HARVARD School of Public Health

Modeling Antimicrobial Resistance: Challenges and Open Questions

Marc Lipsitch

Latsis Symposium

ETH July 3 2015

MIDAS

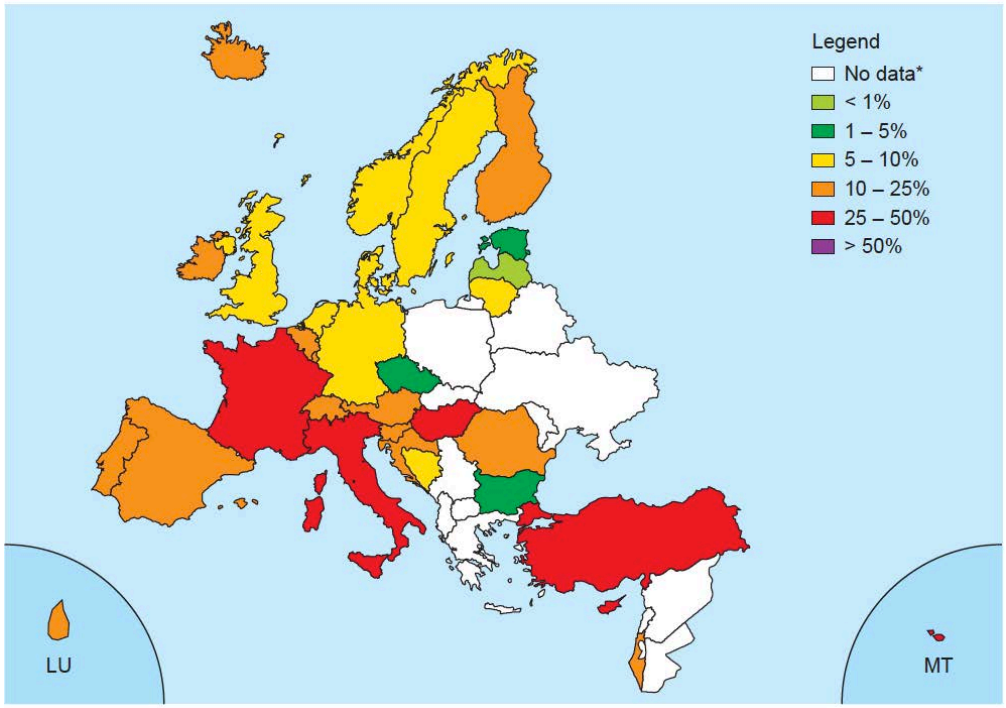
Models of Infectious Disease Agent Study

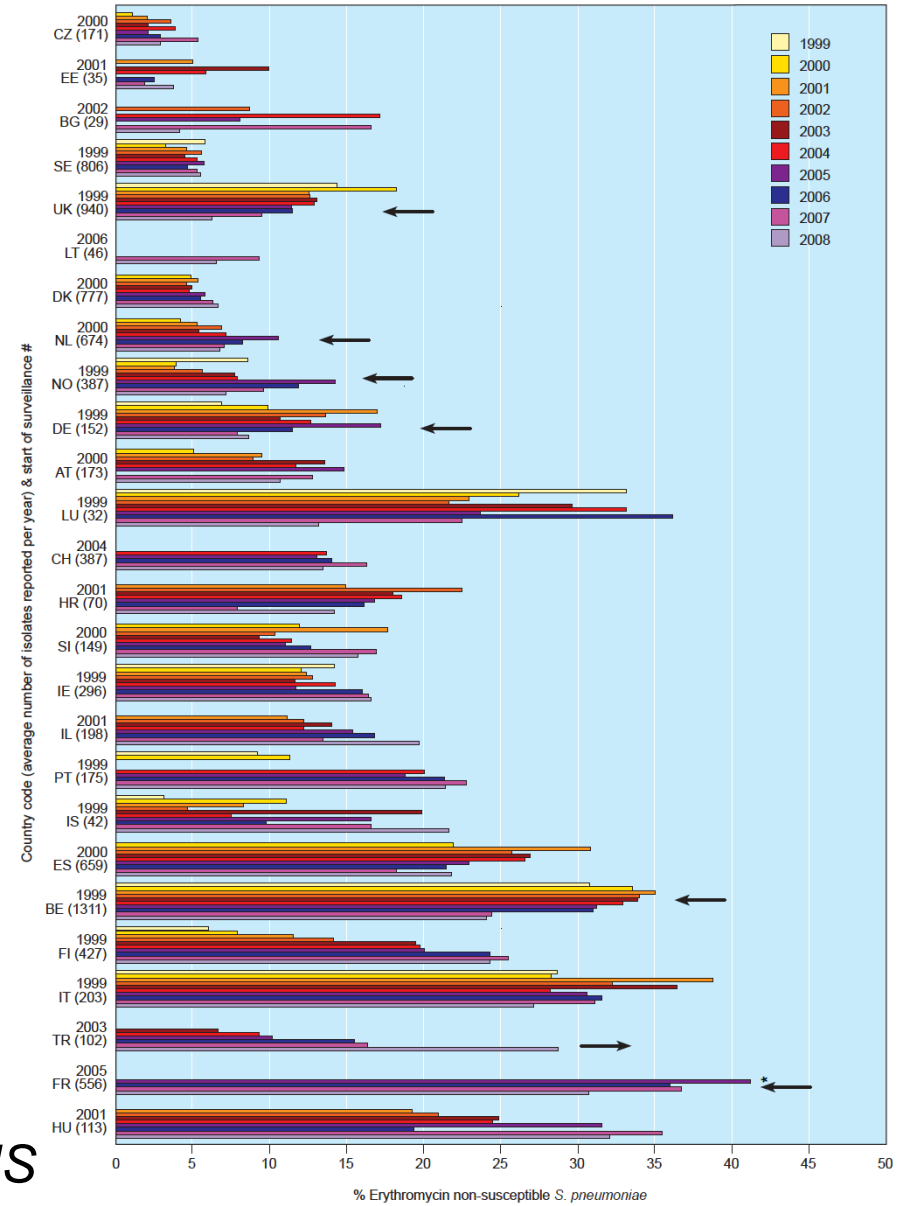
Center *for* Communicable Disease Dynamics

Antibiotic resistance should be boring for ecology and evolution

- Simple selection pressure
- (relatively) simple phenotype, though many mechanisms
- More selection = more resistance

Resistance varies

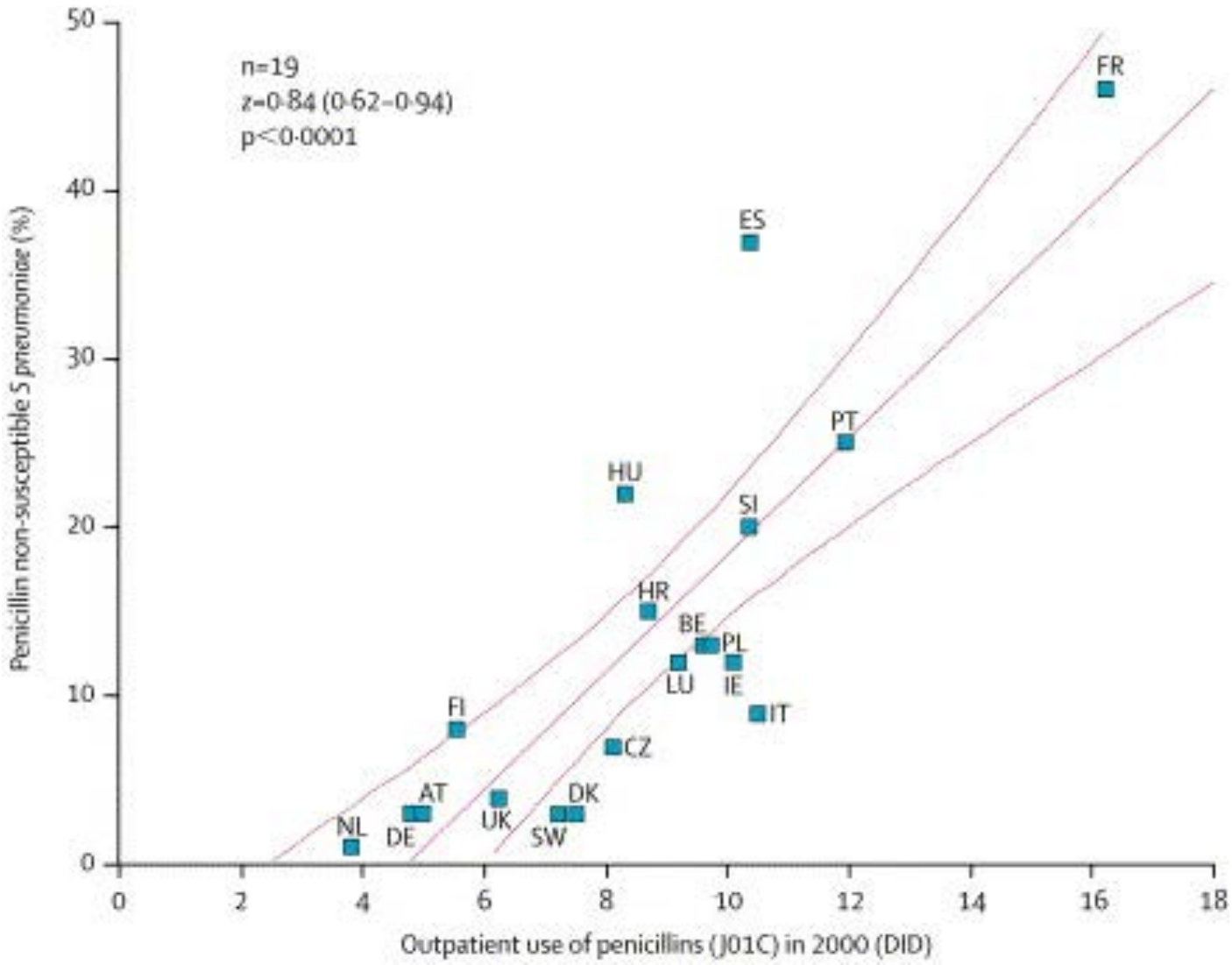




Same pattern for Pen-NS

EARSS 2008 report: erythromycin-R

More Abx use use = more resistance



H. Goossens et al. 2005 *Lancet*

So what are the interesting questions?

Cycling antibiotics may not be good for your health

Bruce R. Levin*† and Marc J. M. Bonten‡

**Department of Biology, Emory University, Atlanta, GA 30322; and ‡Department of Internal Medicine and Dermatology, University Medical Center Utrecht, 3584 CX, Utrecht, The Netherlands*

Save for the career opportunities for those who study it, from a human perspective antibiotic resistance is not a good thing. People are dying or remaining ill for longer with bacterial infections that, if not for resistance, would

real-life observations. A nationwide program of active surveillance for methicillin-resistant *Staphylococcus aureus* (MRSA) that included the implementation of strict barrier precautions for MRSA-colonized patients, temporarily furloughing colo-

Using a simple mathematical model of the epidemiology of antibiotic treatment and resistance in hospitals, they evaluate the efficacy of cycling two antibiotics, relative to their simultaneous application, "mixing." Their analysis predicts that over

Question 1: The puzzle of coexistence. Why, despite continuing selective pressure by abx, have resistant strains not taken over the world (or even any country)?

- This is not (only) academic. If our models can't reproduce the status quo, why should we trust their predictions of the future?
- Alarming projections of $\$10^{14}$ and 10^{8} deaths annually assume takeover of R strains

The RAND Europe scenario modelled what would happen if antimicrobial drug resistance rates rose to 100% after 15 years, with the number of cases of infection held constant. This was done across five of the bacteria and public health

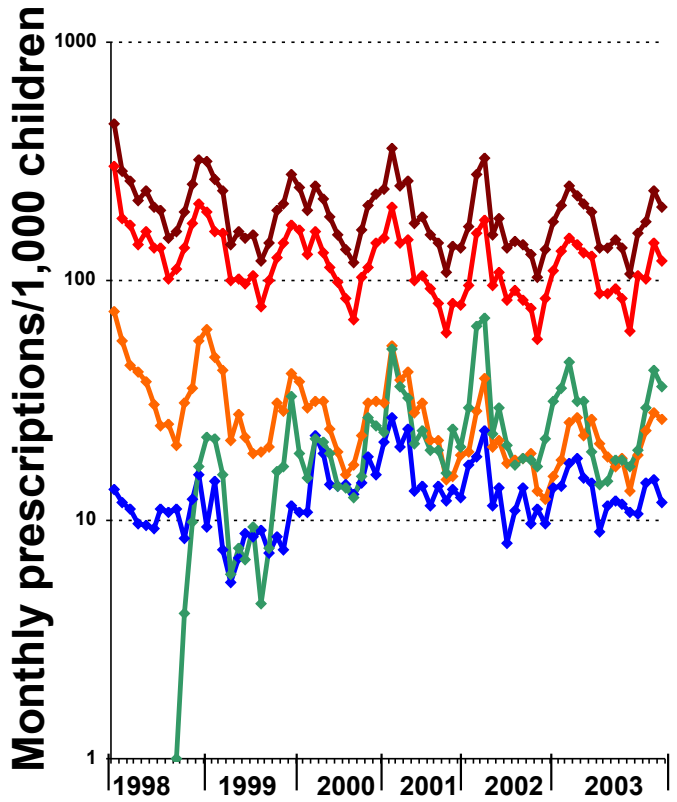
Review of Antimicrobial Resistance 2015

Hypothesis: coexistence is temporary, and 100% resistance is coming slowly

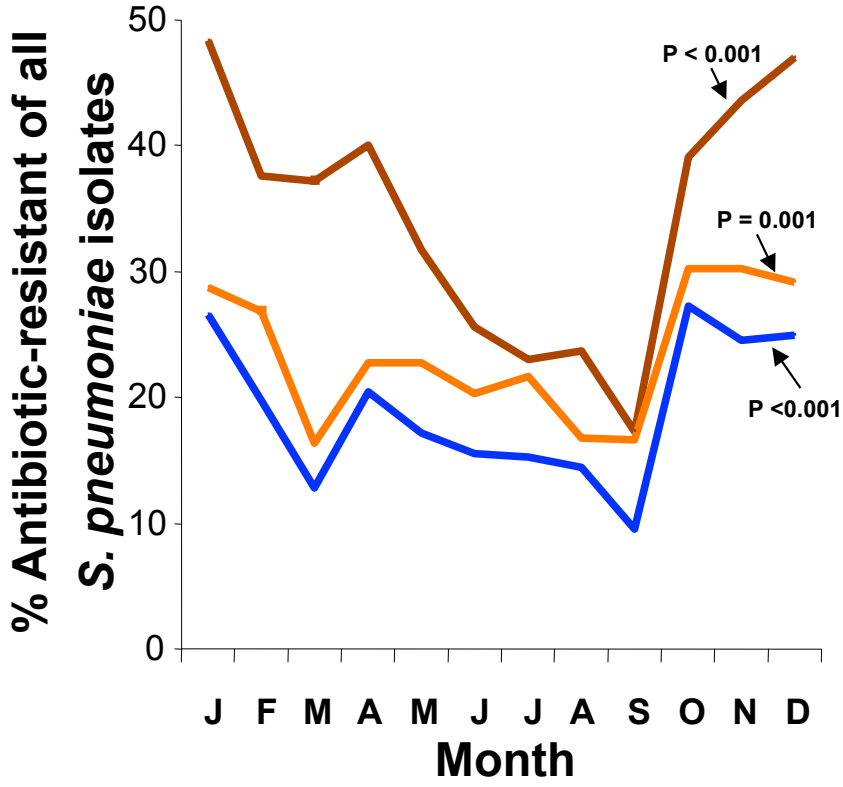
- Proposed despite some counterexamples
  - Little evidence of temporal trend in *S. pneumoniae* resistance
  - 10% of *S aureus* remain penicillin-S despite 60y of use
  - Majority of gonococci remain susceptible to all or nearly all drugs e.g. in US
  - GAS remains pen-S after decades

M Lipsitch
Tr Microbiol 2001

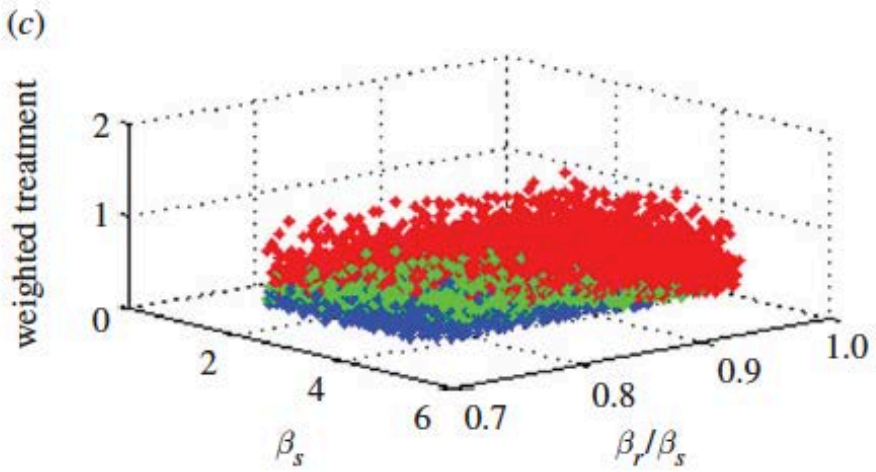
Slow dynamics are not the explanation

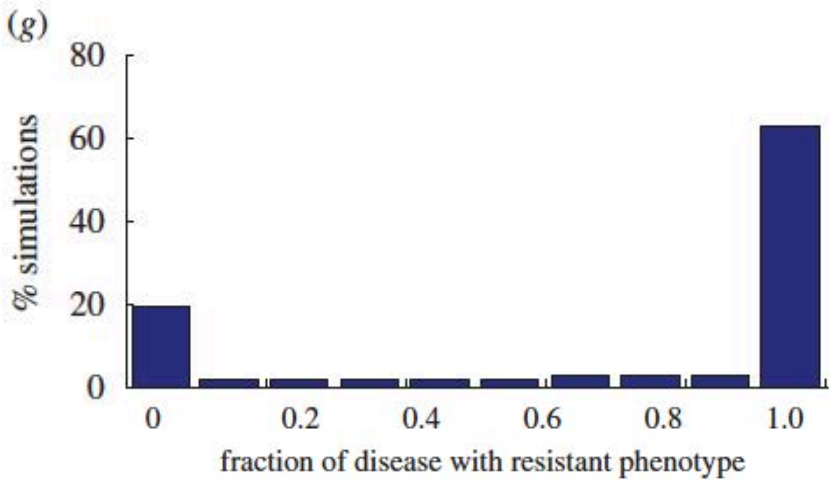


R Dagan et al.
J Inf Dis 2008



Hypothesis: Different subpopulations (day care toddlers vs. healthy older kids) maintain heterogeneous environment





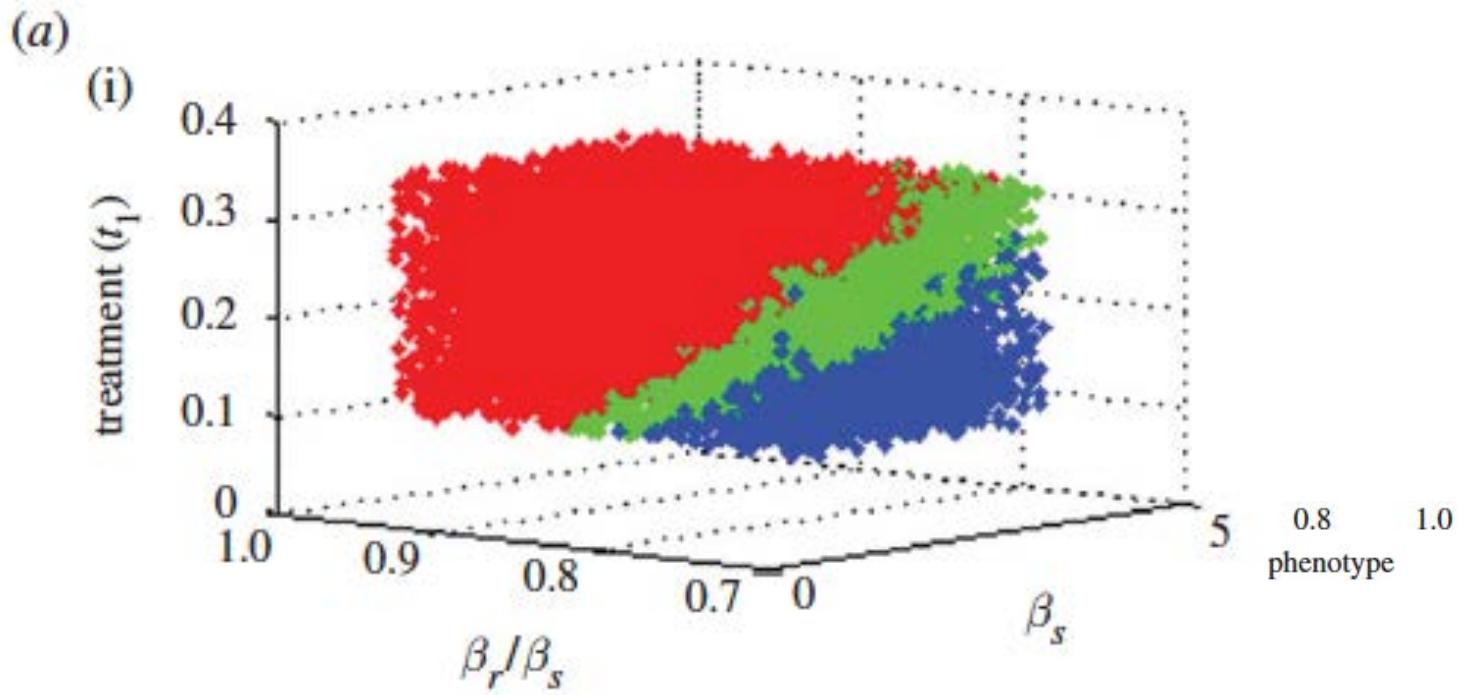
Not promising: tends to favor either all-R or all-S

JOURNAL OF THE ROYAL SOCIETY Interface
FirstCite e-publishing
J. R. Soc. Interface
doi:10.1098/rsif.2009.0400
Published online

What is the mechanism for persistent coexistence of drug-susceptible and drug-resistant strains of *Streptococcus pneumoniae*?

Caroline Colijn[1,*], Ted Cohen[2,4], Christophe Fraser[6], William Hanage[5], Edward Goldstein[2], Noga Givon-Lavi[7], Ron Dagan[7] and Marc Lipsitch[2,3]

Hypothesis: Hosts may be co-colonized with S and R strains and transmit both simultaneously



A bit more promising: 21-29% of plausible parameter combinations produce long-term coexistence

JOURNAL OF THE ROYAL SOCIETY Interface
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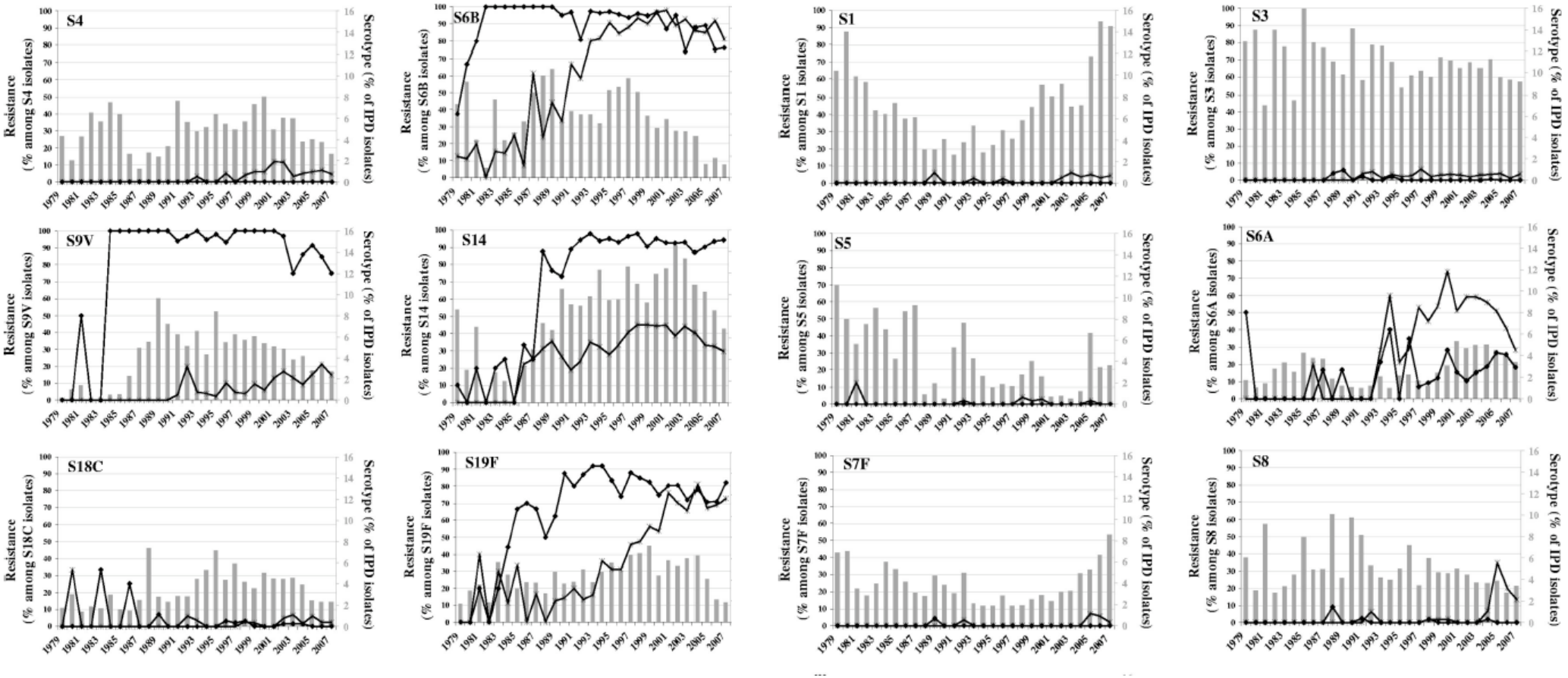
Hypothesis: competitive exclusion of R or S happens within serotypes, so coexistence of S&R = coexistence of serotypes



Fenoll A et al. *J Clin Micro* 2009

Does not seem to be a general phenomenon: fraction R has remained intermediate in many serotypes in USA (ABCs)

We are working on this

Hypothesis: Combining several of the mechanisms tested individually by Colijn et al. with some mechanisms underlying coexistence of pneumococcal serotypes (variable duration, acquired immunity to species and to individual serotypes) may permit coexistence of S,R strains consistent with observation

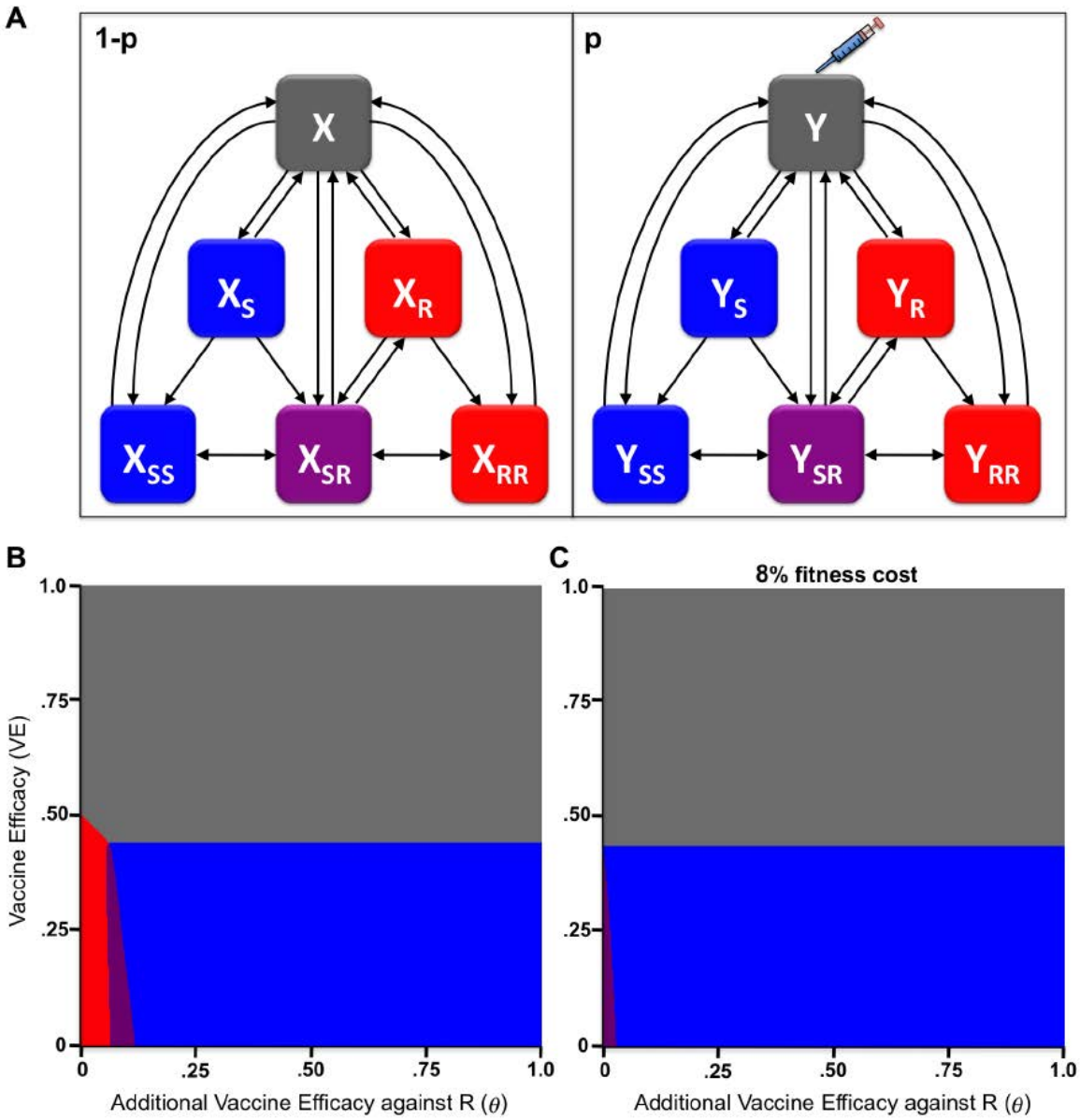
We = Sarah Cobey, Ed Baskerville (Chicago), Christophe Fraser, Caroline Colijn (Imperial), Bill Hanage & your speaker (Harvard Chan SPH)

Can we use coexistence to our benefit?

A vaccine slightly more efficacious against R than S strains could be a powerful selective force countering

- conjugate to resistant PBP
- reverse-genetics vaccines

Joice & Lipsitch P*LoS One* 2013

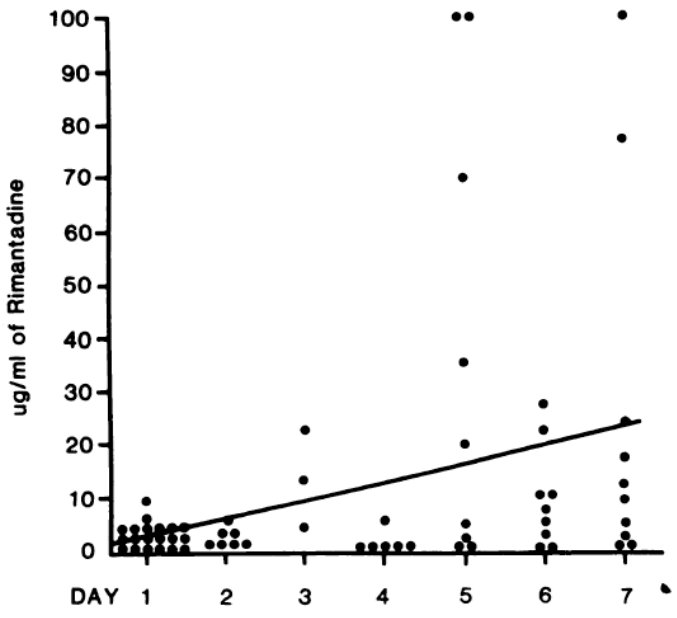


Question 2: What are the limits to predicting the spread of drug resistance?

A tale of two drug classes, with influenza viruses

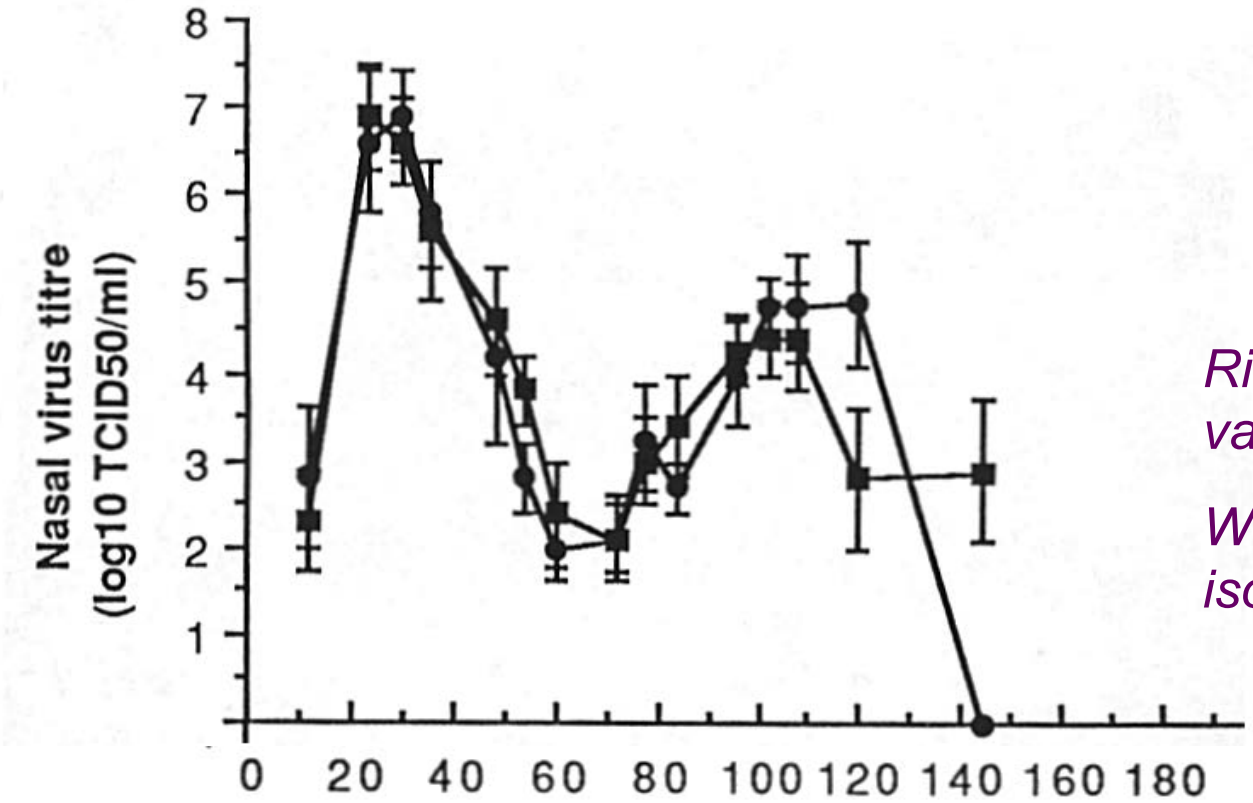
Adamantane resistance commonly emerges during treatment and may spread locally

Increasing IC_{50} (resistance) over time since treatment



CB Hall *Pediatrics* 1987

Adamantane-R shows no fitness cost in animal models

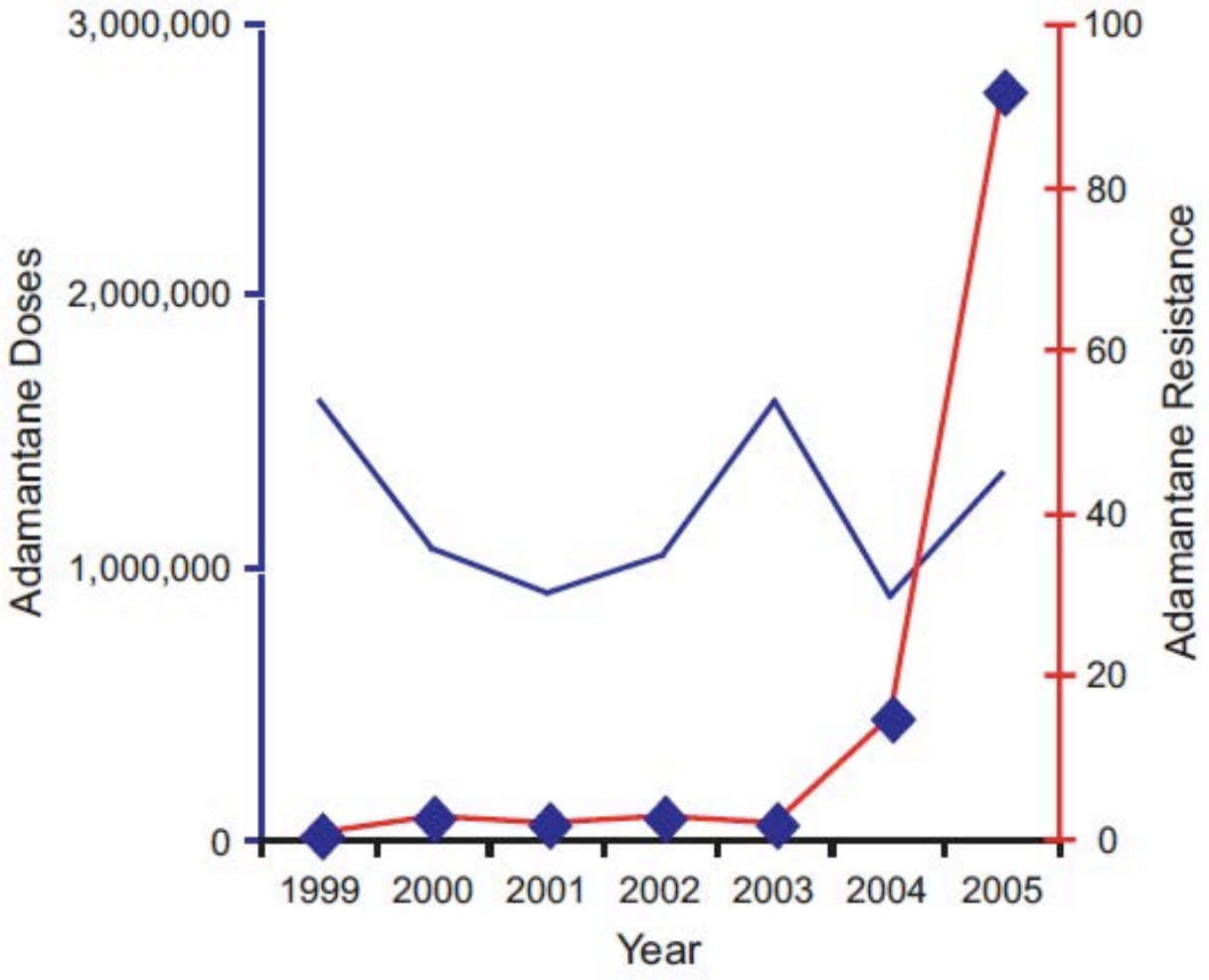


Rimantadine-resistant variant (Ser31Asn)

Wild-type sensitive isolate

Sweet et al. J Infect Dis. 164:969, 1991

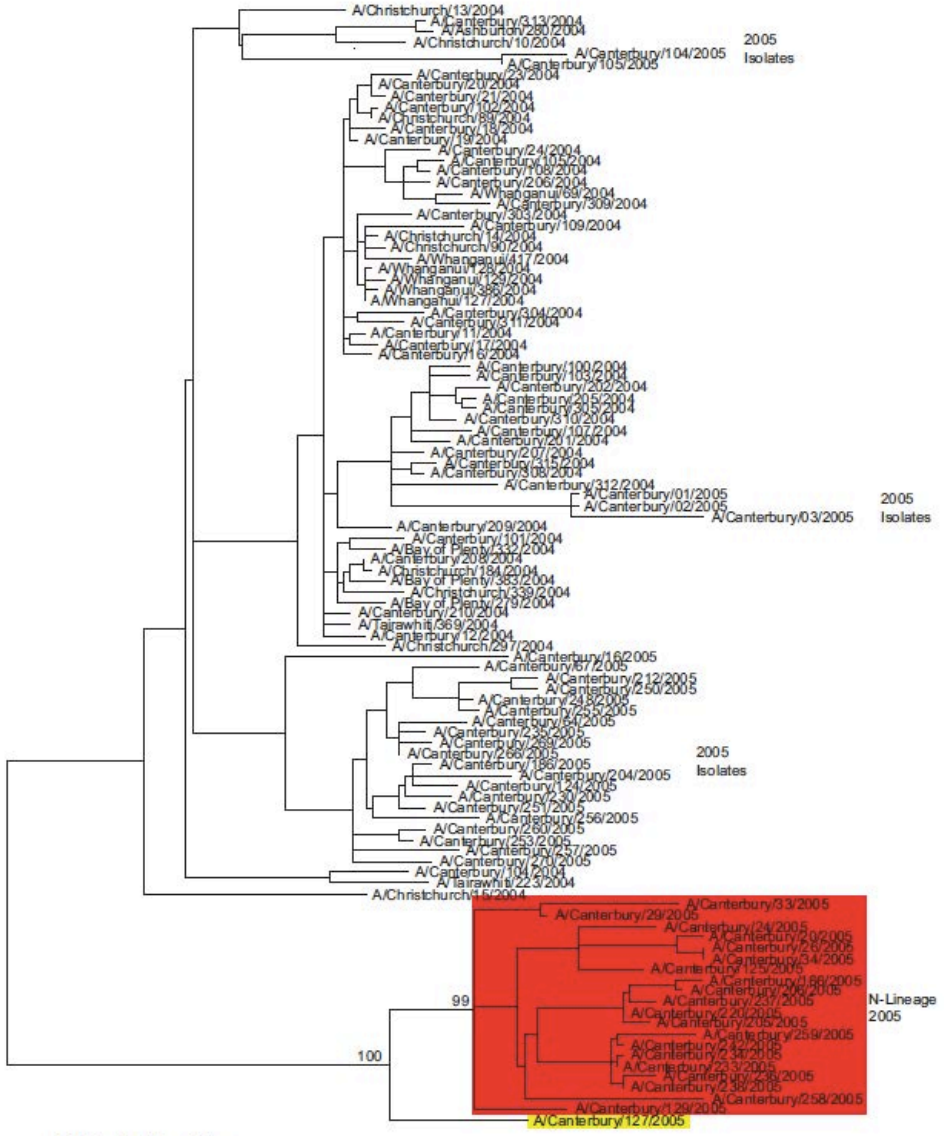
Nonetheless, little resistance in the population up to 2003



L Simonsen et al. *Mol Biol Evol* 2007

What accounted for spread of adamantane resistance?

- Selection by adamantane use?
- Genetic drift?
- Natural selection for some other trait of the strain(s) carrying resistance mutation



L Simonsen et al. *Mol Biol Evol* 2007

Neuraminidase Inhibitors (Tamiflu)

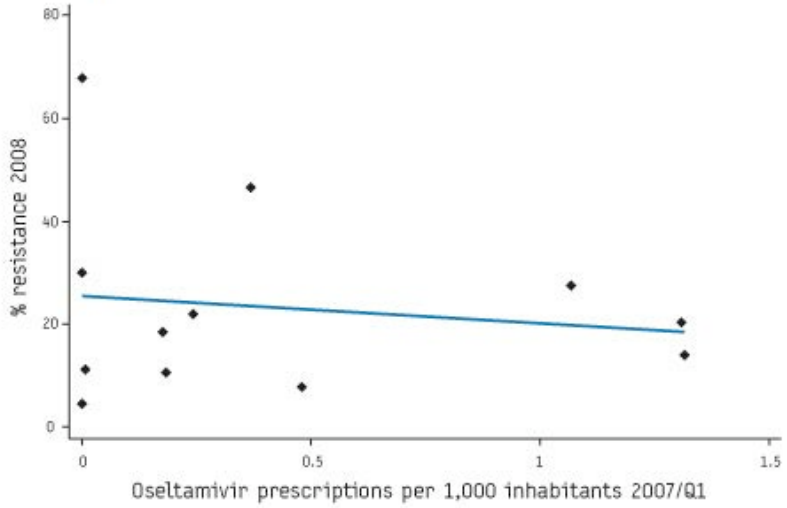
- Oseltamivir resistance arises in 2% of treated, experimentally infected adults, 18% of treated children L Gubareva et al. *J Inf Dis* 2001; Kiso et al. *Lancet* 2004
- H275Y NA mutation 100x attenuated; E119V almost as fit as wildtype ML Herlocher et al. *J Inf Dis* 2002, 2004
- If anything should spread it is E119V

Explosion of H275Y 2007-8

(Unrelated to use)

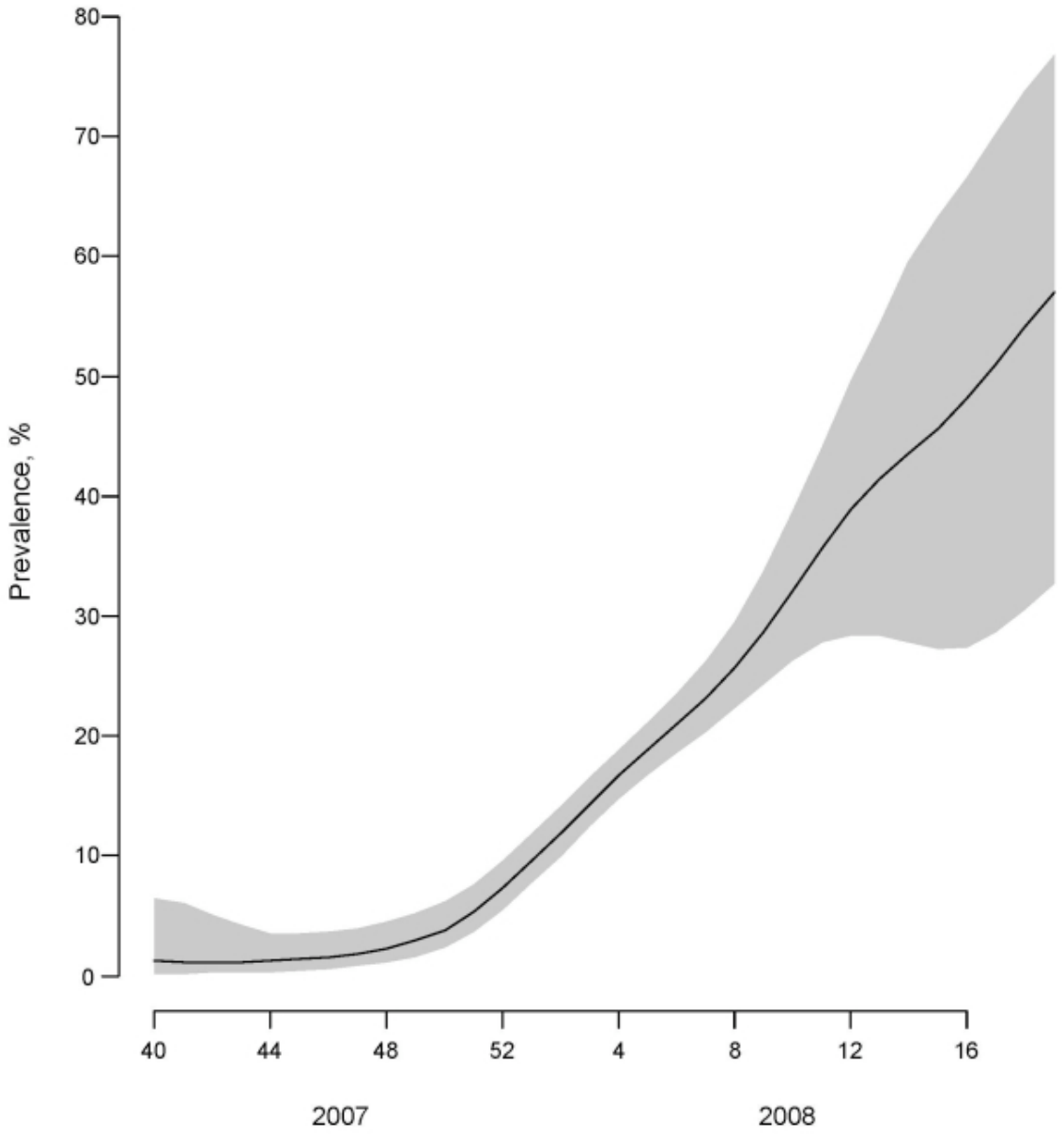
FIGURE 4

Regression of the proportion of resistant strains on the number of prescriptions of oseltamivir per 1,000 inhabitants in European countries



Source as in Figure 3.

P Kramarz et al.
Eurosurveillance
2009



A Meijer et al. *Emerg Inf Dis* 2009

Permissive mutations required before resistant strain could be fit

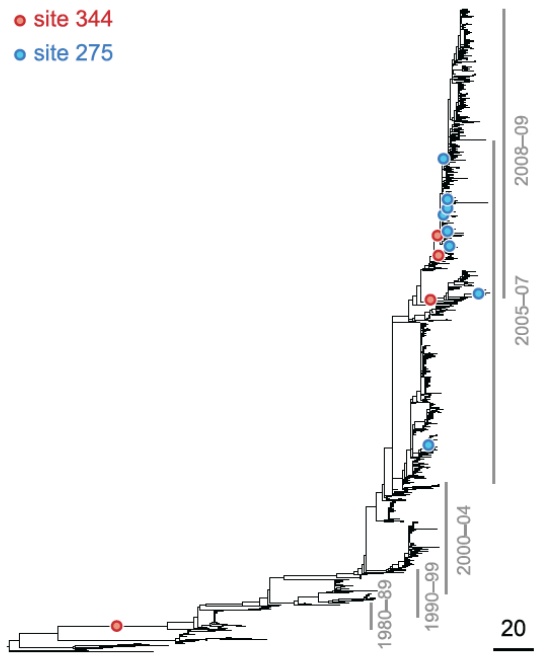
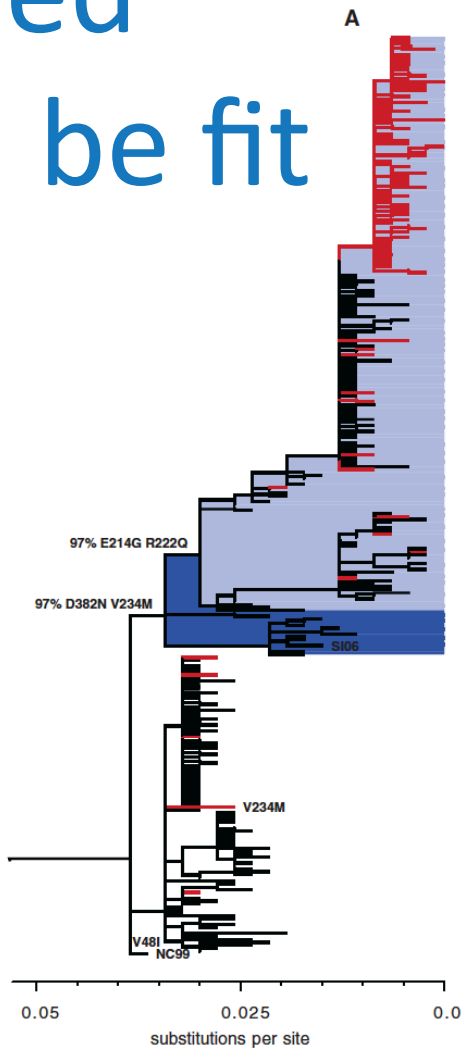


Figure 3. Phylogenetic tree of NA (subtype N1) illustrating a putatively epistatic interaction between the leading site 344 (red circles) and the trailing site 275 (blue circles). Other notations are as in Figure 2.
doi:10.1371/journal.pgen.1001301.g003



OPEN ACCESS Freely available online
PLoS GENETICS

Prevalence of Epistasis in the Evolution of Influenza A Surface Proteins

Sergey Kryazhimskiy[1¤], Jonathan Dushoff[2], Georgii A. Bazykin[3], Joshua B. Plotkin[1,4*]

Permissive Secondary Mutations Enable the Evolution of Influenza Oseltamivir Resistance

Jesse D. Bloom, Lizhi Ian Gong, David Baltimore*

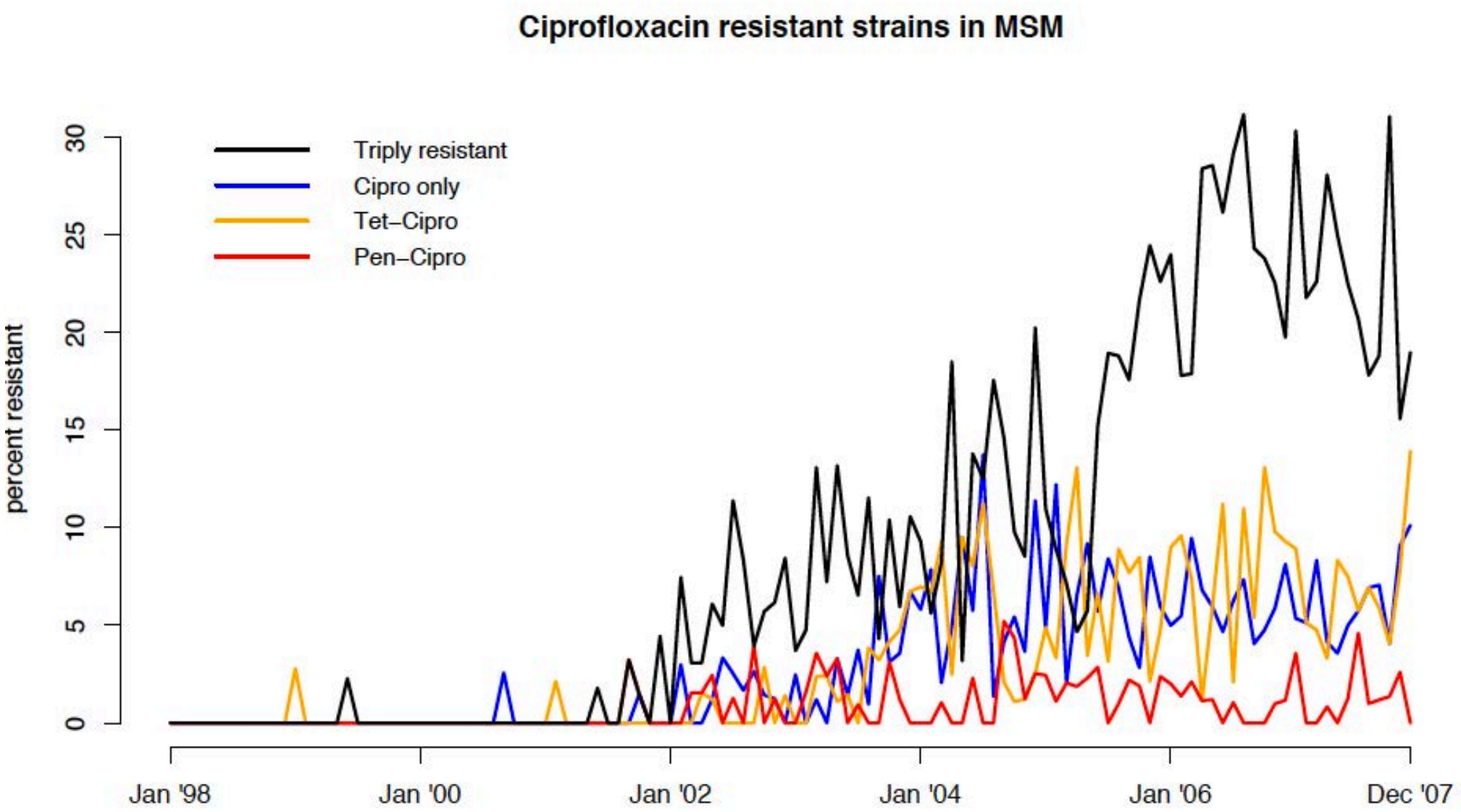
Influenza resistance: lessons

- Selective landscapes change; animal and human data can become outdated
- Ecological approach needs to be supplemented with genetics (epistasis, linkage) to understand what happens
- Resistance doesn't always follow use; may have to wait for favorable genetic background

Question 3: What are the rate-limiting processes in the spread of drug resistant strains?

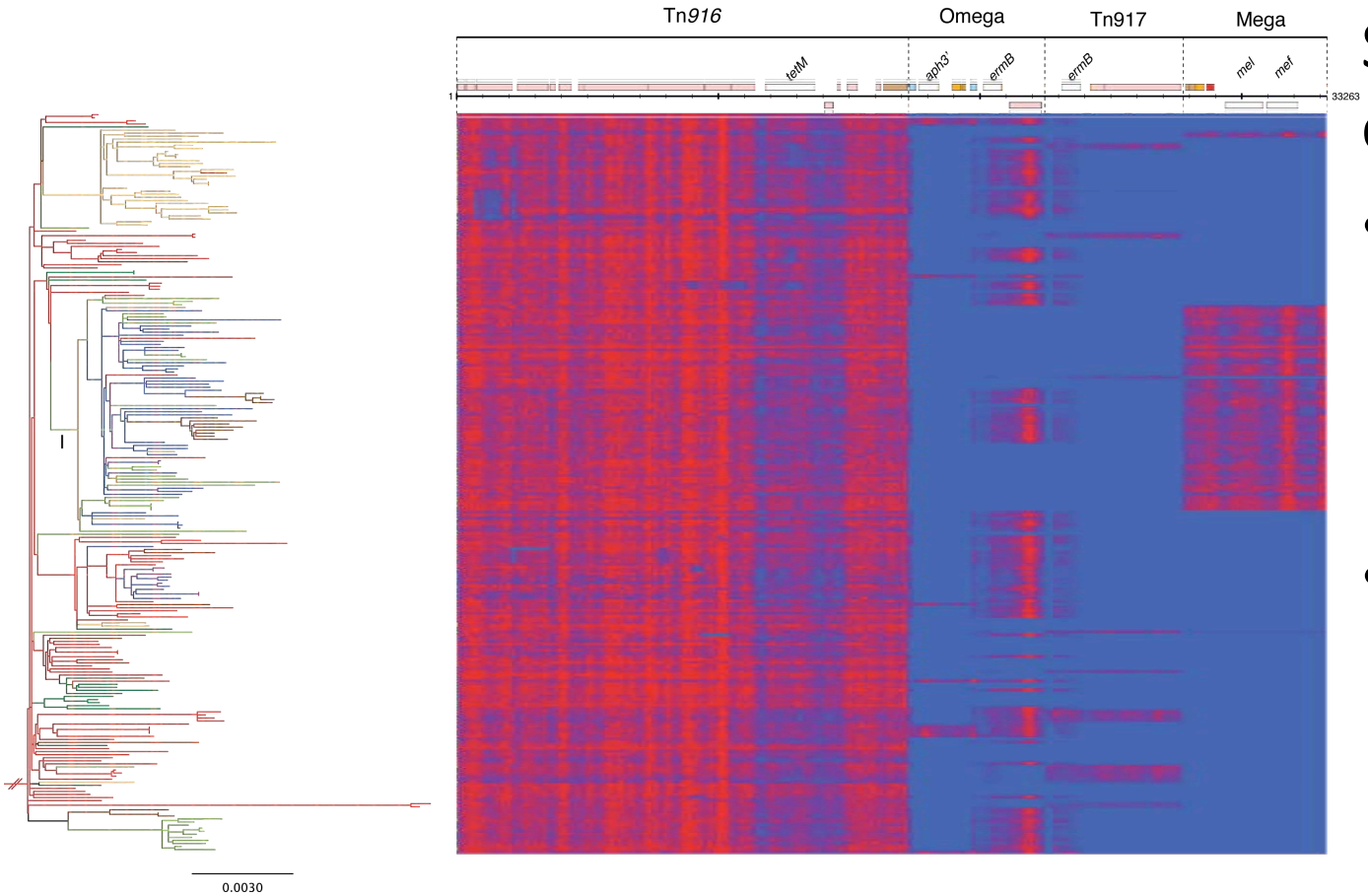
- Hypothesis 1: Mutation/acquisition of resistance determinants
- Hypothesis 2: Selection pressure (by abx use)
- Hypothesis 3: Ecology: antibiotics used only in a “sink” niche
- Hypothesis 4: Russian roulette

Appearance is not limiting



Modified from E Goldstein et al. *Emerg Infect Dis* 2012 in press: Data from CDC GISP

Appearance is not limiting



Single pneumococcal clone over ~40y

- Multiple acquisitions and loss of macrolide resistance
- 26 independent appearances of quinolone-R mutations at 6 sites

NJ Croucher et al. *Science* 2011

Selection pressure is sometimes limiting

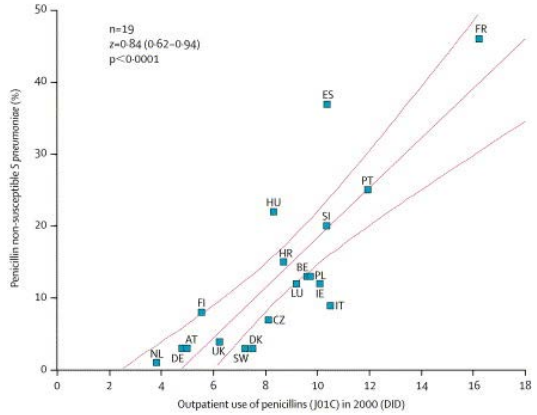
Probably not:

Influenza examples

Gonorrhea: antimicrobial use was present but no spread for some time

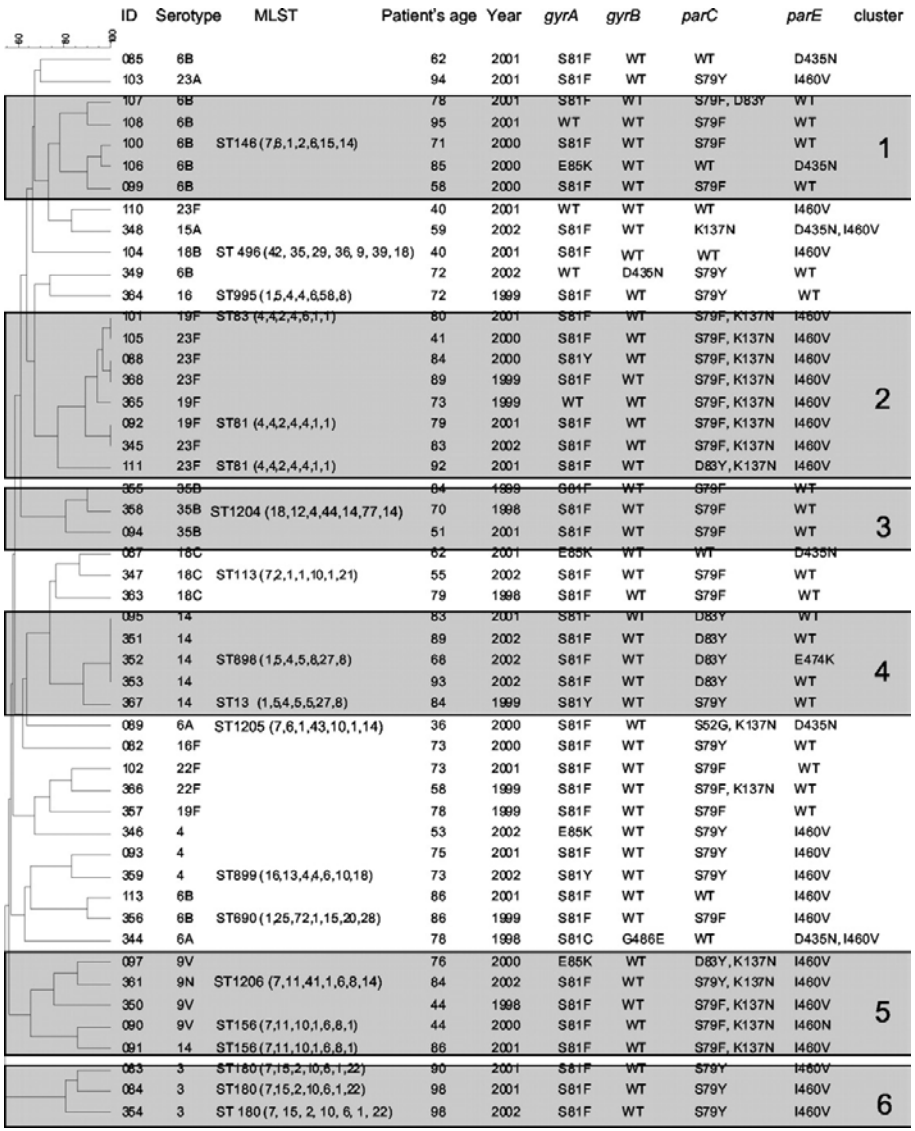
Probably so:

Regional variation in Spn resistance



MRSA in Netherlands vs. elsewhere

Ecology is sometimes limiting



ID	Serotype	MLST	Patient's age	Year	*gyrA*	*gyrB*	*parC*	*parE*	cluster
085	6B		62	2001	S81F	WT	WT	D435N	
103	23A		94	2001	S81F	WT	S79Y	I460V	
107	6B		78	2001	S81F	WT	S79F, D83Y	WT	1
108	6B		95	2001	WT	WT	S79F	WT	1
100	6B	ST146 (7,8,1,2,6,15,14)	71	2000	S81F	WT	S79F	WT	1
106	6B		85	2000	E85K	WT	WT	D435N	1
099	6B		58	2000	S81F	WT	S79F	WT	1
110	23F		40	2001	WT	WT	WT	I460V	
348	15A		59	2002	S81F	WT	K137N	D435N, I460V	
104	18B	ST 496 (42, 35, 29, 36, 9, 39, 18)	40	2001	S81F	WT	WT	I460V	
349	6B		72	2002	WT	D435N	S79Y	WT	
364	16	ST995 (1,5,4,4,6,58,8)	72	1999	S81F	WT	S79Y	WT	
101	19F	ST83 (4,4,2,4,6,1,1)	80	2001	S81F	WT	S79F, K137N	I460V	2
105	23F		41	2000	S81F	WT	S79F, K137N	I460V	2
088	23F		84	2000	S81Y	WT	S79F, K137N	I460V	2
368	23F		89	1999	S81F	WT	S79F, K137N	I460V	2
365	19F		73	1999	WT	WT	S79F, K137N	I460V	2
092	19F	ST81 (4,4,2,4,4,1,1)	79	2001	S81F	WT	S79F, K137N	I460V	2
345	23F		83	2002	S81F	WT	S79F, K137N	I460V	2
111	23F	ST81 (4,4,2,4,4,1,1)	92	2001	S81F	WT	D83Y, K137N	I460V	2
355	35B		84	1999	S81F	WT	S79F	WT	3
358	35B	ST1204 (18,12,4,44,14,77,14)	70	1998	S81F	WT	S79F	WT	3
094	35B		51	2001	S81F	WT	S79F	WT	3
087	18C		62	2001	E85K	WT	WT	D435N	
347	18C	ST113 (7,2,1,1,10,1,21)	55	2002	S81F	WT	S79F	WT	
363	18C		79	1998	S81F	WT	S79F	WT	
095	14		83	2001	S81F	WT	D83Y	WT	4
351	14		89	2002	S81F	WT	D83Y	WT	4
352	14	ST898 (1,5,4,5,8,27,8)	68	2002	S81F	WT	D83Y	E474K	4
353	14		93	2002	S81F	WT	D83Y	WT	4
367	14	ST13 (1,5,4,5,5,27,8)	84	1999	S81Y	WT	S79Y	WT	4
089	6A	ST1205 (7,6,1,43,10,1,14)	36	2000	S81F	WT	S52G, K137N	D435N	
082	16F		73	2000	S81F	WT	S79Y	WT	
102	22F		73	2001	S81F	WT	S79F	WT	
366	22F		58	1999	S81F	WT	S79F, K137N	WT	
357	19F		78	1999	S81F	WT	S79F	WT	
346	4		53	2002	E85K	WT	S79Y	I460V	
093	4		75	2001	S81F	WT	S79Y	I460V	
359	4	ST899 (16,13,4,4,6,10,18)	73	2002	S81Y	WT	S79Y	I460V	
113	6B		86	2001	S81F	WT	WT	I460V	
356	6B	ST690 (1,25,72,1,15,20,28)	86	1999	S81F	WT	S79F	I460V	
344	6A		78	1998	S81C	G486E	WT	D435N, I460V	
097	9V		76	2000	E85K	WT	D83Y, K137N	I460V	5
361	9N	ST1206 (7,11,41,1,6,8,14)	84	2002	S81F	WT	S79Y, K137N	I460V	5
350	9V		44	1998	S81F	WT	S79F, K137N	I460V	5
090	9V	ST156 (7,11,10,1,6,8,1)	44	2000	S81F	WT	S79F, K137N	I460N	5
091	14	ST156 (7,11,10,1,6,8,1)	86	2001	S81F	WT	S79F, K137N	I460V	5
083	3	ST180 (7,15,2,10,6,1,22)	90	2001	S81F	WT	S79Y	I460V	6
084	3	ST180 (7,15,2,10,6,1,22)	98	2001	S81F	WT	S79Y	I460V	6
354	3	ST 180 (7, 15, 2, 10, 6, 1, 22)	98	2002	S81F	WT	S79Y	I460V	6

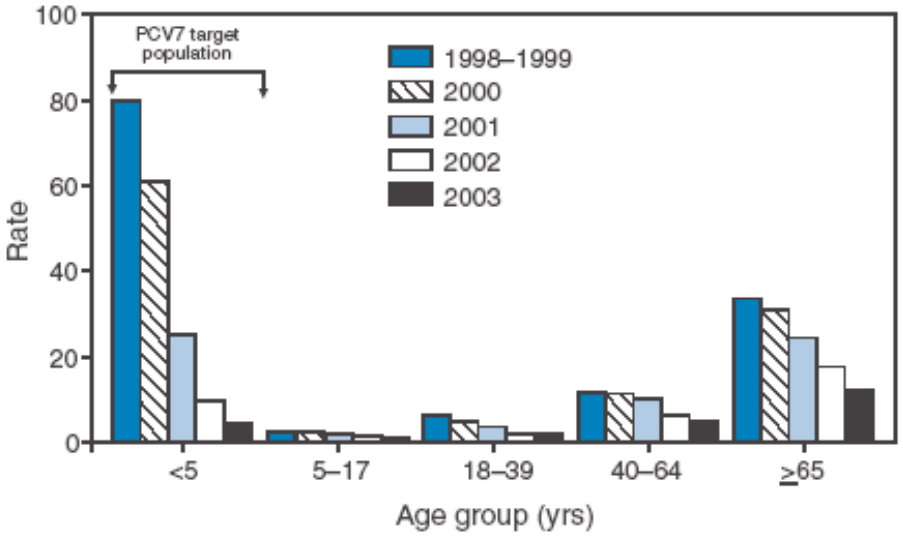
Fluoroquinolone resistance in *S. pneumoniae*: repeated appearance, little clonal spread

W. Pletz et al. *AAC* 2004

FQ use is restricted to adults

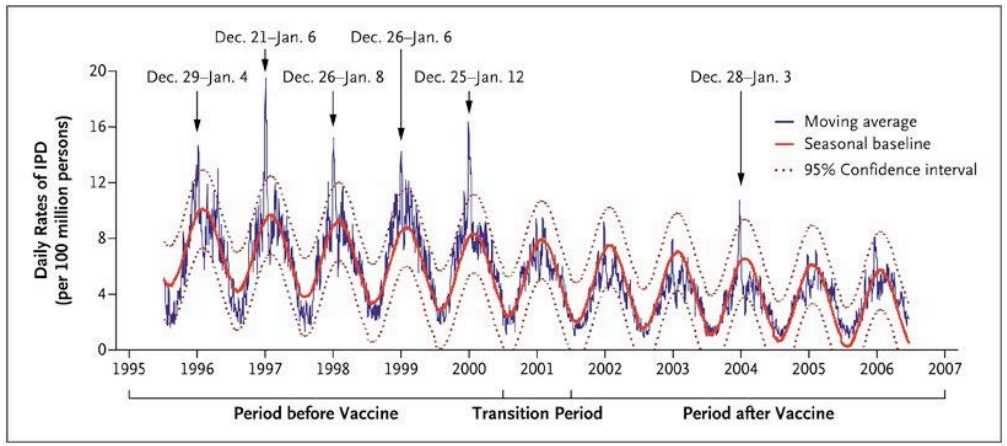
- But children are the "core group" (source of ~everyone's infection)! Thus selection is nearly absent in the "source" population

FIGURE 1. Rate* of vaccine-type (VT) invasive pneumococcal disease (IPD) before and after introduction of pneumococcal conjugate vaccine (PCV7), by age group and year — Active Bacterial Core surveillance, United States, 1998–2003



* Per 100,000 population.
† For each age group, the decrease in VT IPD rate for 2003 compared with the 1998–1999 baseline is statistically significant (p<0.05).

MMWR 2005



Walther et al. *NEJM* 2009

Roulette scenario

- Resistant strains appear frequently and don't spread widely
  - Caused by ineffective treatment (mutation) or within-host gene transfer and within-host selection (acquisition of mobile elements)

Resistance Phase 1: "Genetic Exploration"

INT J TUBERC LUNG DIS 12(1):99–104

Genotypic diversity of extensively drug-resistant tuberculosis (XDR-TB) in South Africa

C. K. Mlambo,* R. M. Warren,† X. Poswa,‡ T. C. Victor,† A. G. Duse,* E. Marais*

Spoligotype family	Sublineage/ST	*n* (%)	Spoligotype patterns	Province	Isolates *n*	Clinics *n*
Beijing	1	14 (34)		N. Cape	5	4
				N. West	4	3
				Limpopo	3	1
				Gauteng	2	1
LAM	LAM4/60	3 (7)		Gauteng	2	2
				Limpopo	1	1
	LAM9/42	2 (5)		Gauteng	2	2
EAI1	EAI1_SOM/48	2 (5)		N. West	1	1
				Limpopo	1	1
	EAI1_SOM/806	2 (5)		Gauteng	1	1
				N. West	1	1
T	T1/53	2 (5)		Gauteng	1	1
				N. West	1	1
	T2/52	1 (2)		Gauteng	1	1
	T3/37	1 (2)		N. West	1	1
H	H1/47	1 (2)		N. West	1	1
	H3/50	1 (2)		Gauteng	1	1
X	X3/92	1 (2)		N. West	1	1
S	71	1 (2)		N. West	1	1
Not in SpolDB4	Type A, possible H	6 (14)		N. West	6	1
		1 (2)		Gauteng	1	1
		1 (2)		Gauteng	1	1
	Possible LAM	1 (2)		Limpopo	1	1
	Possible LAM	1 (2)		Limpopo	1	1
Total		41			41	

Figure 3 Spoligotype family assignment of XDR-TB isolates showing the province of origin and the number of clinics in which each spoligotype was identified. XDR-TB = extensively drug-resistant tuberculosis; ST = spoligotype; N. Cape = Northern Cape Province; N. West = North West Province; LAM = Latino-American-Mediterranean family; EAI1 = East-African-Indian.

Resistance (or here XDR) appears on multiple genetic backgrounds

Each spreads little or not at all due to fitness costs

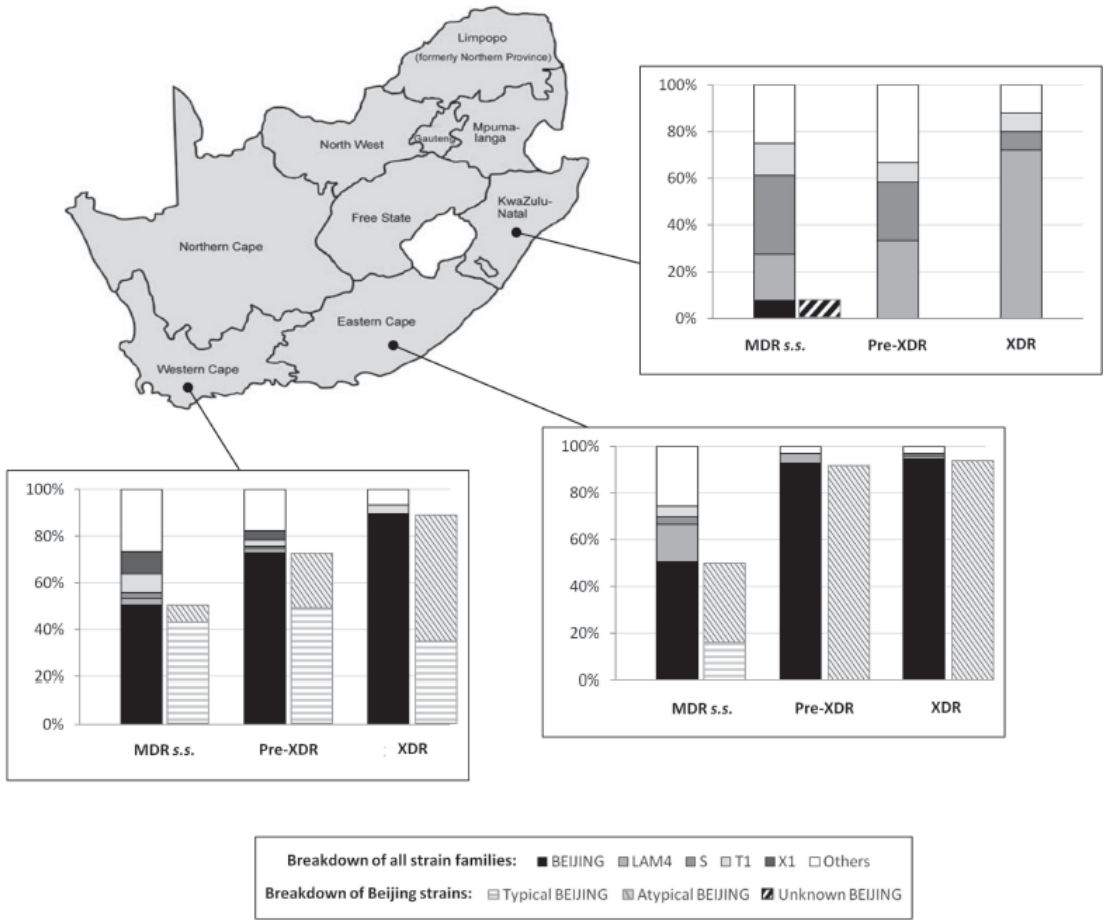
High diversity of resistant strains

63% of XDR strains in this study were unique spoligotype in a geographic setting

Like fluoroquinolone-R in *S. pneumoniae?*

Resistance Phase 2: Clonal spread of highly fit(?) resistant (here, XDR) strains

- "This study shows an intriguing, increasingly marked predomination of one single or two strain families from MDR *s.s.* to XDR-TB in all three provinces analyzed"



VN Chihota et al. *J Clin Micro* 2012. The population structure of multi- and extensively drug-resistant tuberculosis in South Africa

Other examples

- Influenza: waiting to hitch a ride on advantageous (adamantane) or permissive (oseltamivir) mutant backgrounds
- Gonorrhea: multiply resistant strains take off after several genetic “false starts”

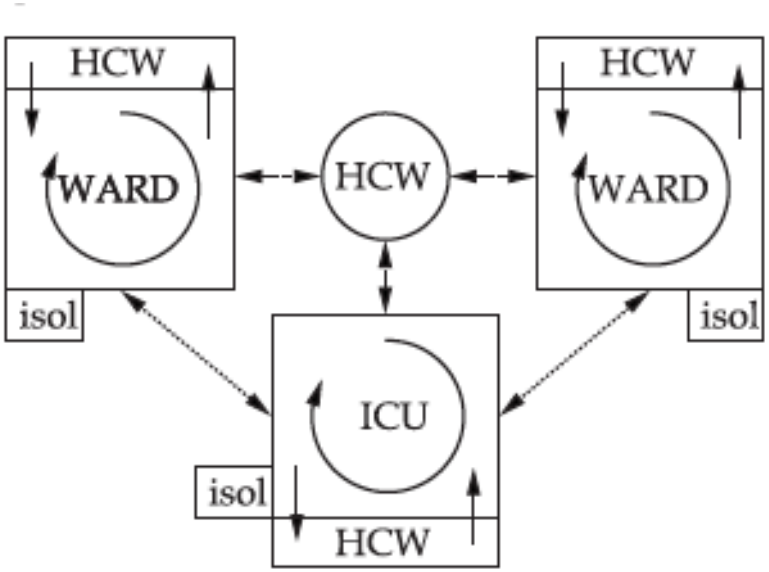
Roulette scenario

- If true, each failed treatment is an opportunity to create “superbug”
- Emphasizes importance of preventing resistance even when transmission is rare
- Need for stochastic models that incorporate changing genetic background

Question 4: How should we structure models of resistance? (what are the boxes and arrows?)

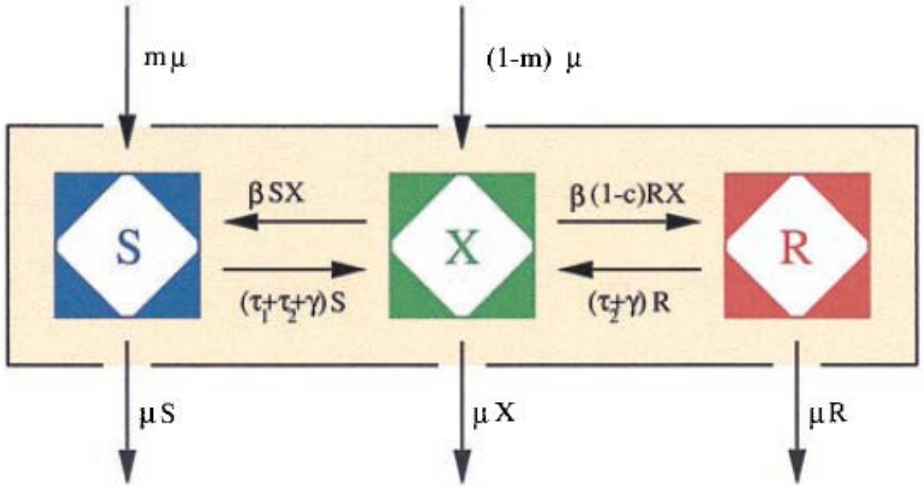
4A: Do we include drug-sensitives?

MRSA: NO



MCG Bootsma et al. *PNAS* 2006

Generic nosocomial infection: YES



M Lipsitch et al. *PNAS* 2000

No consensus, little evidence

Table 3 Variables associated with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) acquisition

Variable	Odds ratio [a] (95% CI)	*P* Value
MRSA		
MSSA carrier	0.52 (0.29, 0.95)	0.03
Intubation	4.65 (1.77, 12.26)	0.002
Fluoroquinolone	1.91 (1.20, 3.04)	0.01
ICU admit to negative swab		< .0001
1 day	1.0, reference	
2 days	1.97 (1.17, 3.30)	
≥ 3 days	15.59 (8.40, 28.94)	
VRE		
VSE carrier	1.37 (0.54, 3.48)	0.51
End-stage renal disease	2.60 (1.19, 5.70)	0.02
Albumin < 2	2.07 (1.12, 3.83)	0.02
Fluoroquinolone	1.90 (1.14, 3.17)	0.01
Third generation Cephalosporin	1.89 (1.15, 3.10)	0.01
ICU admit to negative swab		< .0001
1 day	1.0, reference	
2 days	1.42 (0.79, 2.56)	
≥ 3 days	15.13 (7.86, 29.14)	

YES

NO

If you do include the sensitives, make sure they don't persist due to a mathematical artifact

Epidemics 1 (2009) 2–13

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

No coexistence for free: Neutral null models for multistrain pathogens

Marc Lipsitch [a,b,*], Caroline Colijn [a,c], Ted Cohen [a,d], William P. Hanage [e], Christophe Fraser [f]

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4B: By what mechanism(s) does treatment select for resistance?

1. Emergence of R during treatment
2. Cure S infections, reducing $R_{OS}<R_{OR}$
3. Increase bacterial load of R in mixed commensal flora, increasing risk of R infection for an individual and R transmission to others?
4. Increasing susceptibility to acquire R by killing resident S flora

1000 flowers bloom

Core groups, antimicrobial resistance and rebound in gonorrhoea in North America

Christina H Chan,[1,2] Caitlin J McCabe,[1,2] David N Fisman[1,2]

1,2

1,2

How could preventive therapy affect the prevalence of drug resistance? Causes and consequences

Amber Kunkel[1,3], Caroline Colijn[2], Marc Lipsitch[1] and Ted Cohen[3]

The path of least resistance: aggressive or moderate treatment?

Roger D. Kouyos[1,2,†], C. Jessica E. Metcalf[1,3,†], Ruthie Birger[1,†], Eili Y. Klein[1,8], Pia Abel zur Wiesch[4], Peter Ankomah[5], Nimalan Arinaminpathy[1,16], Tiffany L. Bogich[1,15], Sebastian Bonhoeffer[6], Charles Brower[1,20], Geoffrey Chi-Johnston[7], Ted Cohen[4], Troy Day[9], Bryan Greenhouse[10], Silvie Huijben[19], Joshua Metlay[13], Nicole Mideo[14], Laura C. Pollitt[11,12,18], Andrew F. Read[11,12,15], David L. Smith[3], Claire Standley[17], Nina Wale[11,12] and Bryan Grenfell[1,15]

1

3,4

A Simulation-Based Assessment of Strategies to Control *Clostridium Difficile* Transmission and Infection

Michael A. Rubin[1,2*], Makoto Jones[1,2], Molly Leecaster[1,2], Karim Khader[1], Willy Ray[1], Angela Huttner[3], Benedikt Huttner[3], Damon Toth[1], Theodore Sablay[1,2], Robert J. Borotkanics[4], Dale N. Gerding[5], Matthew H. Samore[1,2]

ORIGINAL INVESTIGATION

The Role of "Colonization Pressure" in the Spread of Vancomycin-Resistant Enterococci

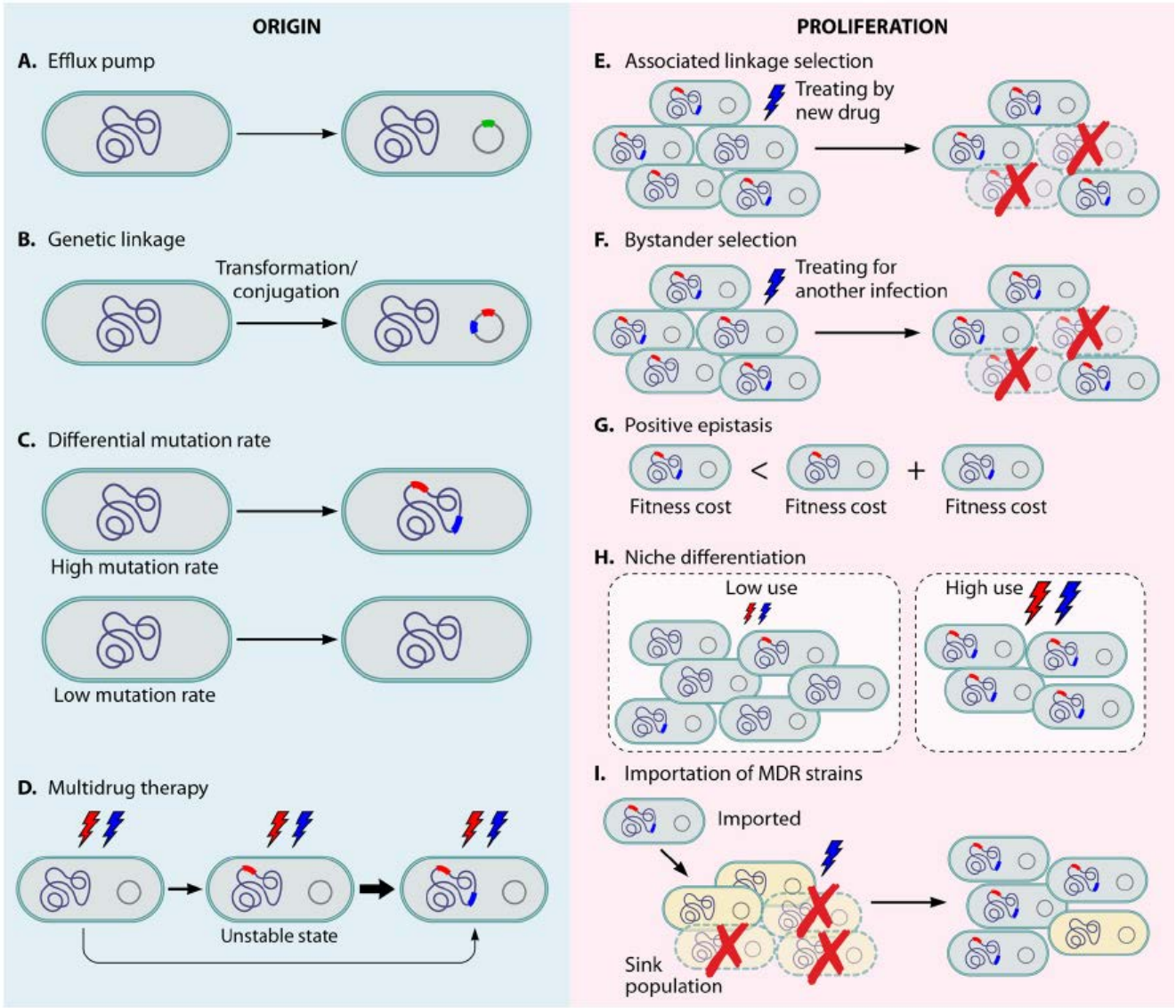
An Important Infection Control Variable

Marc J. M. Bonten, MD; Sarah Slaughter, MD; Anton W. Ambergen; Mary K. Hayden, MD; Jean van Voorhis, RN, MS; Catherine Nathan, MS; Robert A. Weinstein, MD

4

4C: How should we incorporate multiple drugs and cross-resistance?

HH Chang et al. *MMBR* 2015



4D:How do we model host heterogeneity?

Reclassification of *Staphylococcus aureus* Nasal Carriage Types

Alex van Belkum,[1] Nelianne J. Verkaik,[1] Corné P. de Vogel,[1] Hélène A. Boelens,[1] Jeroen Verveer,[1] Jan L. Nouwen,[1] Henri A. Verbrugh,[1] and Heiman F. L. Wertheim[1,2]

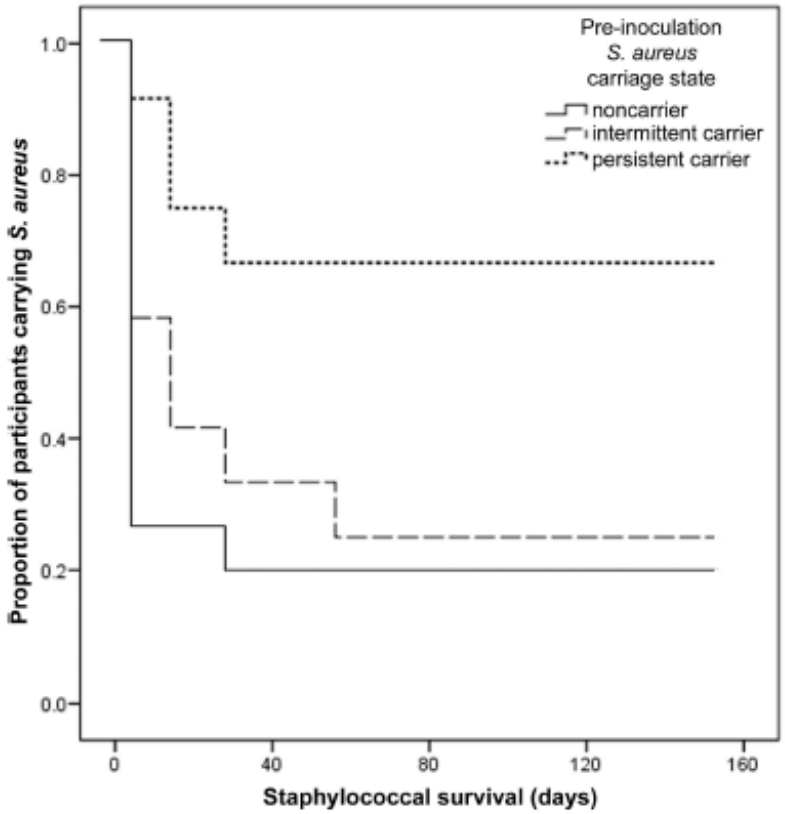
[1]Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands; and [2]Oxford University Clinical Research Unit, National Institute for Infectious Tropical Diseases, Bach Mai Hospital, Hanoi, Vietnam

Background. Persistent nasal carriers have an increased risk of *Staphylococcus aureus* infection, whereas intermittent carriers and noncarriers share the same low risk. This study was performed to provide additional insight into staphylococcal carriage types.

Methods. Fifty-one volunteers who had been decolonized with mupirocin treatment and whose carriage state was known were colonized artificially with a mixture of *S. aureus* strains, and intranasal survival of *S. aureus* was compared between carriage groups. Antistaphylococcal antibody levels were also compared among 83 carriage-classified volunteers.

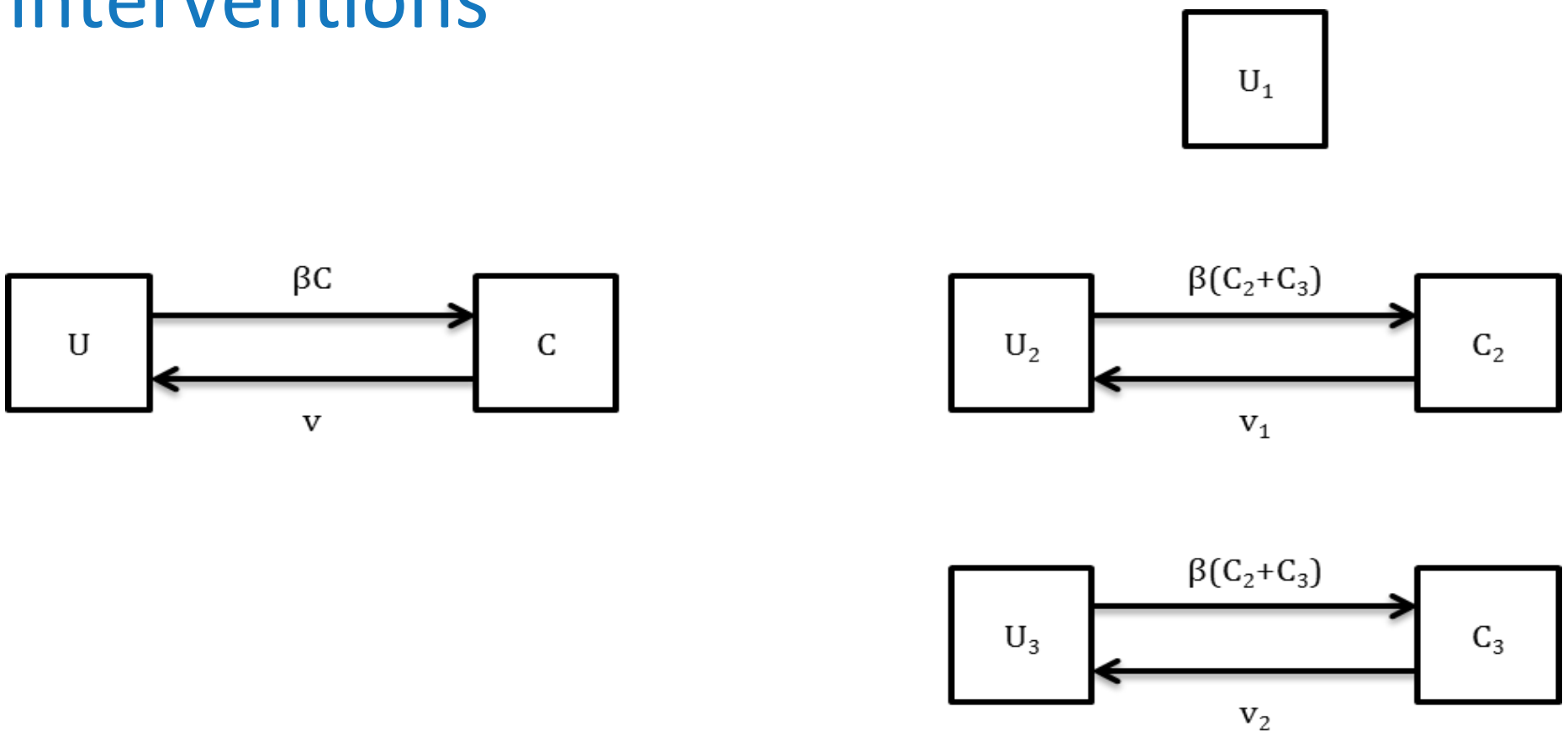
Results. Persistent carriers preferentially reselected their autologous strain from the inoculum mixture ($P = .02$). They could be distinguished from intermittent carriers and noncarriers on the basis of the duration of postinoculation carriage (154 vs. 14 and 4 days, respectively; $P = .017$, by log-rank test). Cultures of swab samples from persistent carriers contained significantly more colony-forming units per sample than did cultures of swab samples from intermittent carriers and noncarriers ($P = .004$). Analysis of serum samples showed that levels of immunoglobulin G and immunoglobulin A to 17 *S. aureus* antigens were equal in intermittent carriers and noncarriers but not in persistent carriers.

Conclusions. Along with the previously described low risk of infection, intermittent carriers and noncarriers share similar *S. aureus* nasal elimination kinetics and antistaphylococcal antibody profiles. This implies a paradigm shift; apparently, there are only 2 types of nasal carriers: persistent carriers and others. This knowledge may increase our understanding of susceptibility to *S. aureus* infection.

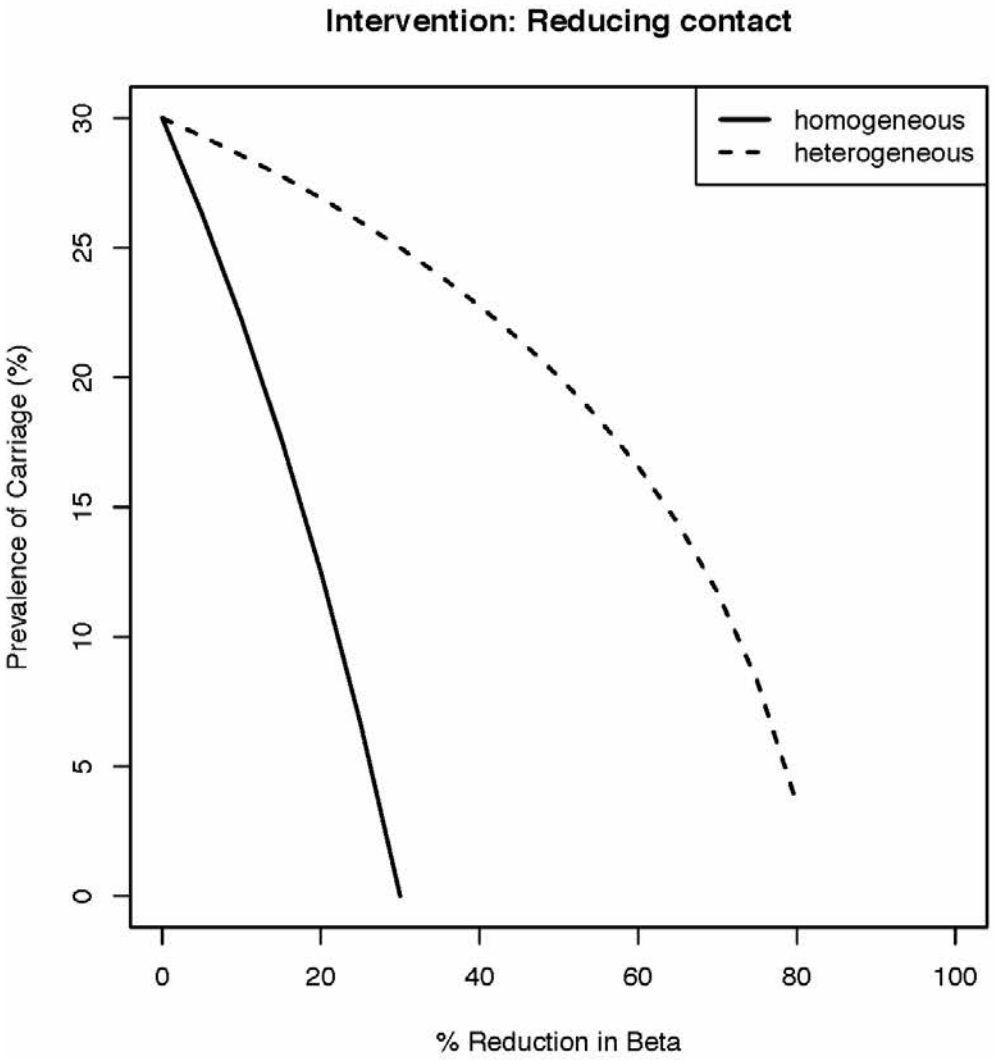


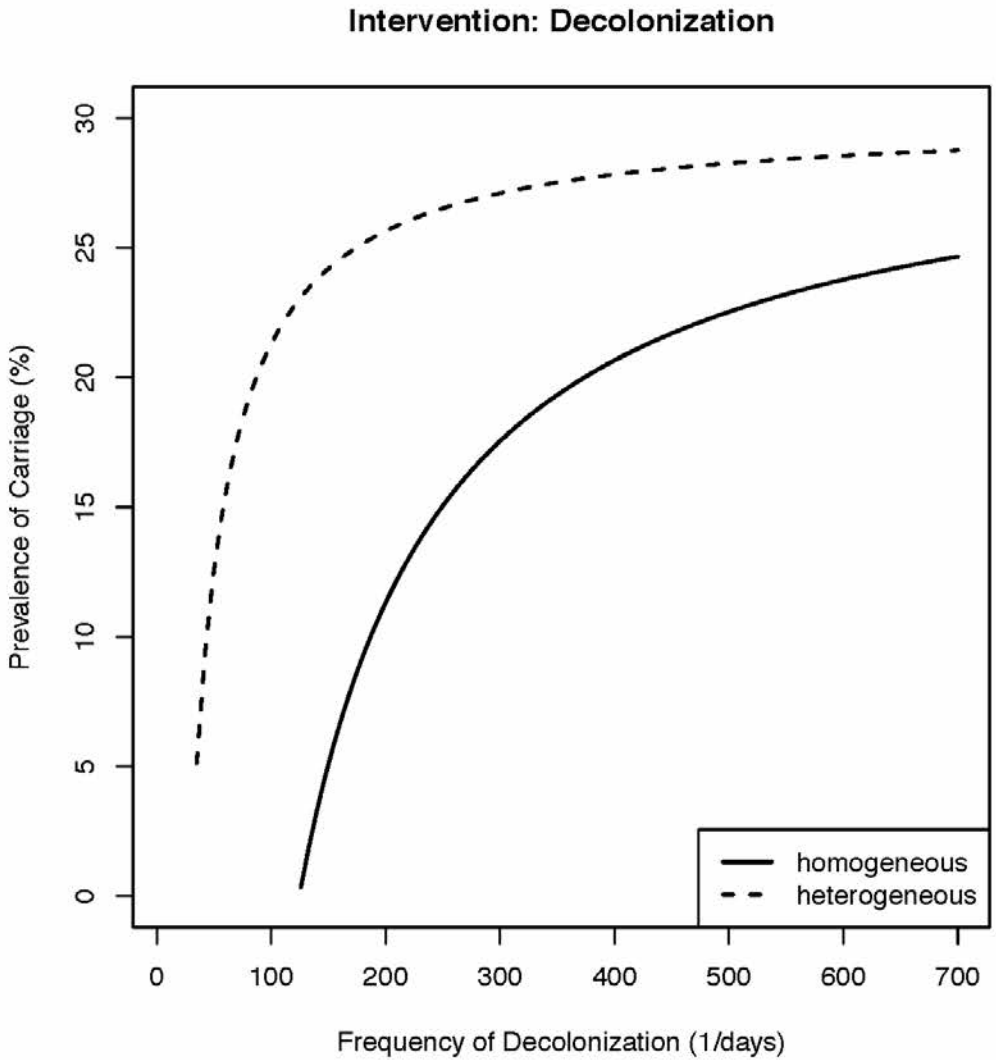
Heterogeneity invalidates: R0-prevalance relationship, acquisition-loss-prevalence relationship, etc.

Heterogeneous-population models predict usually much lower effectiveness of interventions



Heterogeneous-population models predict usually much lower effectiveness of interventions





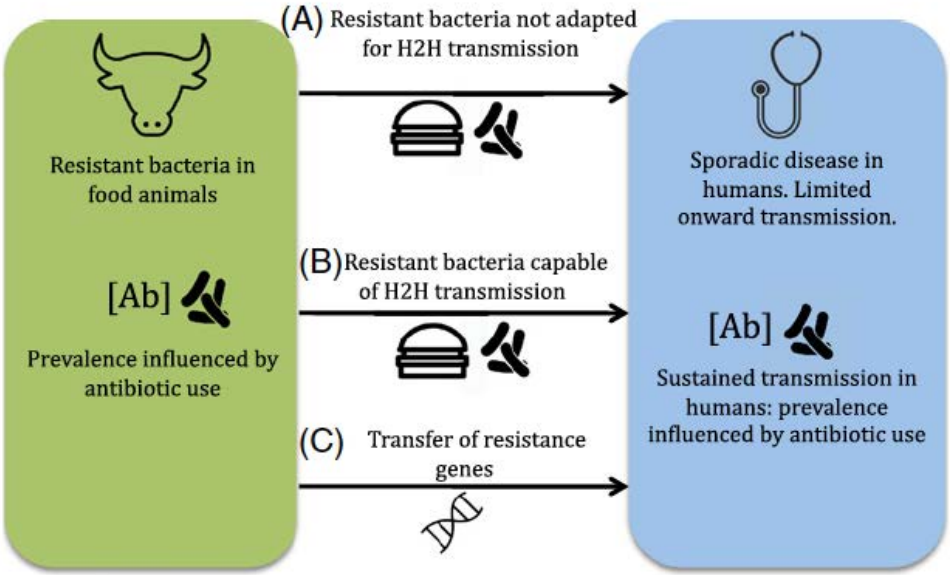
Q Chang et al. unpublished

4E: How (much) does agricultural use matter?

To Your Health

White House opens 'superbug' summit, orders federal cafeterias to use meat raised with 'responsible antibiotic use'

Top 3 pathogens in O'Neill review are TB, malaria, *E. coli* – only one has plausible link to ag



Q Chang et al. *Evol Appl* 2014

Selected conclusions

- Antibiotic resistance remains a big field with many fundamental, unanswered population-level questions
  - Need all approaches because you can't tell a priori the relative importance of ecology, genetics and other factors
- More attention needed on the appearance and early spread of resistant strains, including genetic background and where it appears
- Poorly-understood heterogeneity of persons limits our ability to make quantitative predictions

Collaborators

Coexistence etc.

Caroline Colijn

Ted Cohen

Bill Hanage

Christophe Fraser

Sarah Deeny

Heterogeneity

Bill Hanage

Qiuzhi (Rose) Chang

Israel dynamics & coexistence:

Ron Dagan

Noga Givon-Lavi

Gonorrhea:

Ed Goldstein

Pardis Sabeti

David Reshef

Bob Kirkcaldy/CDC

GISP Investigators

Much discussion:

Lone Simonsen

Josh Plotkin

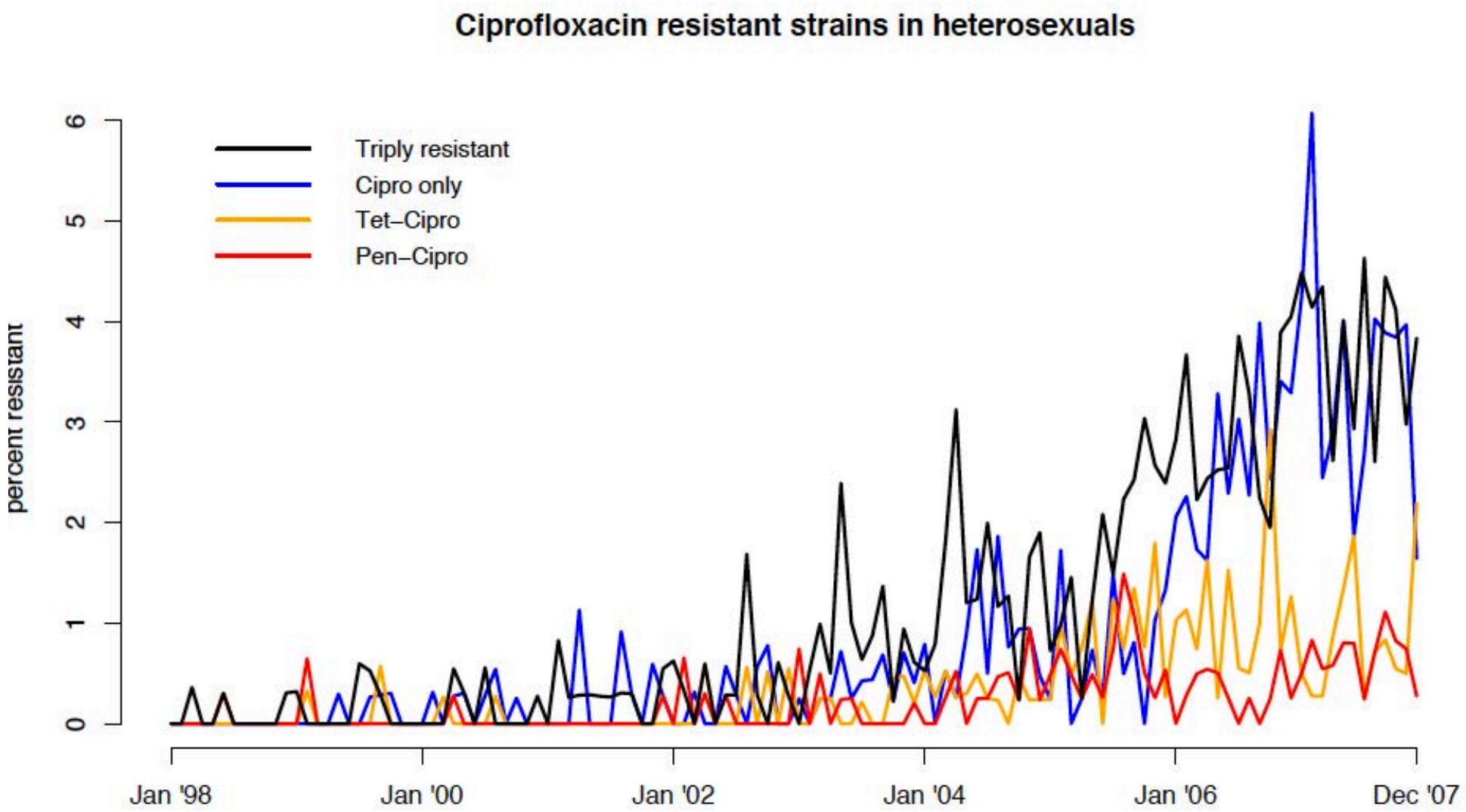
Barry Bloom

Yonatan Grad

Gili Regev-Yochay

Betz Halloran (heterogeneity)

Appearance is not limiting



Modified from E Goldstein et al. *Emerg Infect Dis* 2012 in press: Data from CDC GISP