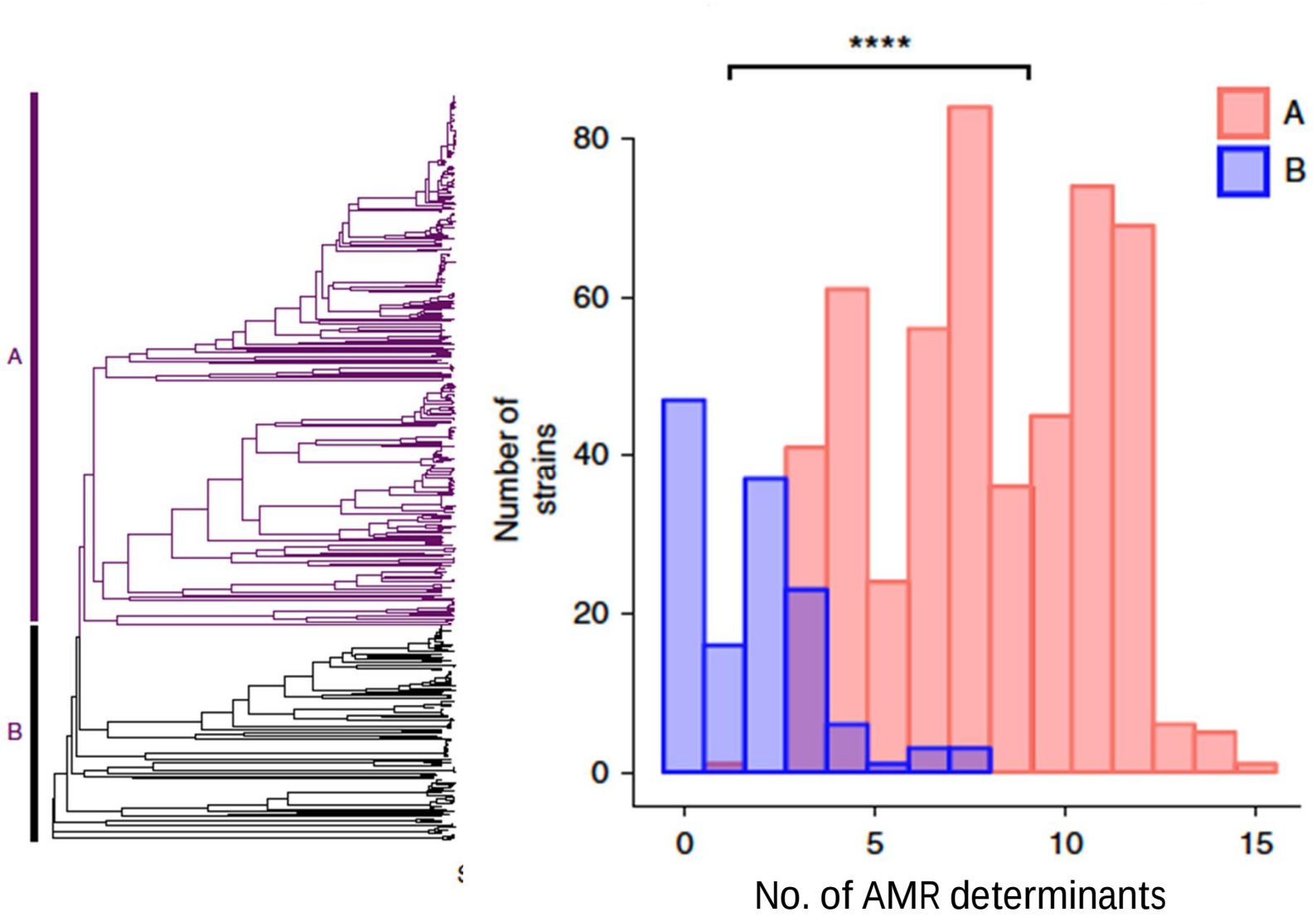
The impact of antimicrobials on gonococcal evolution

- WGS phylogeographical analysis of 419 gonococcal isolates from 5 continents 1960-2013
- ++ admixture
- No significant differentiation between continents (except Africa)

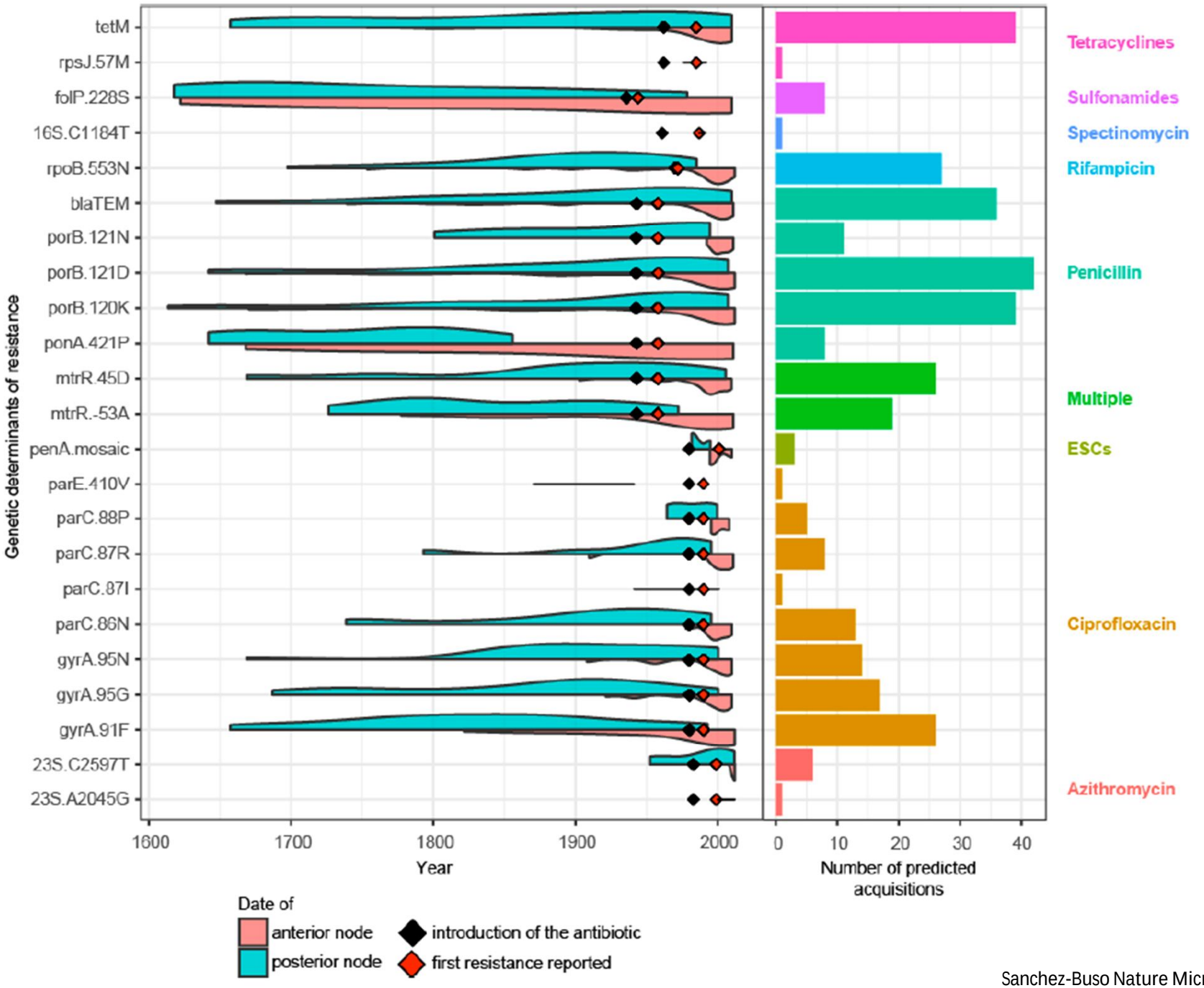


Sanchez-Buso Nature Micro 2019; Hamilton Mol Micro 2015

Lineage B -> hope

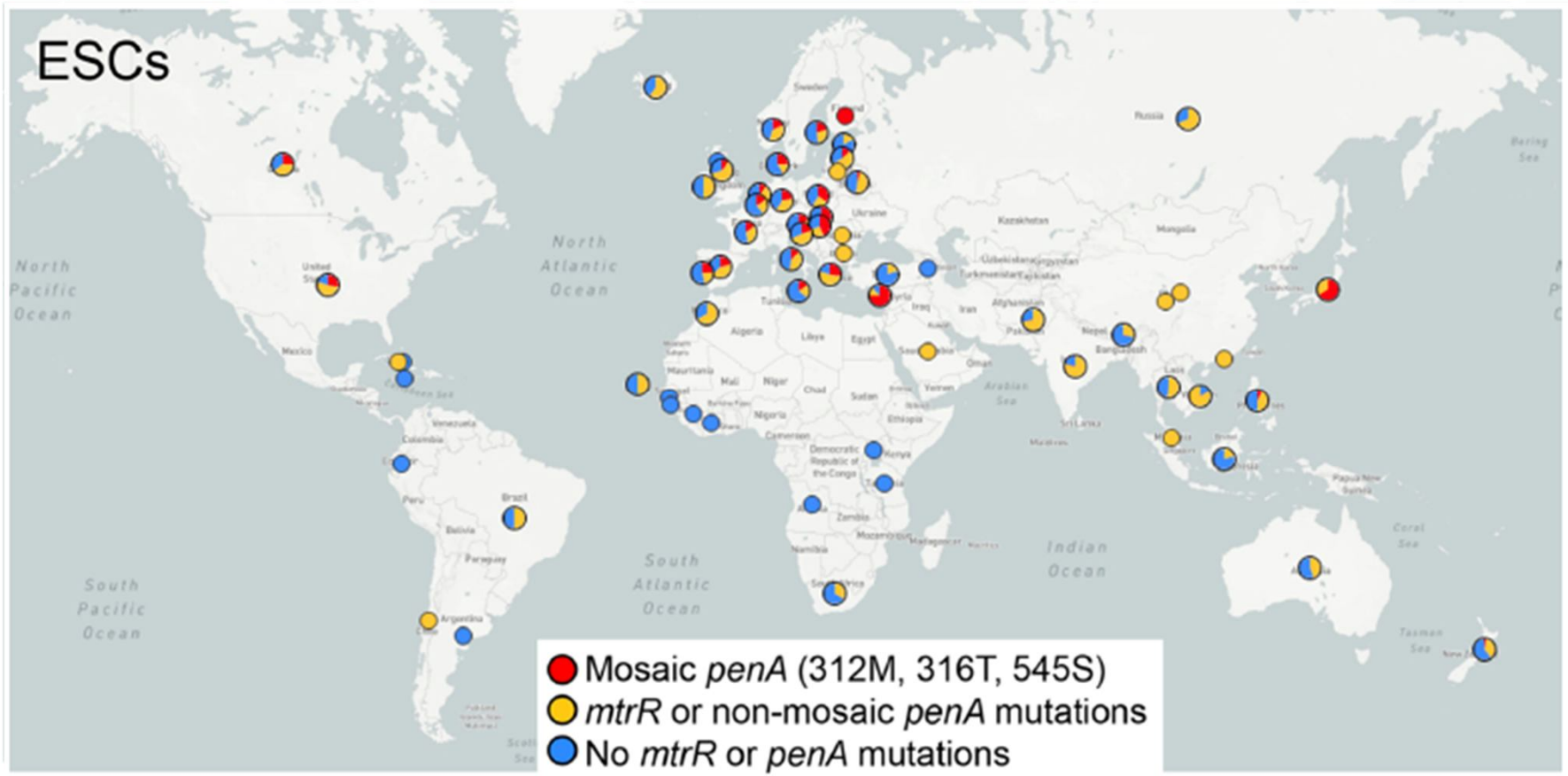


Sanchez-Buso Nature Micro 2019



Sanchez-Buso Nature Micro 2019

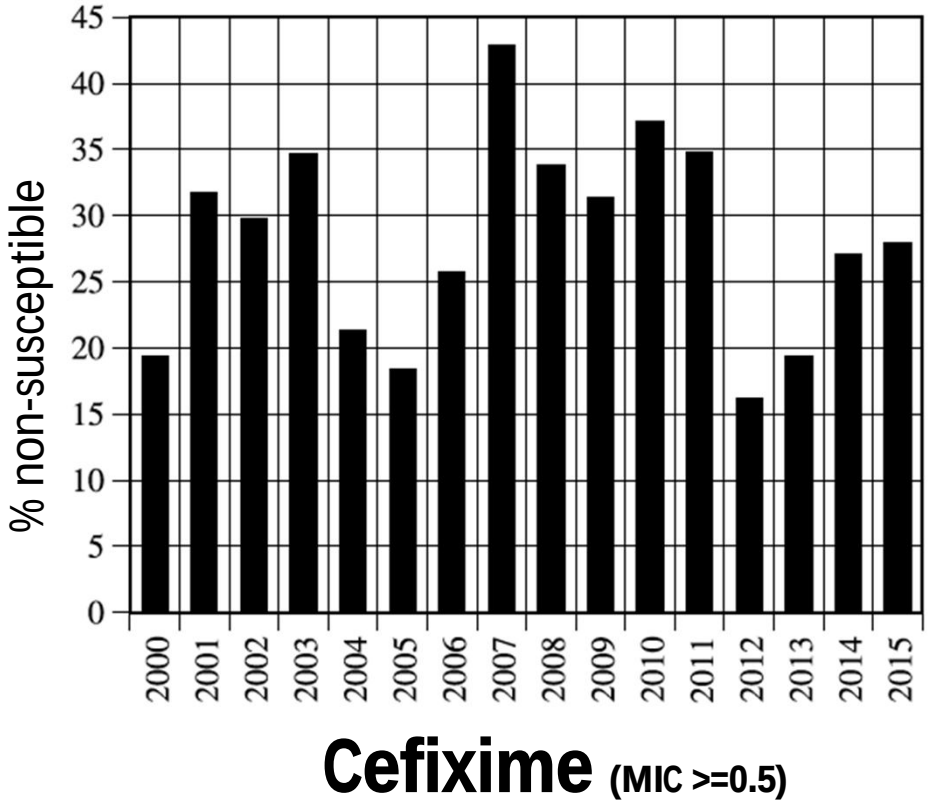
AMR freq. emerges in core groups in Asia



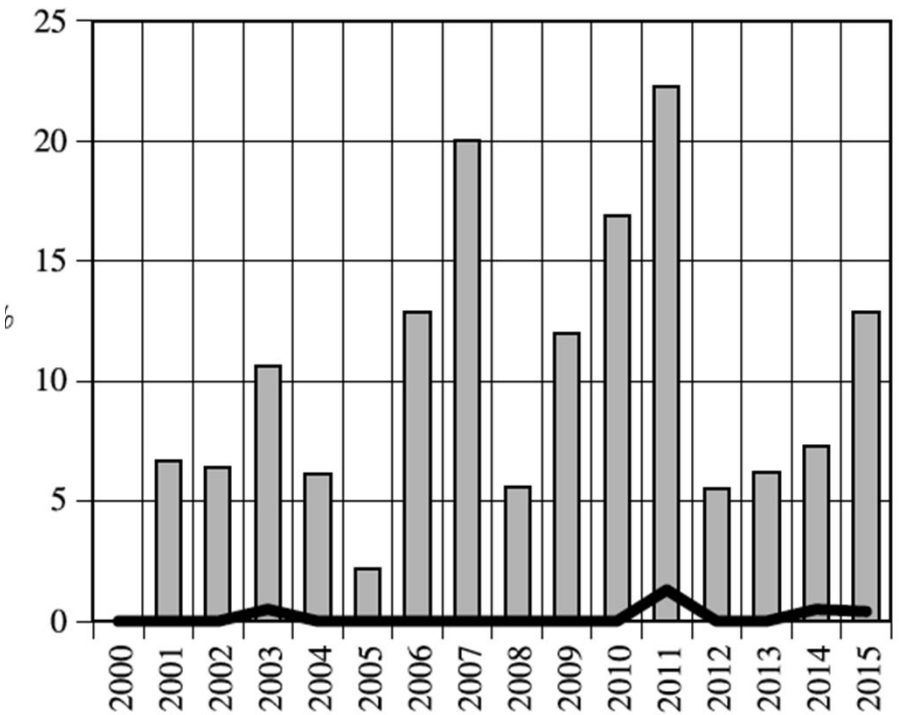
Sanchez Buso 2019 Micro genetics

ESCephalosporin AMR arises in Japan

- 1995 – world's first case cefixime R (mosaic penA)
- 2009 – world's first case ceftriaxone R (FSW) (mosaic penA –less fit so doesn't spread)
- 2014 – 2 new cases (mosaic penA - spreads)



Cefixime **(MIC >=0.5)**

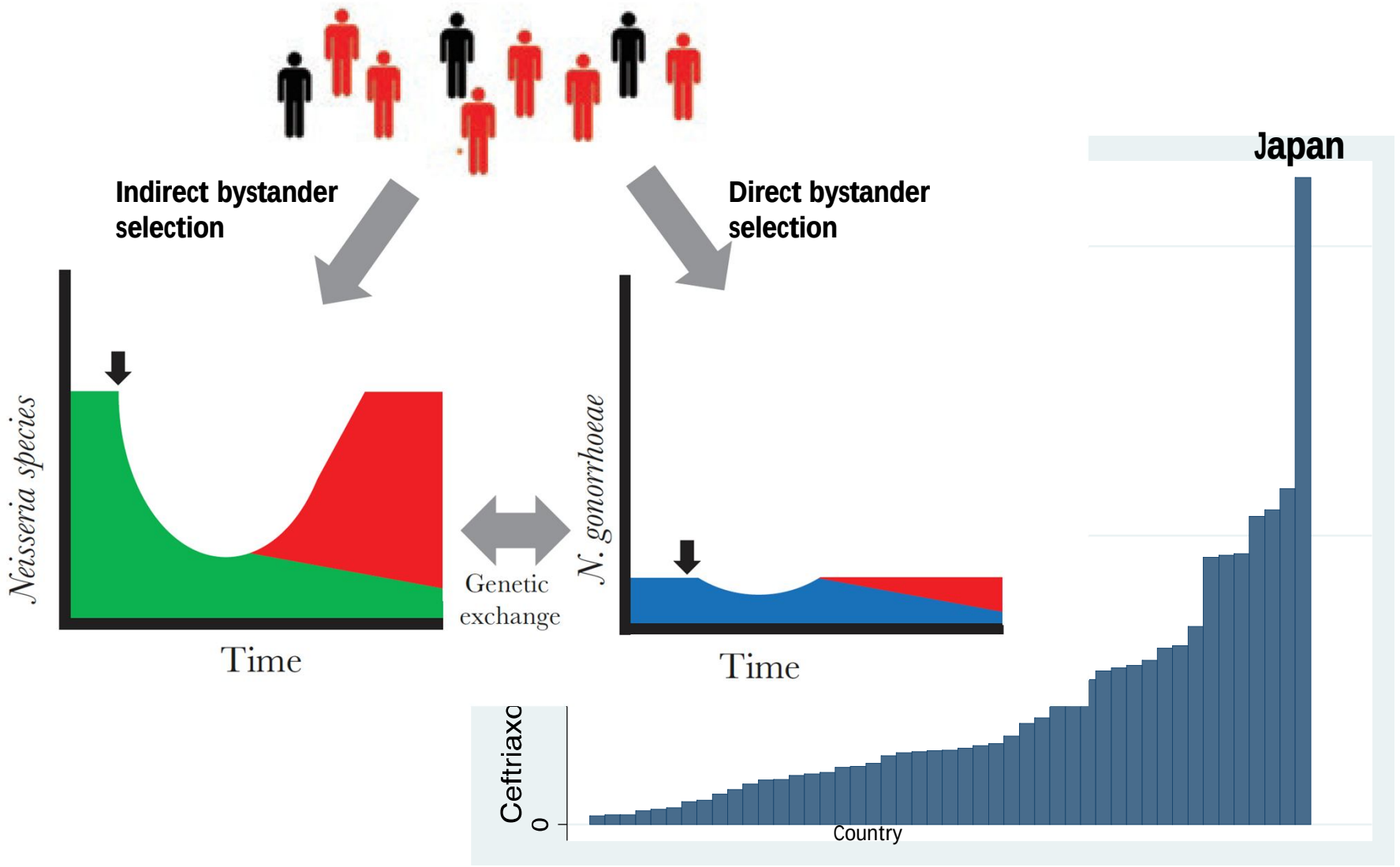


Ceftriaxone

(MIC >=0.25 – bars, >=.5 = line)

Yasuda 2017 STDs

Why Japan?

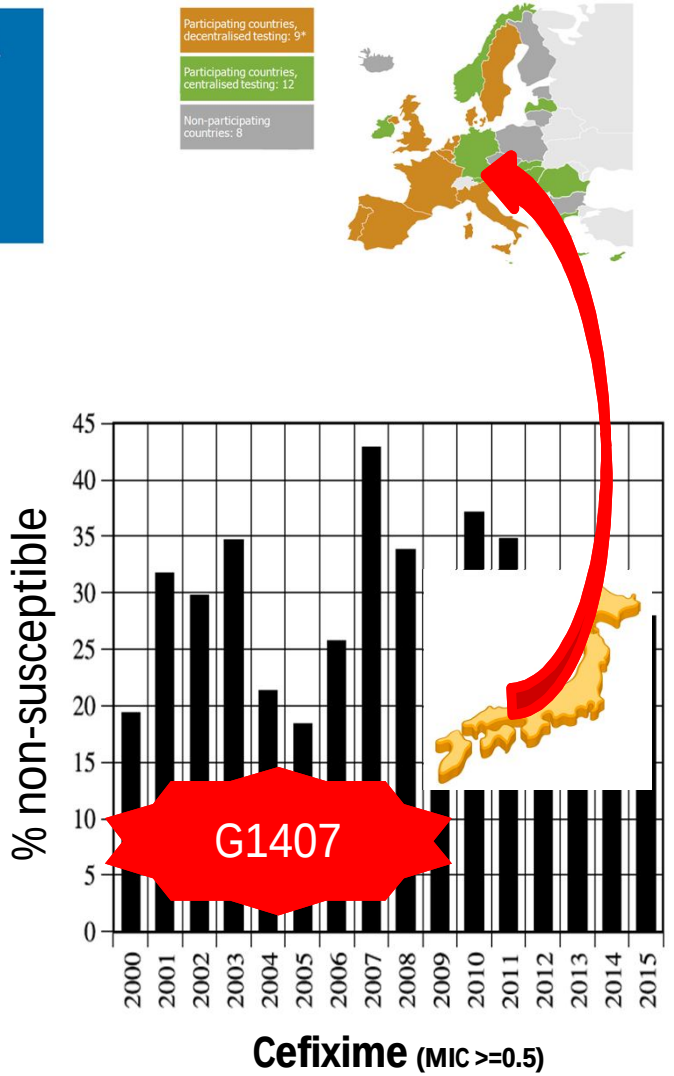


Kenyon Frontiers in Med 2018

Molecular epidemiological typing within the European Gonococcal Antimicrobial Resistance Surveillance Programme reveals predominance of a multidrug-resistant clone

- G1407

	2009
Prevalence	23%
Ciprofloxacin R	100%
Cefixime RS (≥0.06)	96%
Transmission	MSM (OR 1.8)



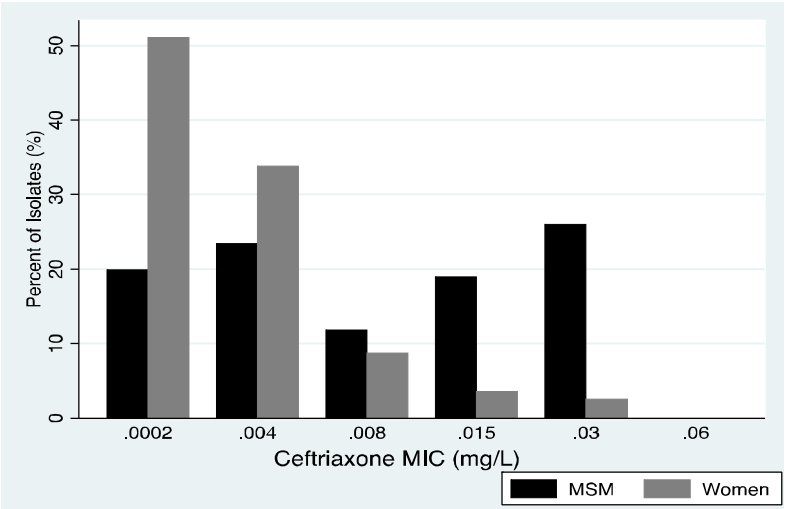
CFX-> CRO/AZM

Chisholm EuroSurveill 2013

Cefixime Era -> Direct selection of AMR in MSM

Direct selection

CFX used to treat Ng



Indirect bystander selection

Direct bystander selection

High CFX consumption in population

Ceftriaxone/AZM Era -> indirect selection in general population

Direct selection

CRO/AZM used to treat Ng

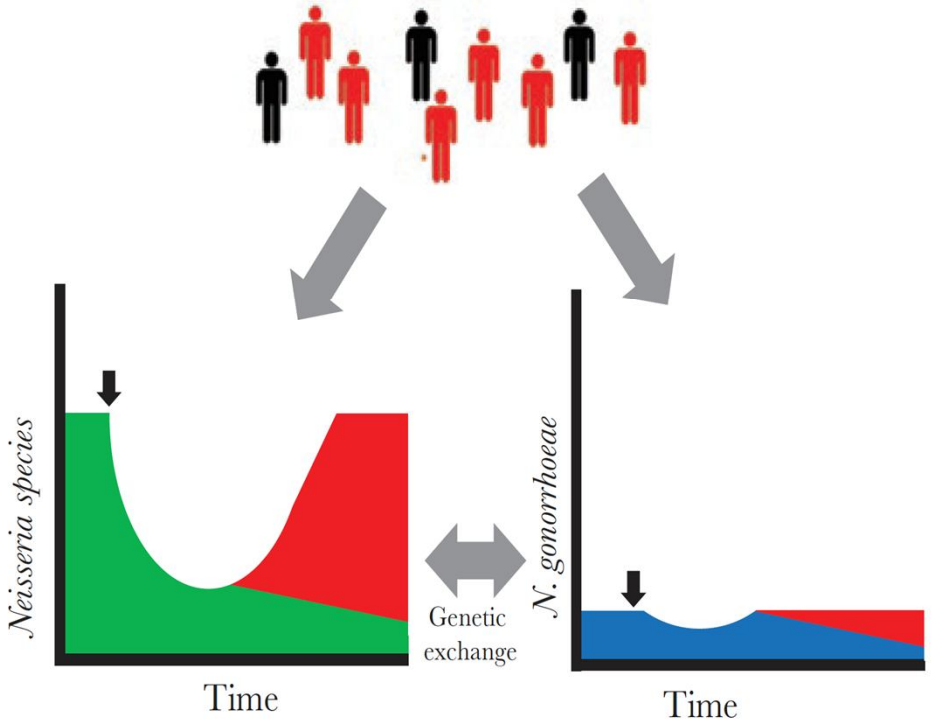
MSM

Hetero

Indirect bystander selection

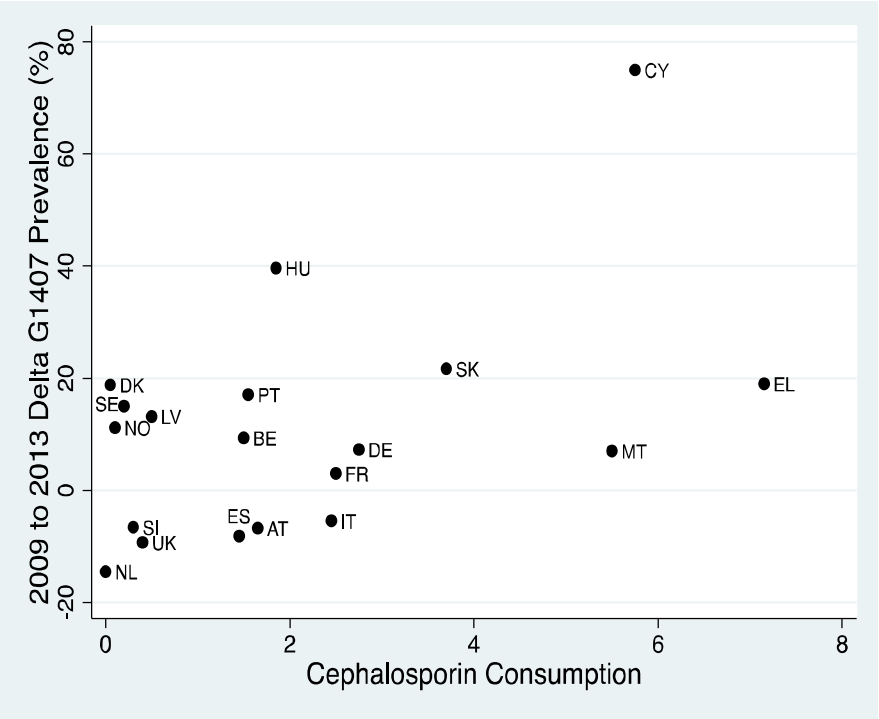
Direct bystander selection

High Cef/Macro/FQ consumption in population

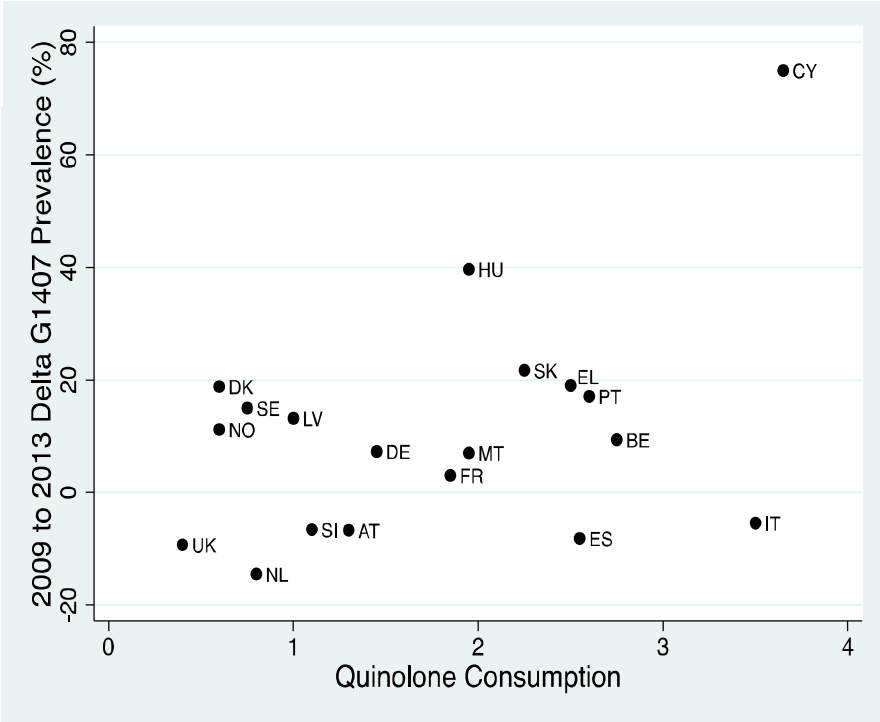


Cephalosporin/FQ consumption selects for mosaic penA/G1407 in Europe ?

- 1054 Ng WGS from 24 countries EURO GRASP 2013
- AB Consumption from ESAT 2011/12



Coeff. 3.9, 95% CI 0.5-7.4



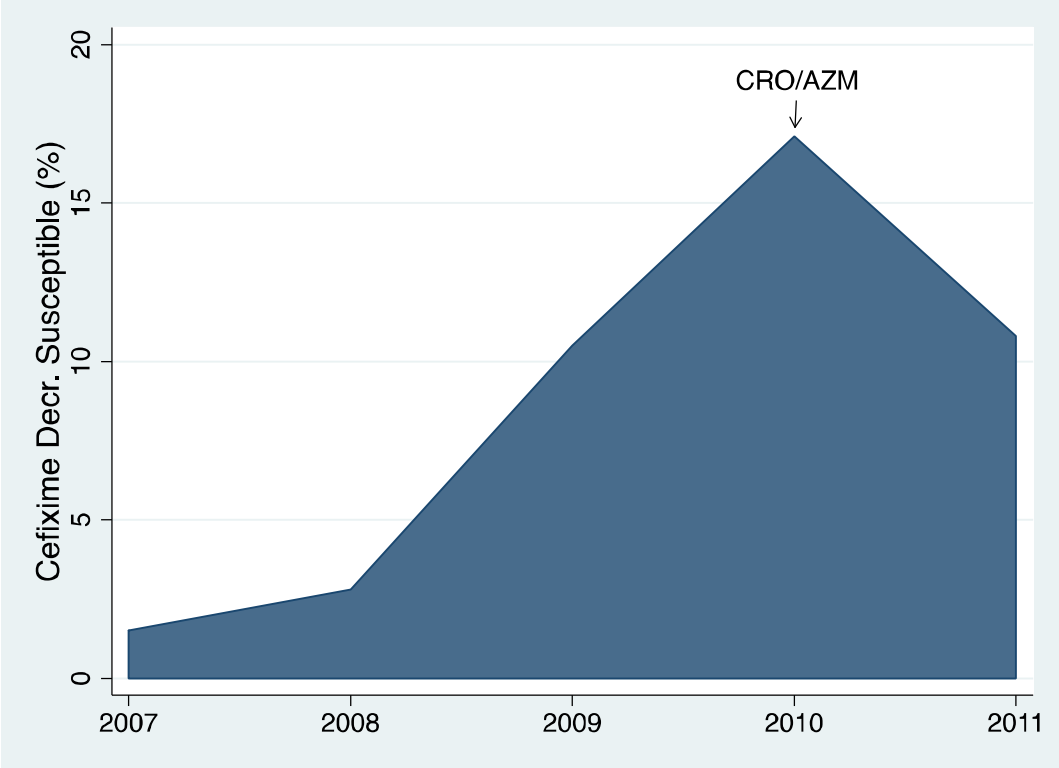
Coeff. 9.4, 95% CI 2.4-16.3

Unpublished

Rise and fall of CFX DS/G1407 in UK

G1407:

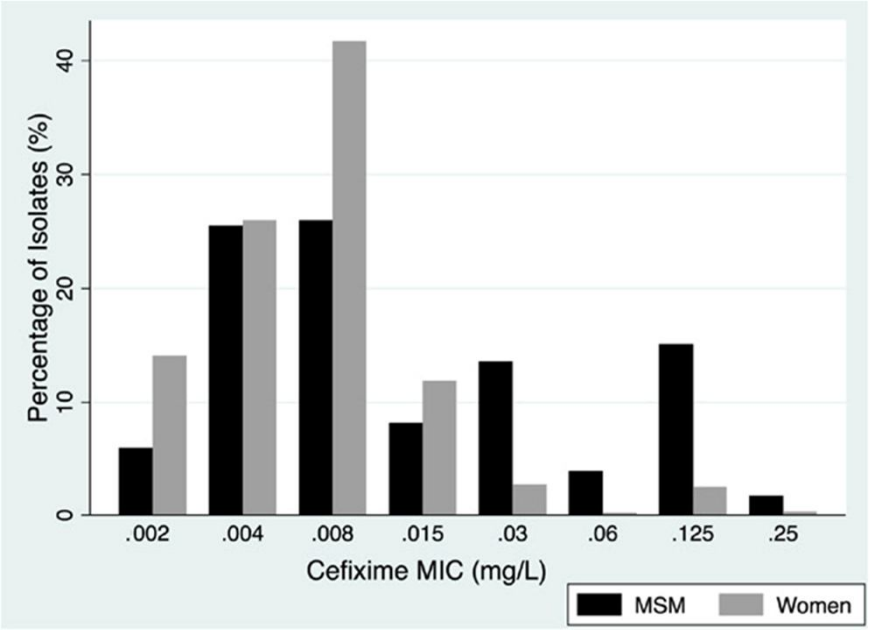
- Accounts for almost all CFX DS
- MSM OR -5.8



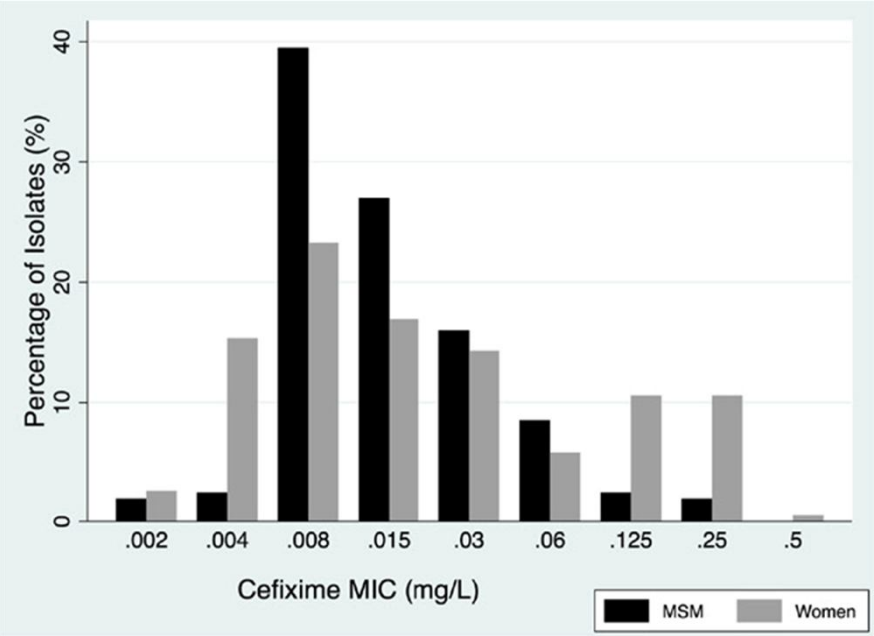
Ison Lancet 2013

UK: MICs of isolates from MSM no longer right shifted

2011

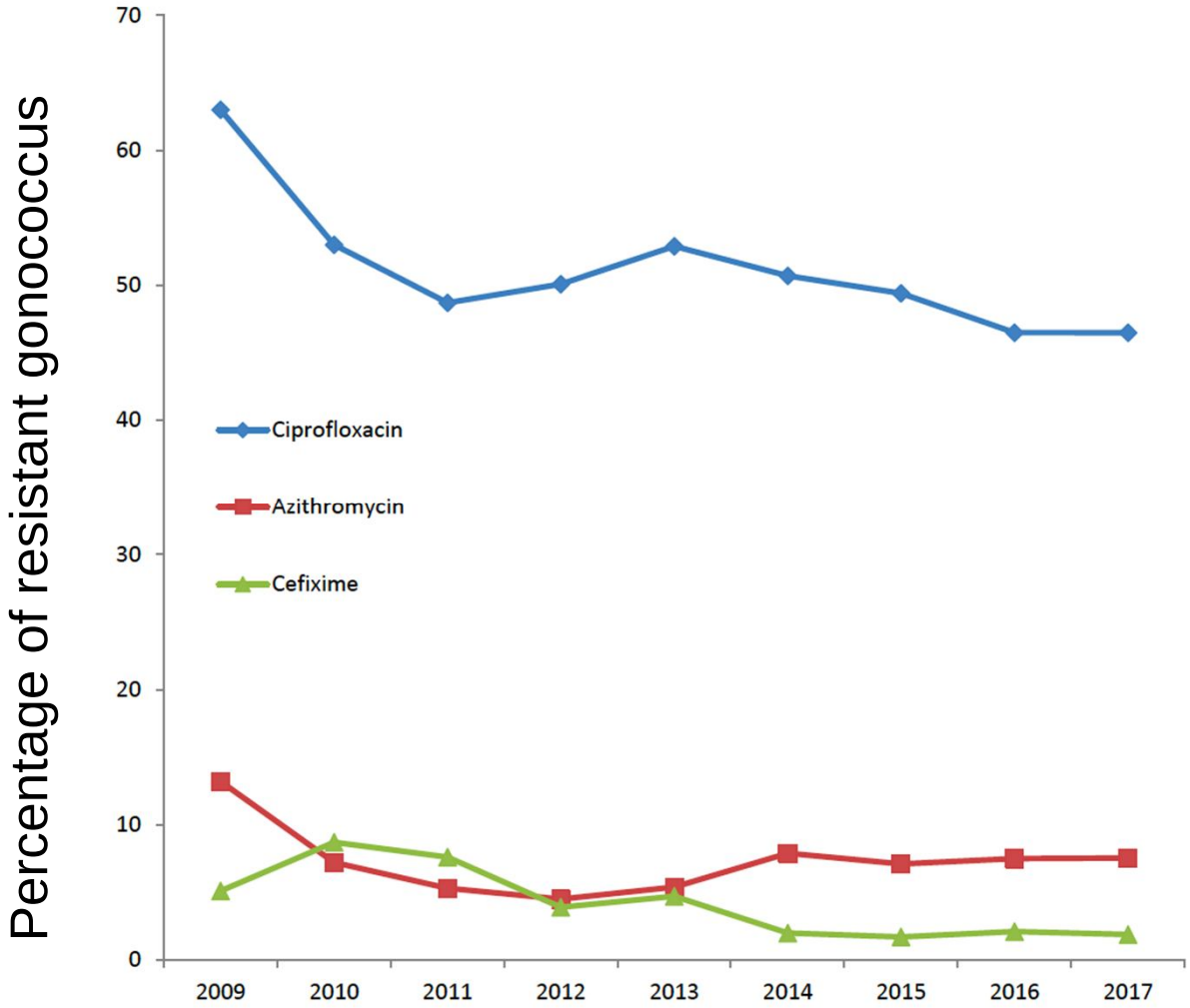


2013



Kenyon F1000Res 2018

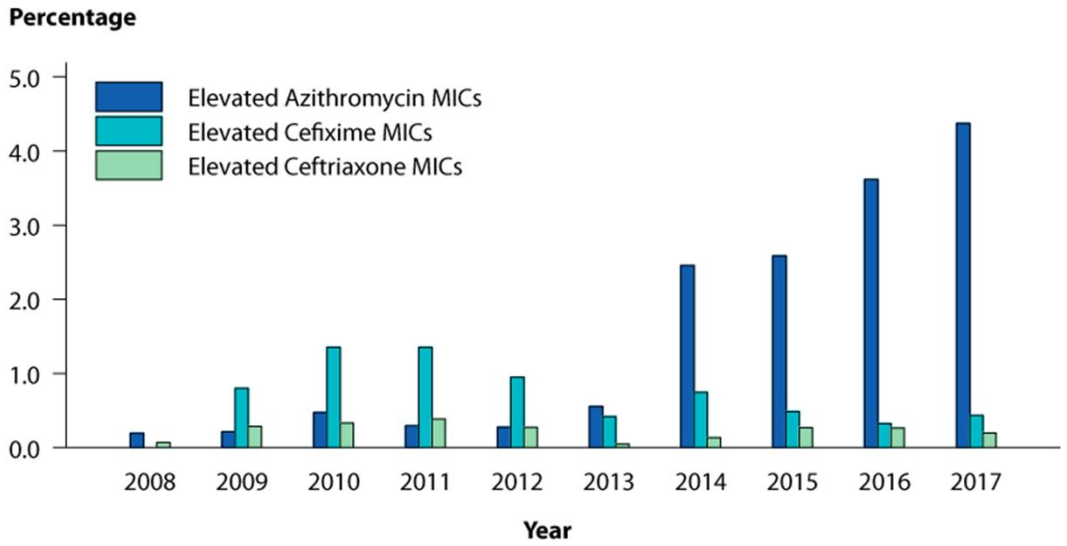
Cefixime resistance declines in Europe



Euro-GASP 2018

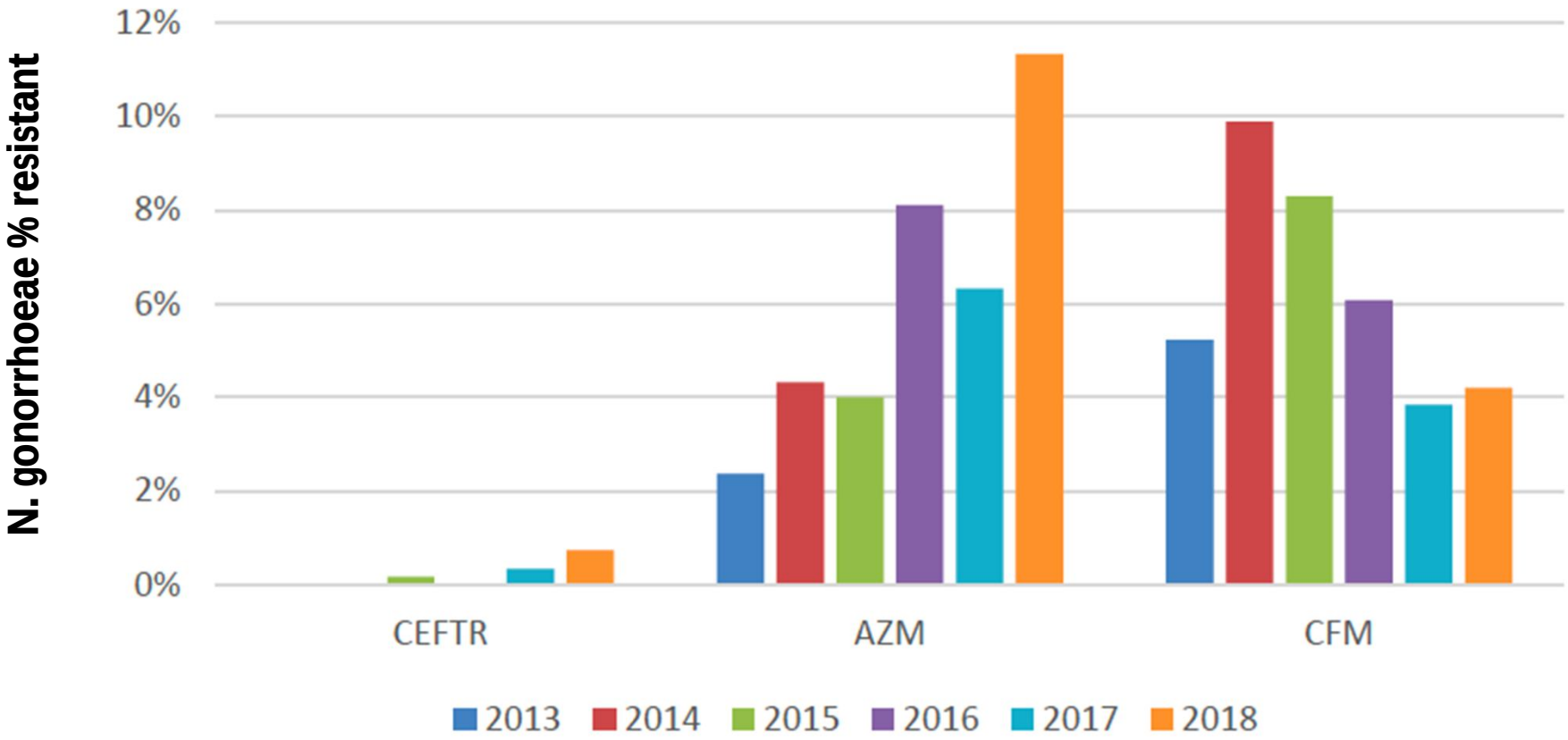
USA – similar story

- Switch to CRO/AZM
  - Decline in CFX resistance 1.4% -> 0.4%
  - CFX resis MSM vs. hetero 11-fold to 3-fold



GISP 2018: Unemo Microbiol Spectr 2016

Belgium

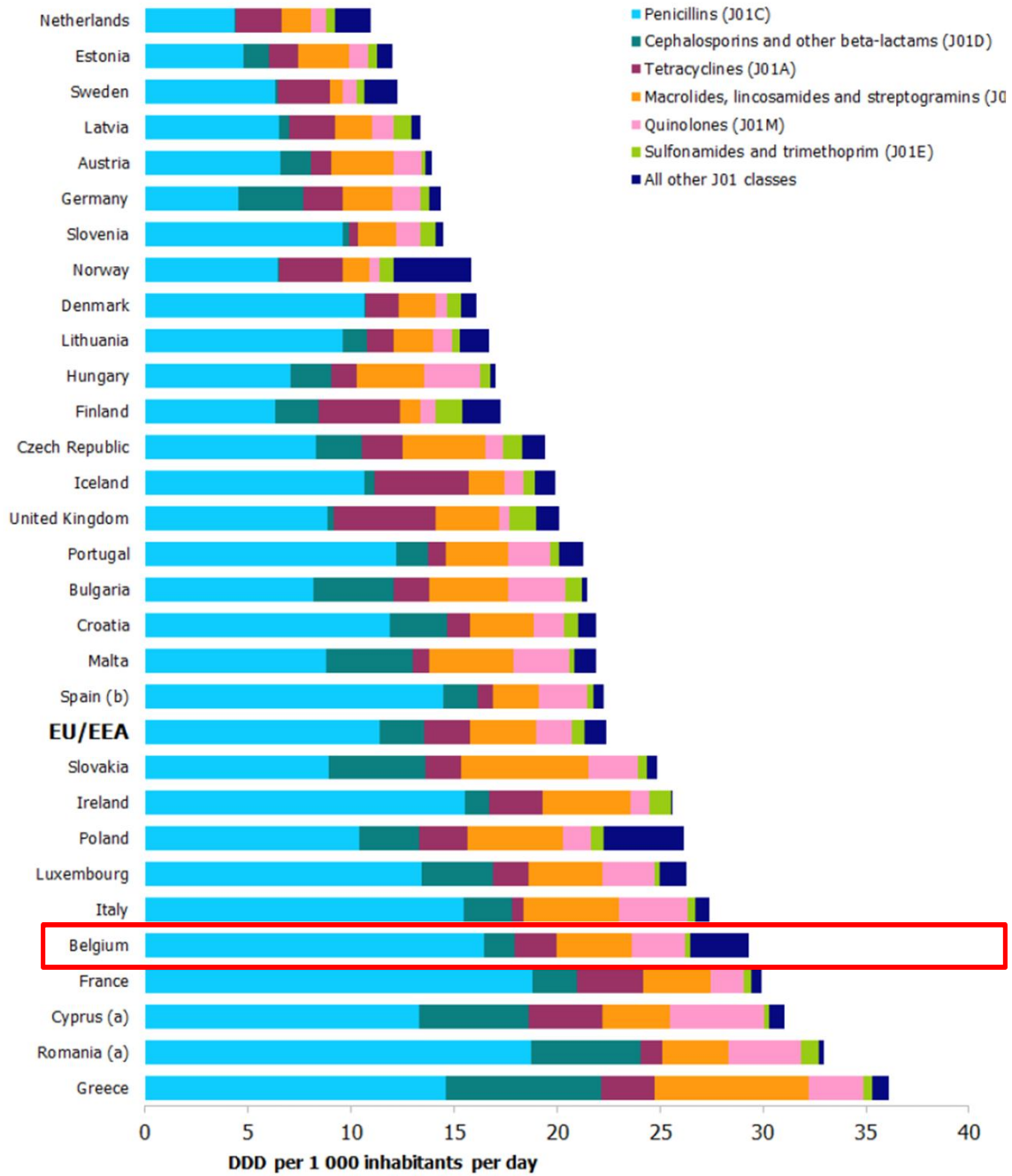


AZM R: >=1mg/L

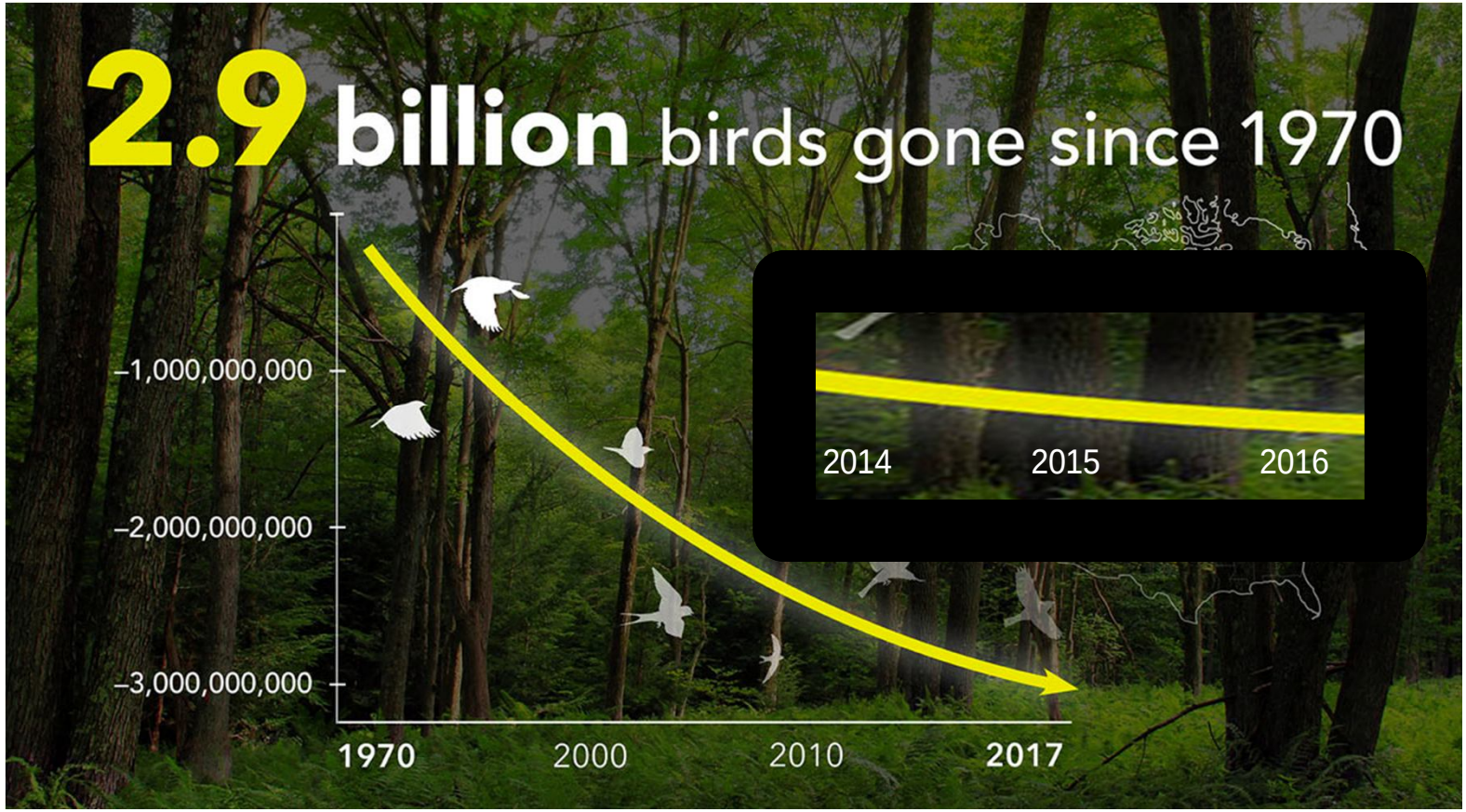
De Baetselier 2019 Jaarrapport Gonokokken surveillance 2018

Bystander selection

Figure 2. Consumption of antibacterials for systemic use (ATC group J01) and ATC group level the community, EU/EEA, 2015, expressed as DDD per 1 000 inhabitants per day



ECDC 2018



Part 4

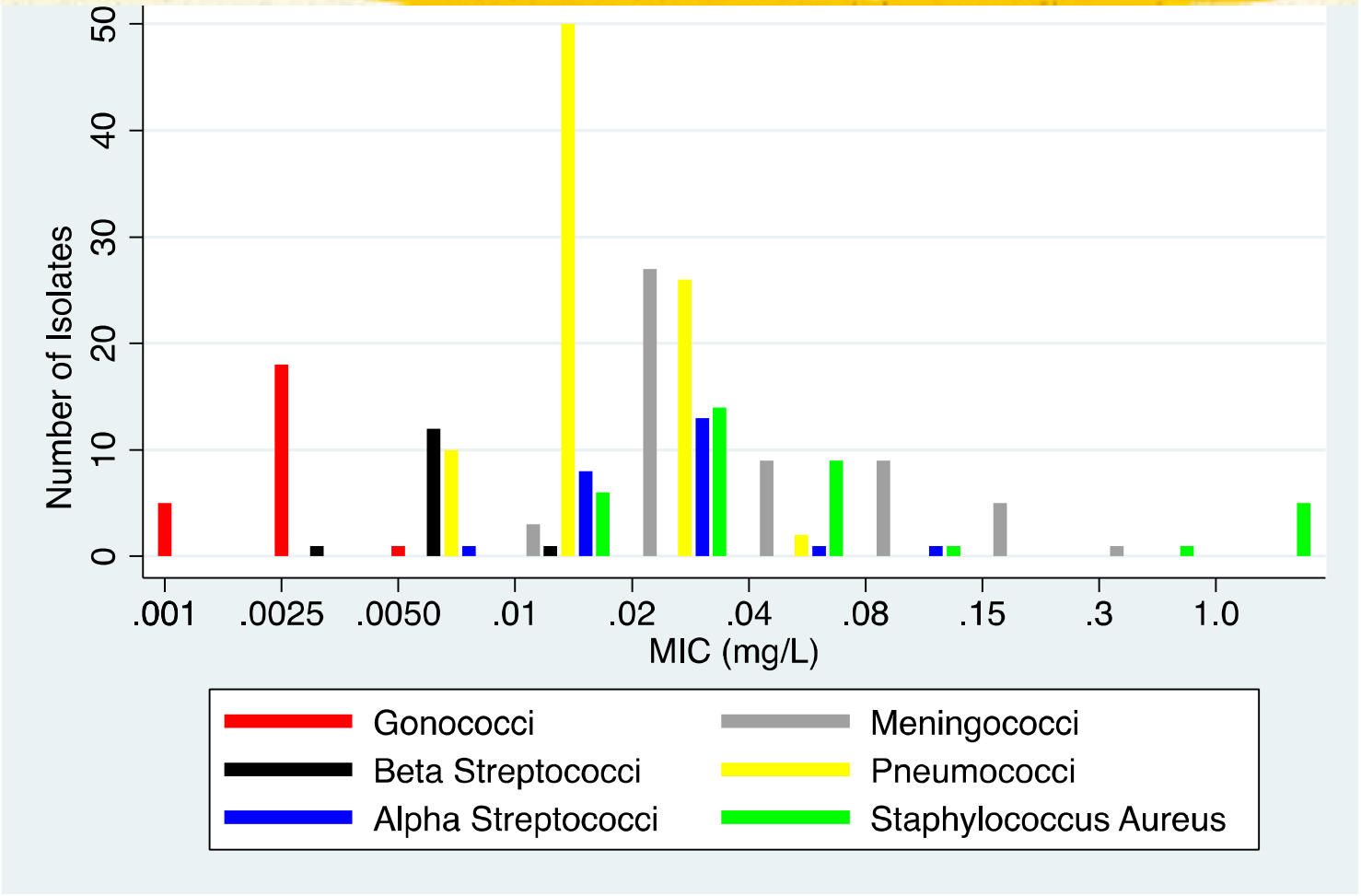
EVOLUTION OF NG MIC DISTRIBUTIONS OVER LAST 75 YEARS –

OVERCOMING THE SHIFTING BASELINE SYNDROME

PENICILLIN SENSITIVITY OF STRAINS OF SIX COMMON PATHOGENS AND OF HEMOPHILUS HEMOLYTICUS

MANSON MEADS, M.D., EDWIN M. ORY, M.D.,
CLARE WILCOX, AND MAXWELL FINLAND, M.D.
BOSTON, MASS.

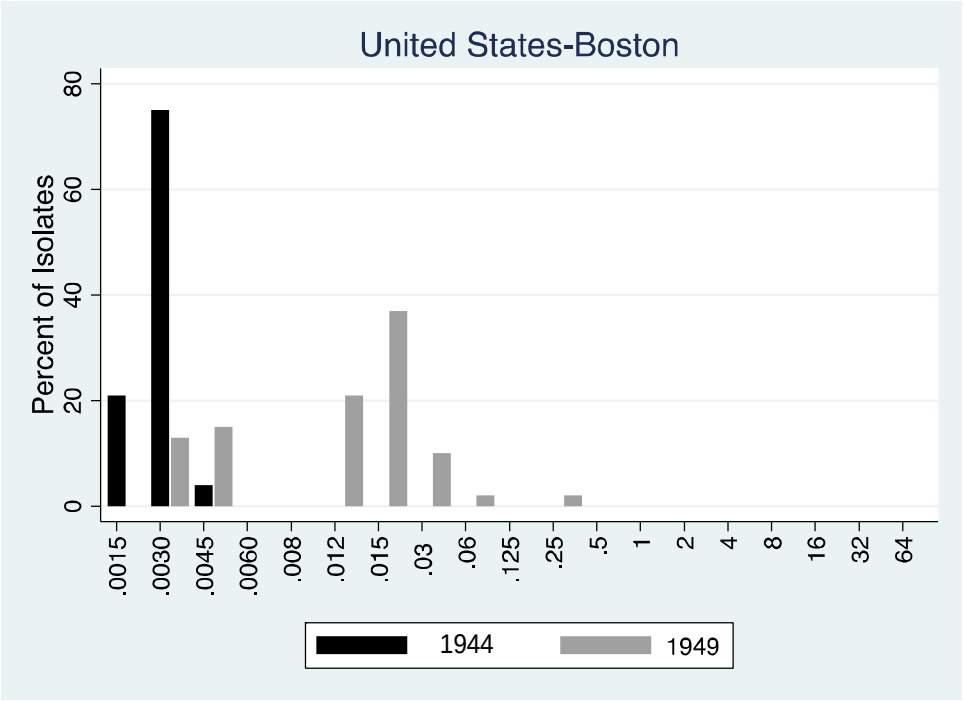
Gonococcus was the most sensitive of the organisms studied.

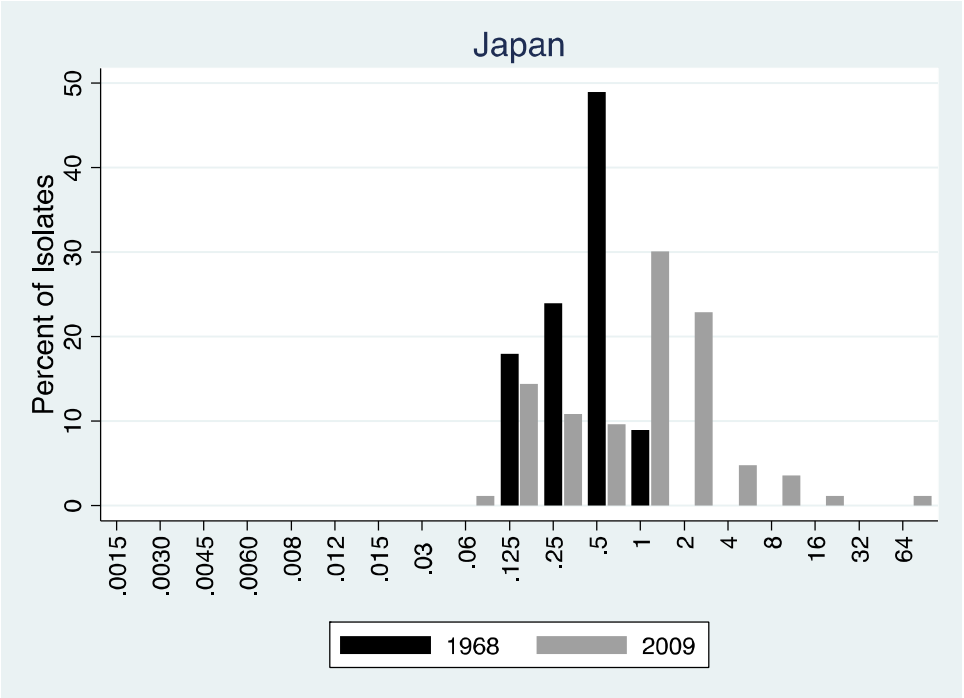


* MICs determined with agar dilution

Meads J Lab & Clin Med 1945

Penicillin

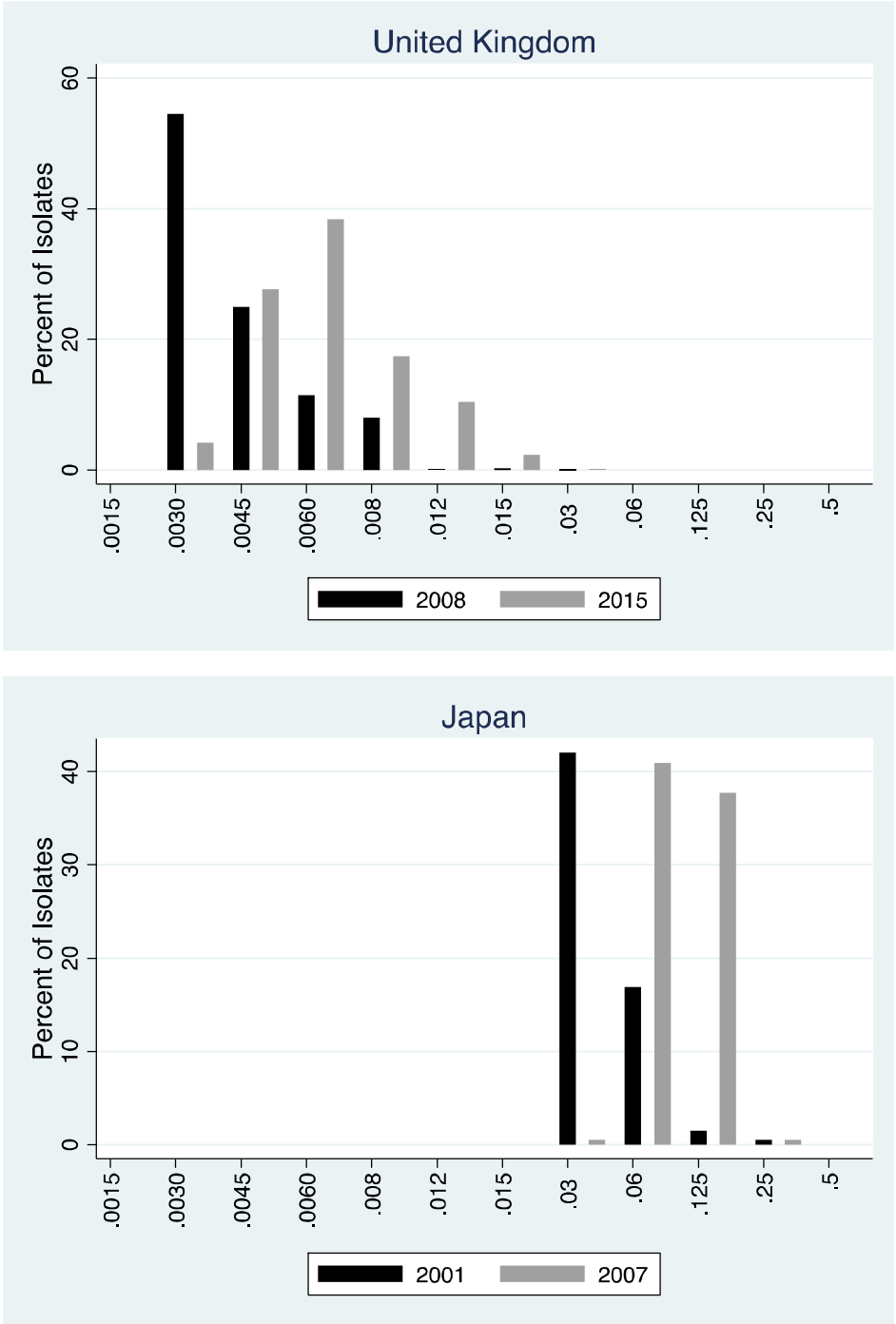




* MICs determined with agar dilution

Kenyon Unpublished

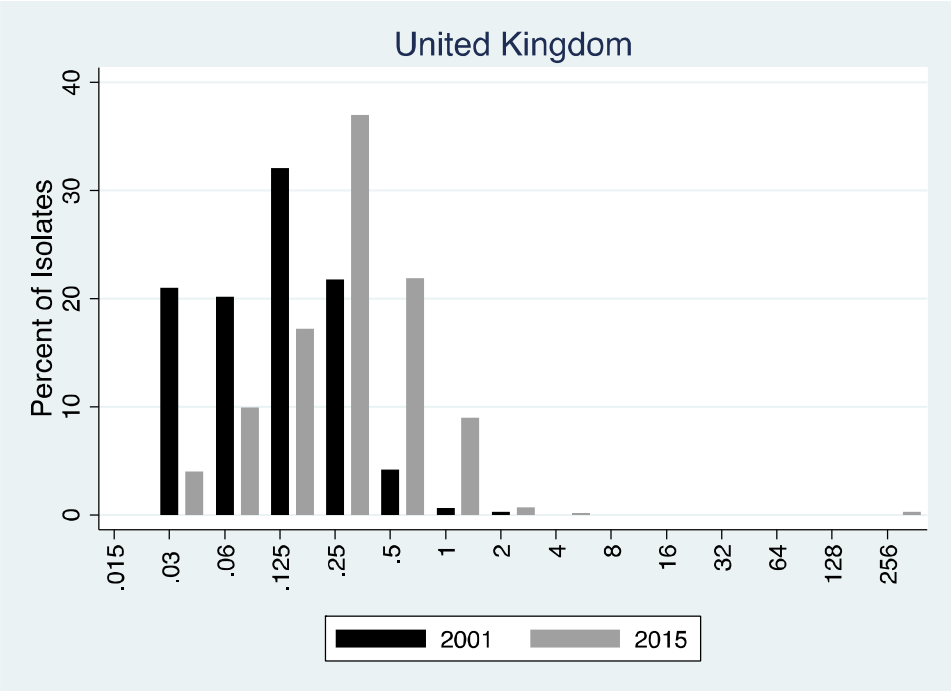
Ceftriaxone

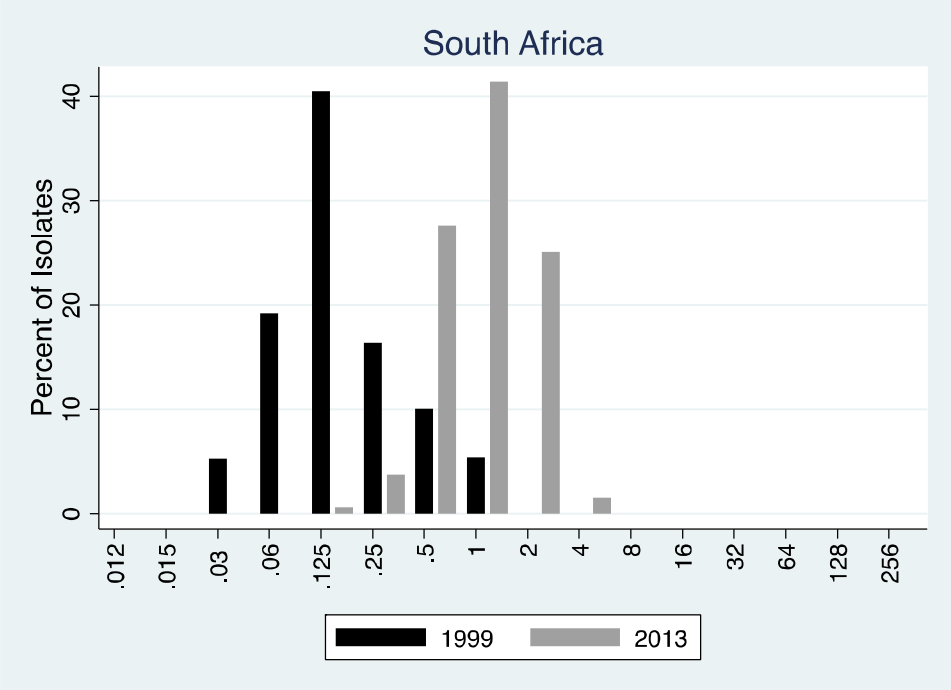


* MICs determined with agar dilution

Kenyon Unpublished

Azithromycin

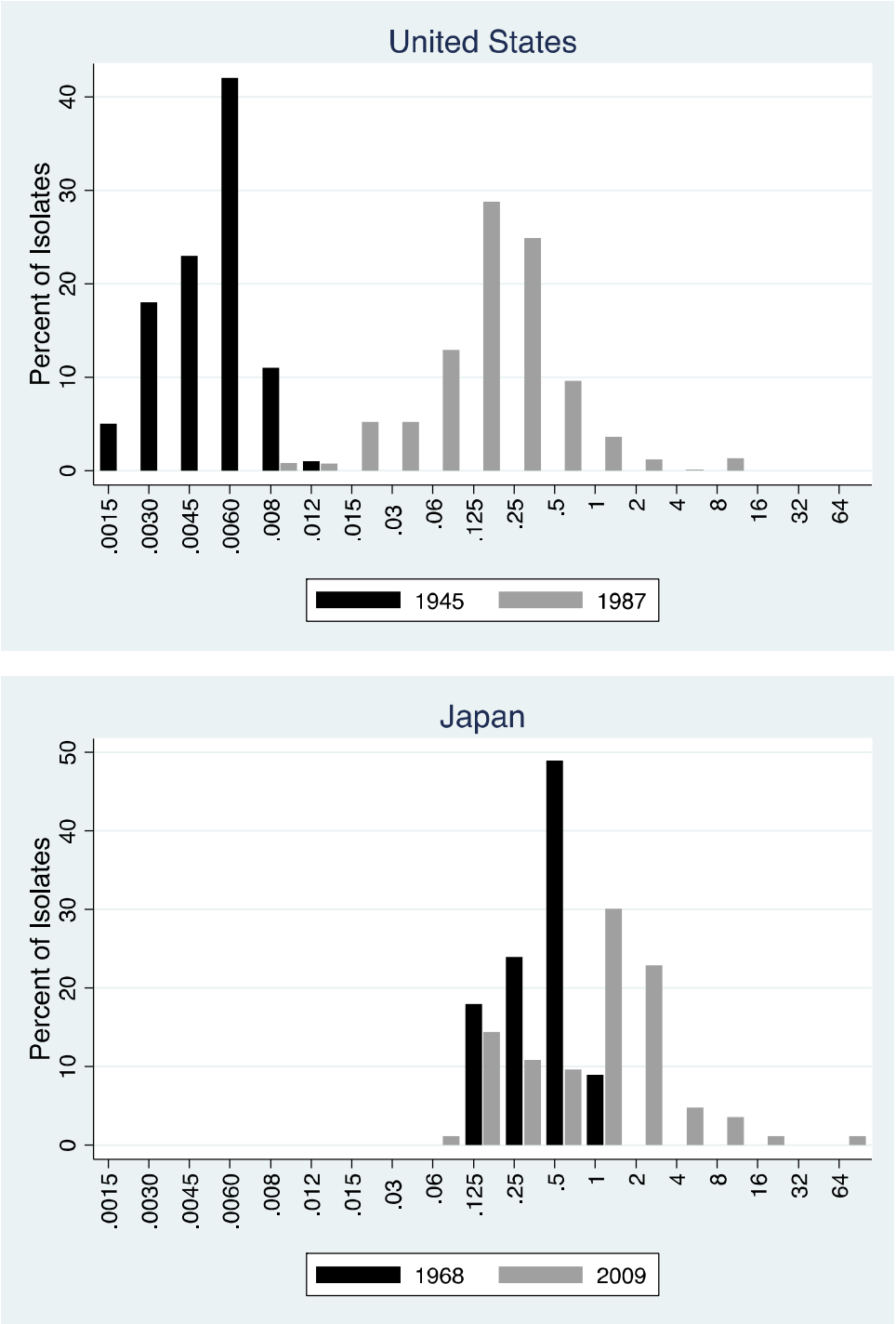




* MICs determined with agar dilution

Kenyon Unpublished

Penicillin



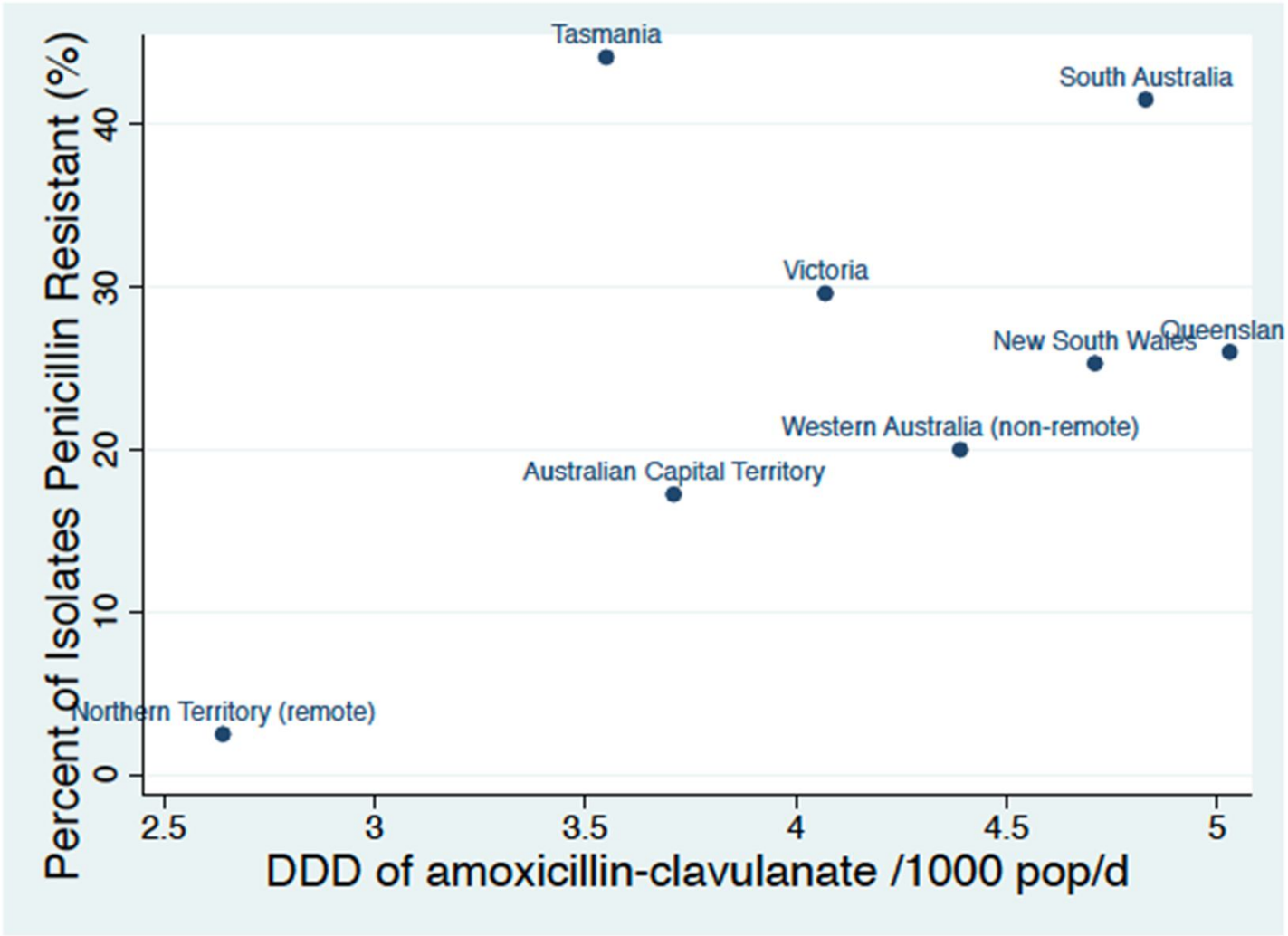
Kenyon Unpublished

	Northern Territories (Australia) 2015	Japan 2015
Azithromycin	0%	53%
Ciprofloxacin	2%	90%
Ceftriaxone	0%	14%
Penicillin	2%	?
	Whiley EID 2017	Yasuda STD 2017

Why not me?

Why me?

AB consumption lower in NT?



Kenyon F1000Res 2019

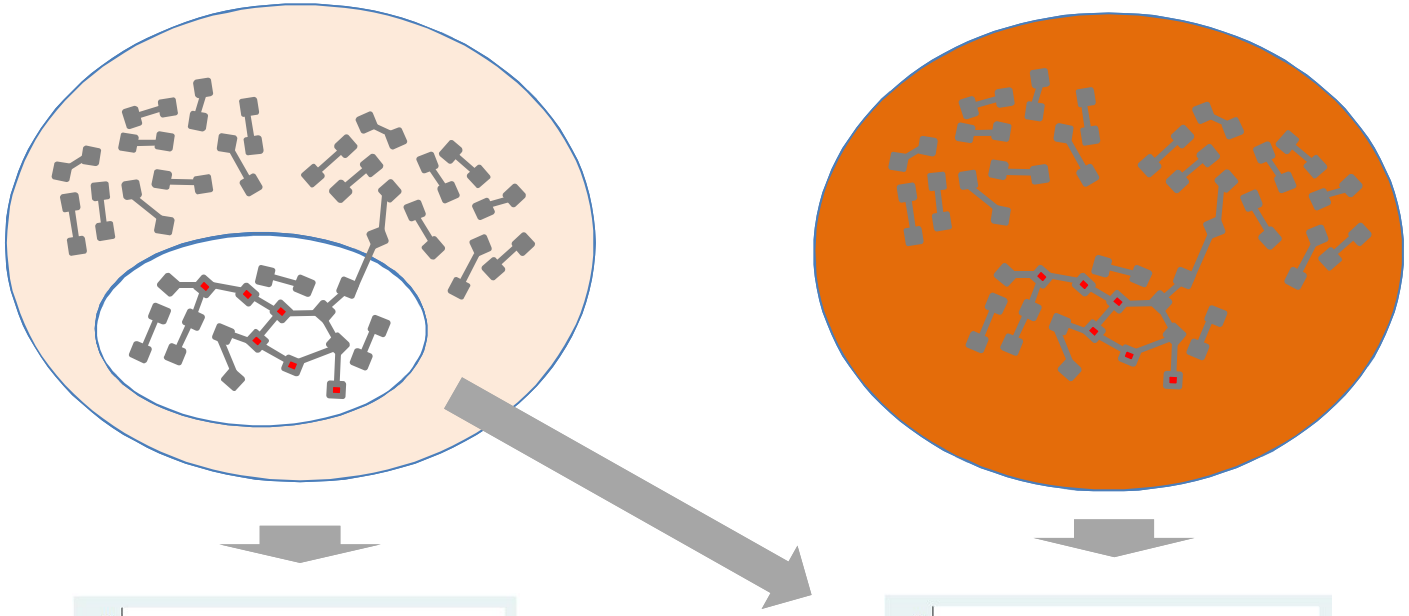
Northern Territories

Japan

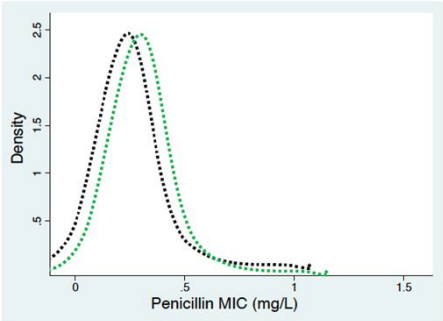
AB consumption

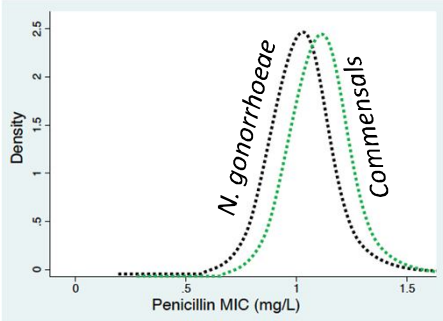
Low

High



Right shifting MIC distribution*





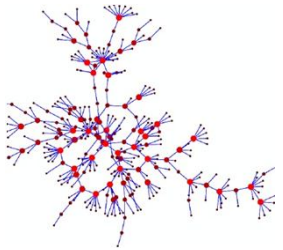
AMR

Azithromycin	0%
Ciprofloxacin	2%
Ceftriaxone	0%
Penicillin	2%

Azithromycin	53%
Ciprofloxacin	90%
Ceftriaxone	14%
Penicillin	?

*MIC distribution stylized

AMR prevention acc. pharmacoecologic theory

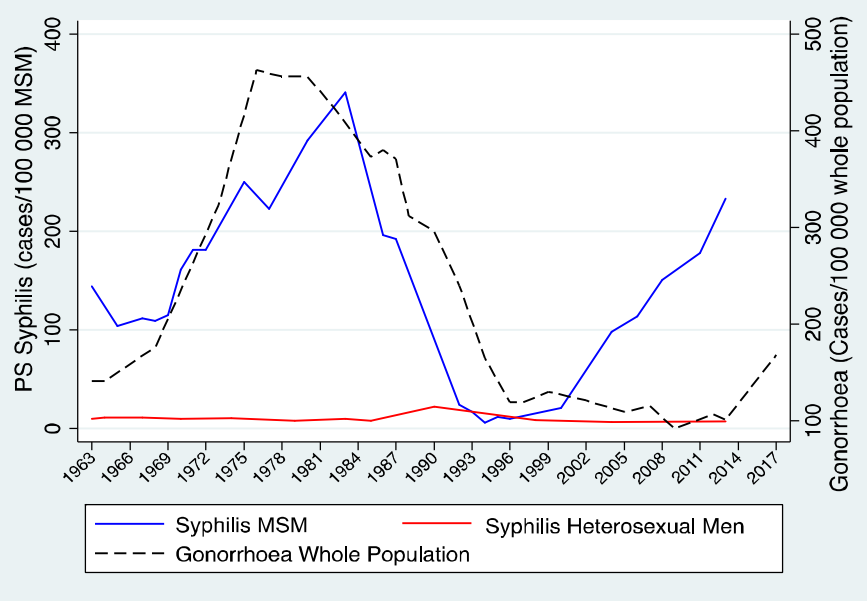


AB-sparing interventions

- Overall AB stewardship
- Precautionary principle for ABs
  - No screening Ng/Ct till proof
  - GonoScreen RCT
- EO Mouthwash -> PReGo RCT
- Bacteriophages
- Chlorhexidine to treat pharyngeal Ng
- Vaccines
  - Flu
  - MenB
- Condoms
- Circumcision
- Urethritis
  - Only R/ if wcc>5
  - Doxycycline for NGU
- Switch Ng R/ CRO/AZM -> CRO
- Stop empiric therapy for contact tracing
- Avoid multiplex STI PCRs

Reduce network connectivity

- Partner reduction
- Safer partner sequencing
  - Serial monogamy/polyandry
  - Closed local networks (Group screening)



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