PennState

THE HUCK INSTITUTES OF THE LIFE SCIENCES

CIDD Center for Infectious Disease Dynamics

NIH

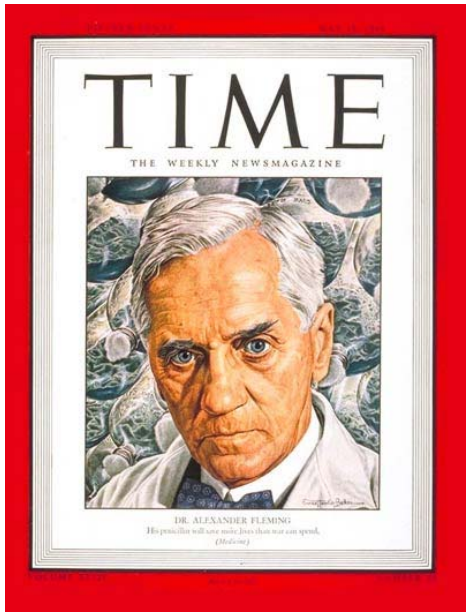
Departments of Biology and Entomology
www.thereadgroup.net

R01 GM105244 (PI: Read)
R01AI089819 (PI Juliano, UNC)
RAPIDD, Fogarty

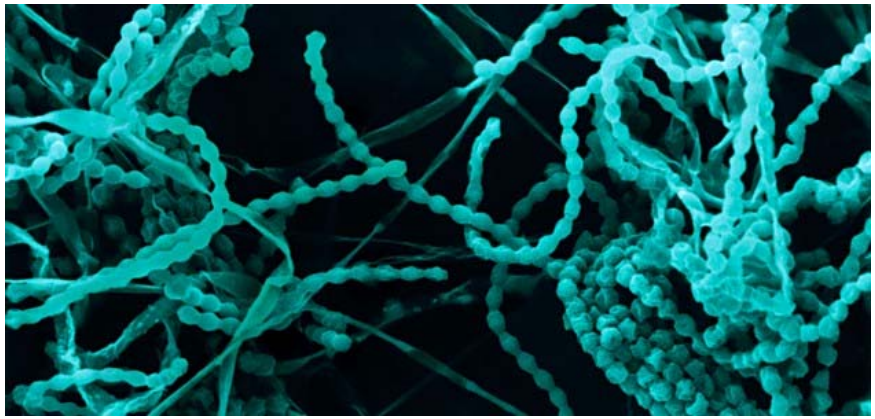
Overwhelming Evolution.
Patients, Microbes and the Drug Resistance Problem

Andrew F. Read PhD

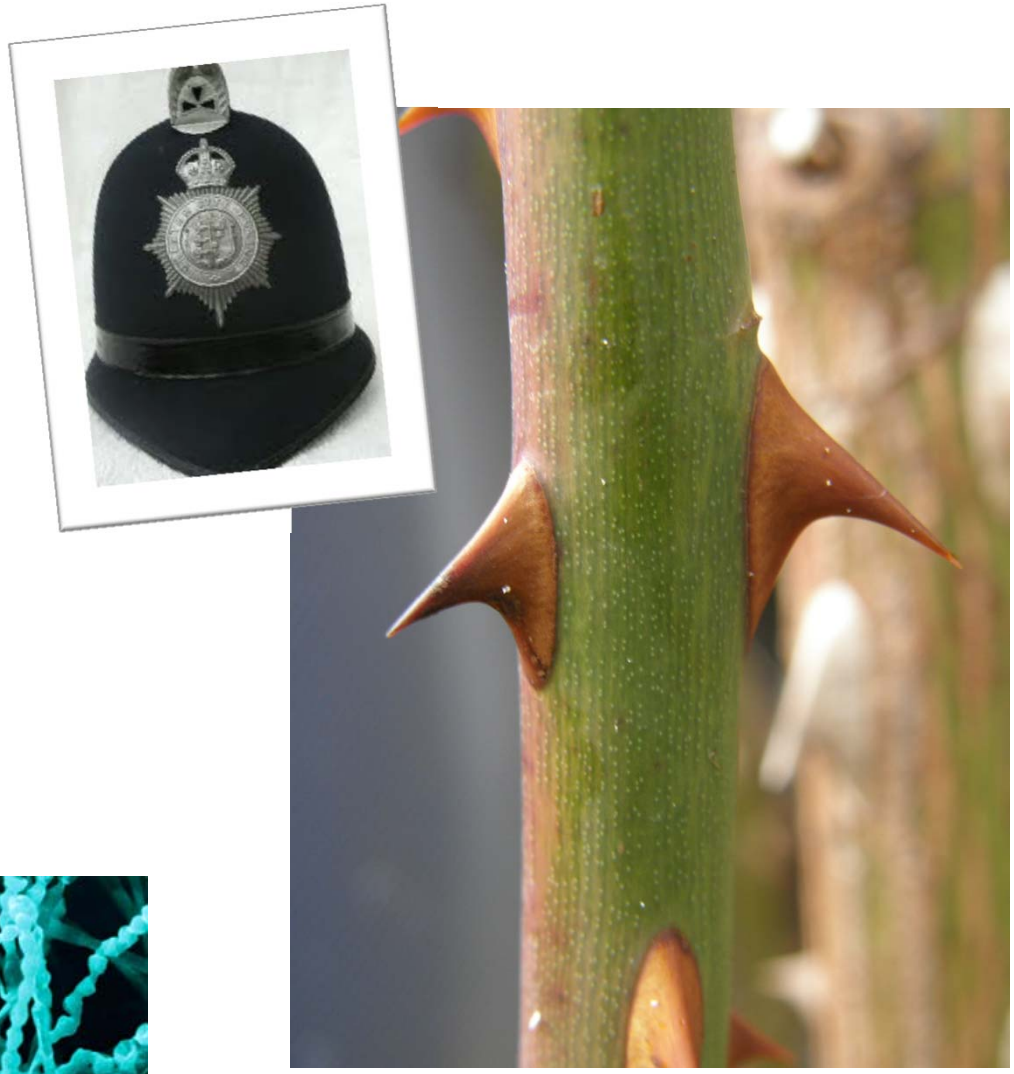
Antibiotics



Alexander Fleming



Penicillium mold



Police Const. Albert Alexander
(1897-1941)

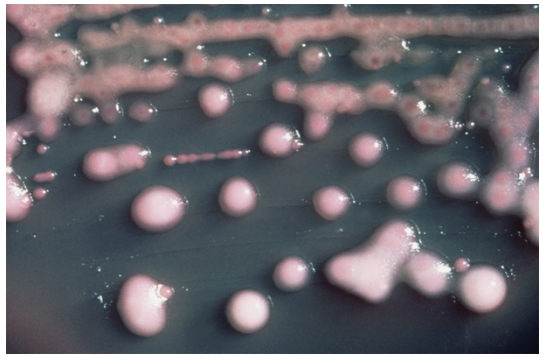
Rebecca Lohsen

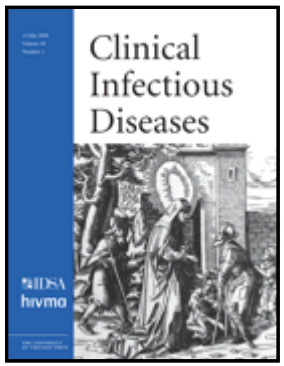
b. 1989
d. 2006

“Rebecca’s death has changed me, has changed all of us. Once I believed that the dangers that were out there would stay out there. That modern medicine can avert these dangers. I no longer have the confidence in medicine that I did. I believe we have made great advances, that there are cures to be had, but I’ve watched the dismay in the faces of doctors who are supposed to be the best in their field as they told me they didn’t have any more “cures in their bag.”

And I know that it truly is a PRACTICE of medicine, not a finished product.”

Infection with Panresistant *Klebsiella pneumoniae*: A Report of 2 Cases and a Brief Review of the Literature





Azza Elemam, Joseph Rahimian, and William Mandell

Section of Infectious Diseases, Saint Vincent's Hospital, New York, New York

Clinical Infectious Diseases 2009; 49:271–4

It is a rarity for a physician in the developed world to have a patient die of an overwhelming infection for which there are no therapeutic options. These cases were the first instance in our clinical experience in which we had no effective treatment to offer. Trends in urban hospitals are often the harbinger of the future. We share these cases to highlight some troubling issues that soon may be relevant to increasing numbers of physicians and patients across the United States.

The New York Times

The World Wakes Up to the Danger of Superbugs

By THE EDITORIAL BOARD SEPT. 28, 2016

A technician scanning the X-ray of a patient suspected of having Tuberculosis. Justin Mott for The New York Times

Tuberculosis. Malaria. Syphilis. Gonorrhea. The microbes that cause these diseases are increasingly resistant, and sometimes even impervious, to antibiotics that worked in the past. Last week, amid other pressing business, 193 nations at the United Nations General Assembly signed a declaration summoning each of them to a war against a powerful and resourceful enemy: superbugs that have learned to evade science's last remaining defenses.

Photo credit: Photonewzealand/Stephen Blecher

kakapo

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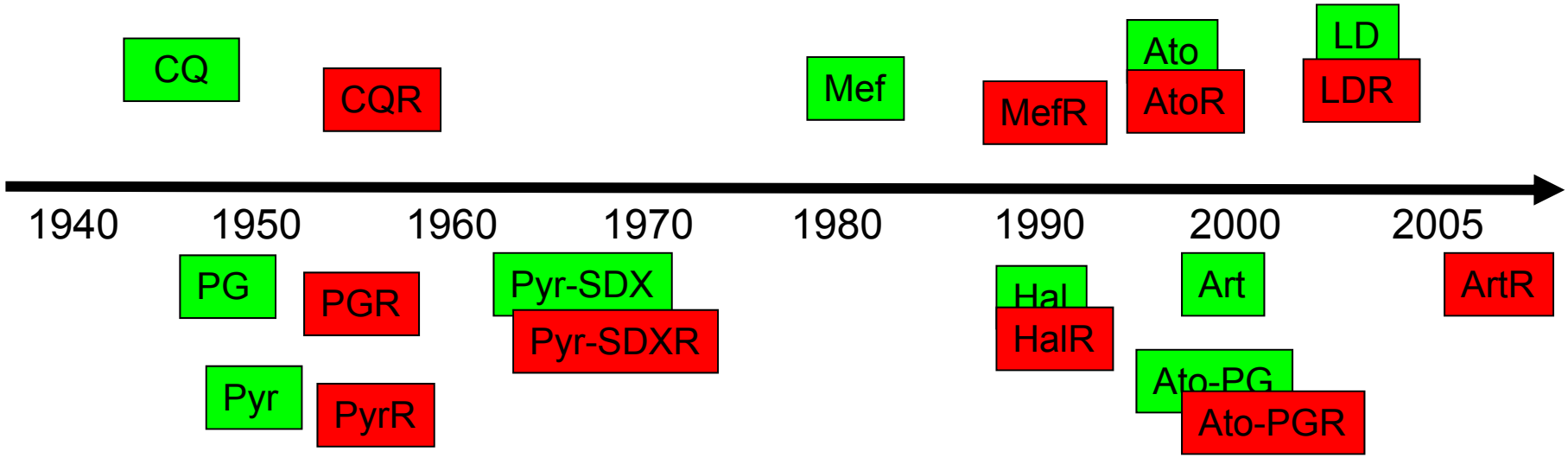
Evolution in Action 1.

Evolution in Action 2. Malaria drugs

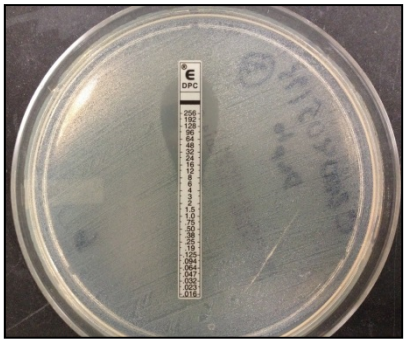


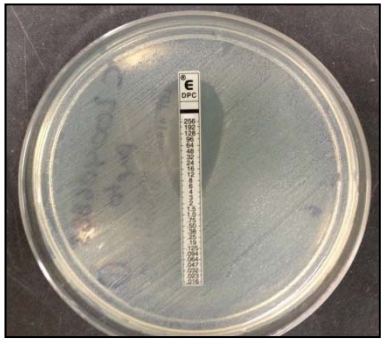
WHO (2006): Drugs eventually undermined by pathogen evolution

Requires open-ended drug discovery pipeline

Hyde 2005, Read and Huijben 2009

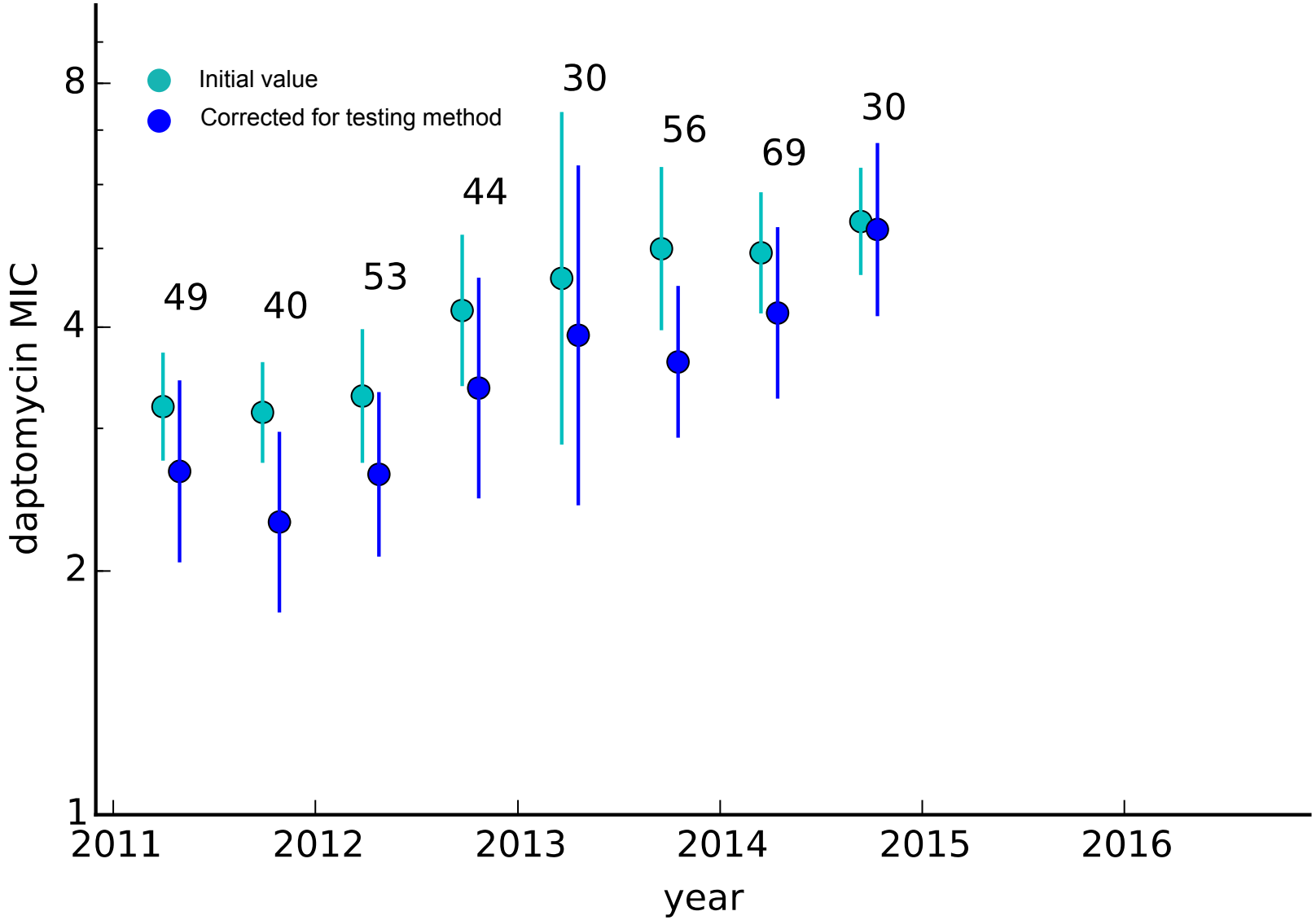
Evolution in Action 3. A US hospital





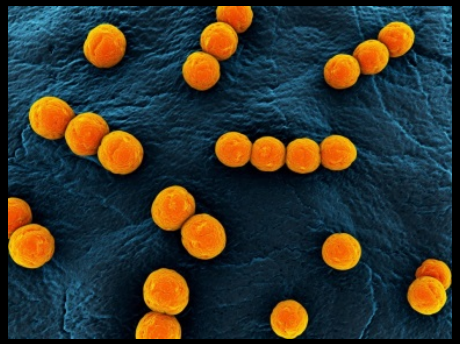
Daptomycin and Vancomycin-Resistant *Enterococcus* (VRE)

Blood stream VRE: daptomycin resistance

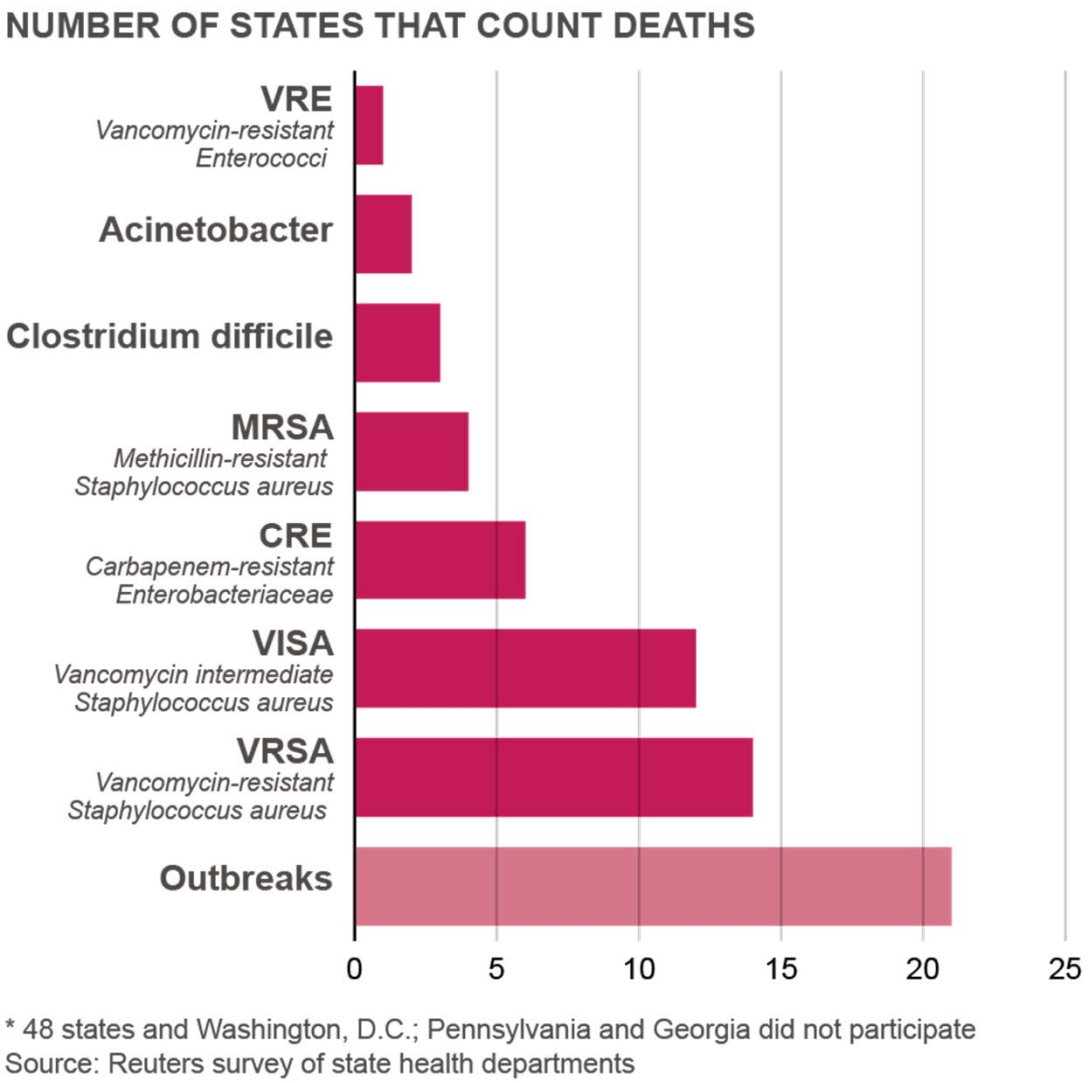


How serious is the problem?

CDC estimate:
23,000 Americans die each year from resistant infections



State health departments that count deaths due to the seven most prevalent infections



http://www.reuters.com/investigates/special-report/usa-uncounted-surveillance/

Deaths due to resistant bacteria
(2003-2014)

State counts
vs
Death Certificates

STATE	STATE COUNT	REUTERS COUNT
Alabama	*	2,513
Alaska	0	151
Arizona	*	5,337
Arkansas	*	1,545
California	*	20,316
Colorado	*	1,780
Connecticut	2,084	3,039
D.C.	*	521
Delaware	0	723
Florida	21	11,582
Georgia	*Did not participate*	3,740
Hawaii	*	450
Idaho	338	533
Illinois	*	6,431
Indiana	0	3,869
Iowa	*	1,733
Kansas	0	1,515
Kentucky	9	3,027
Louisiana	0	1,718
Maine	*	1,208
Maryland	*	4,486
Massachusetts	0	4,683
Michigan	78	5,200
Minnesota	363	2,456
Mississippi	*	1,175
Missouri	84	4,796
Montana	0	304
Nebraska	0	939
Nevada	1	984
New Hampshire	*	1,221
New Jersey	*	5,004
New Mexico	*	1,010
New York	*	10,623
North Carolina	0	6,038
North Dakota	*	512
Ohio	*	10,469
Oklahoma	27	2,955
Oregon	*	1,760
Pennsylvania	*Did not participate*	10,533
Rhode Island	0	1,430
South Carolina	*	2,627
South Dakota	*	666
Tennessee	*	5,619
Texas	*	10,138
Utah	*	647
Vermont	206	475
Virginia	*	3,973
Washington	4	4,573
West Virginia	86	1,819
Wisconsin	0	2,399
Wyoming	3	157

Source: Reuters survey of state health departments * Does not count superbug deaths

How serious is the problem?

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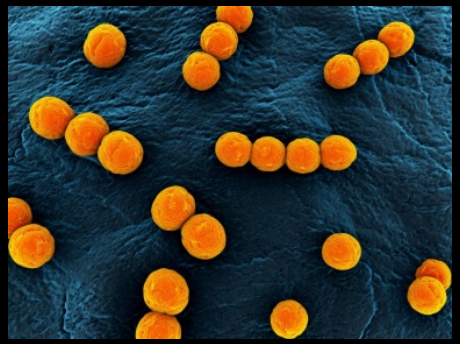
Possible upper bound: 100,000



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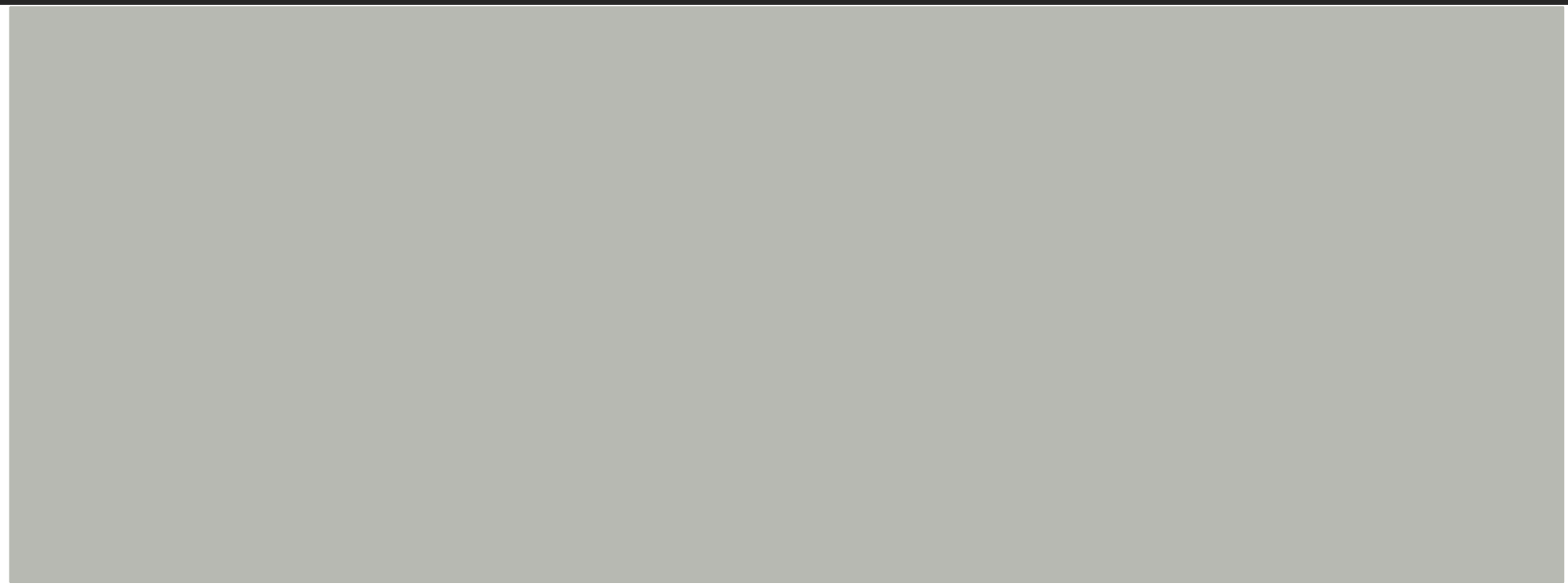
"**Two forces at work**:

- Scientists and pharma failing to develop new drugs to keep pace with failing drugs
- Excessive and improper use of existing drugs by doctors, patients, farmers"

Solutions:

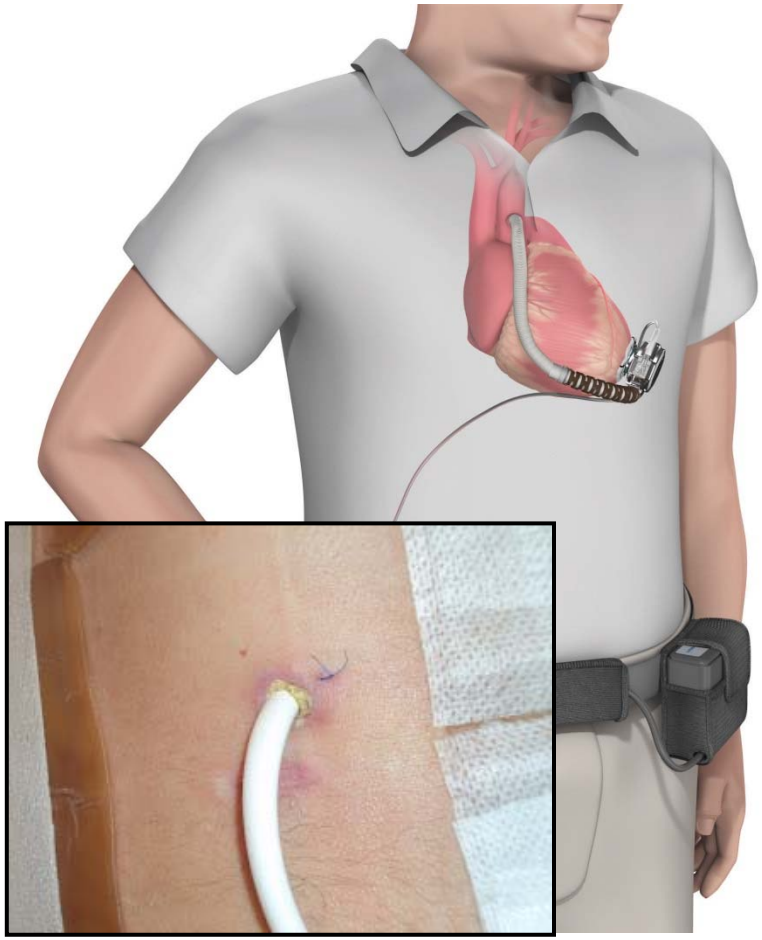
- Drug discovery
- Reduce antibiotic use in livestock
- Consumers: vaccines
- Doctors and nurses: hygiene
- Regulate and educate doctors

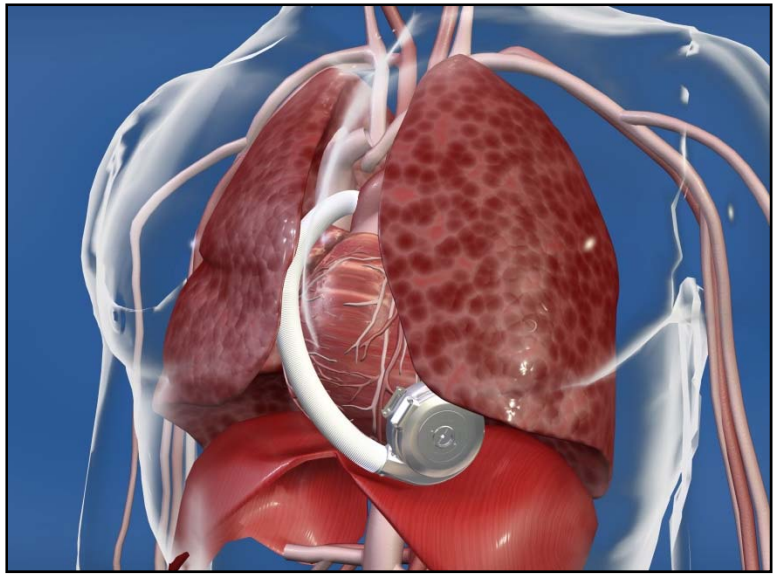
How to treat patients when patient treatment causes resistance?



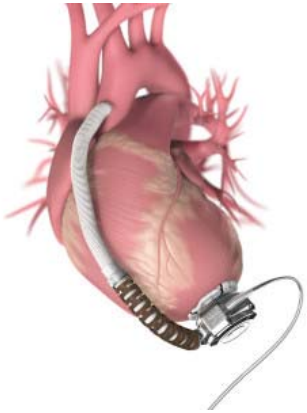
A patient

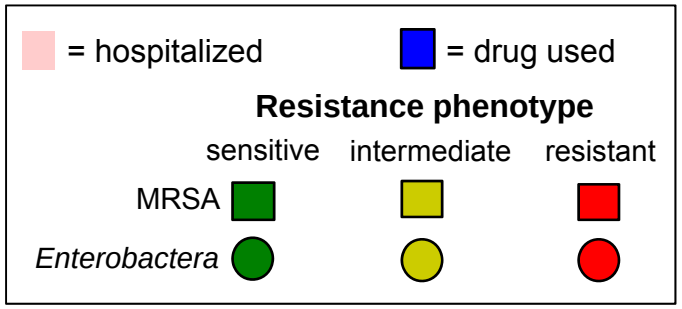
Robert J. Woods
PhD MD
U of Michigan

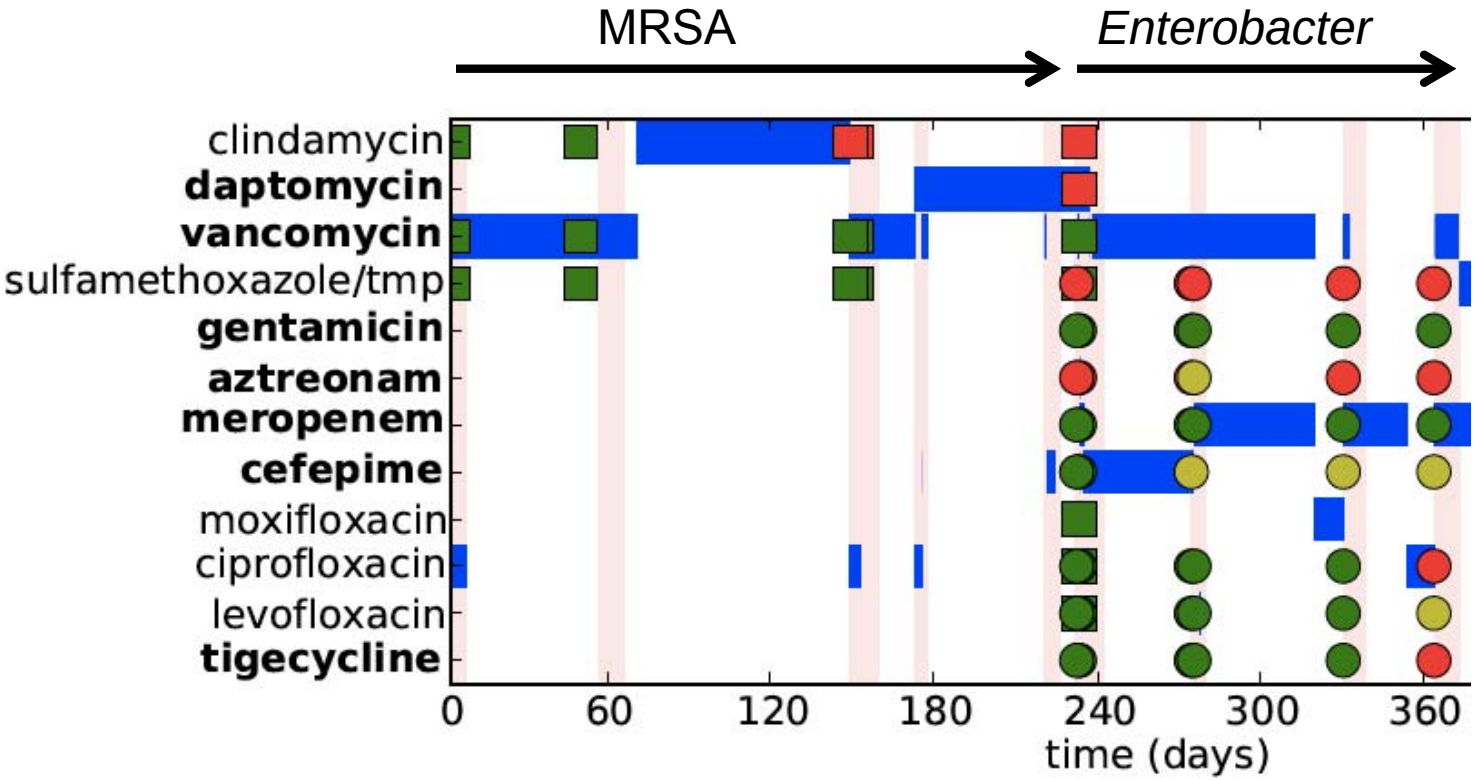




Left ventricular assist device



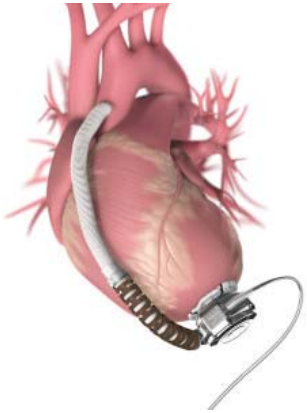




bold = i.v. drugs

What now?

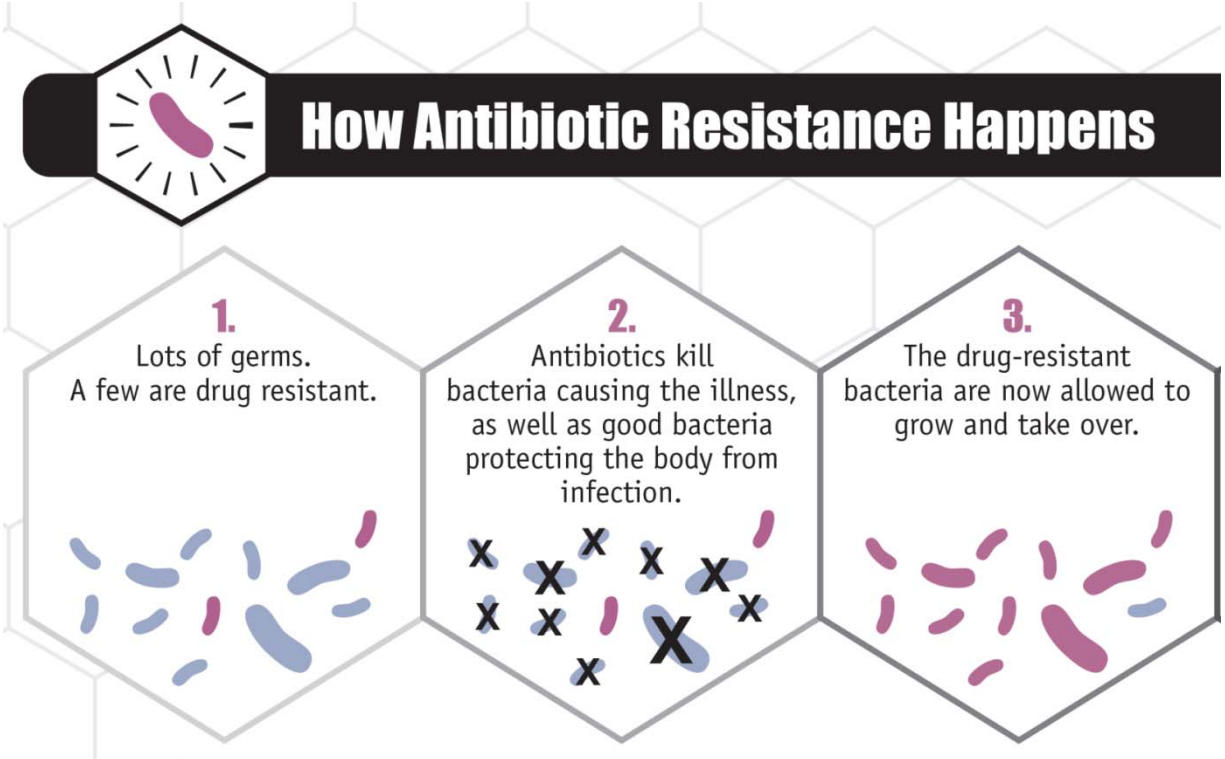
Woods & Read (2015) *Evolution, Medicine and Public Health*



What now?

Choice of drug(s), dose, infusion time, dosing frequency
One regimen until it fails, then switch or fixed rotation of regimens?
Only treat reactively?

‘Simplify’ the problem: choice of drug



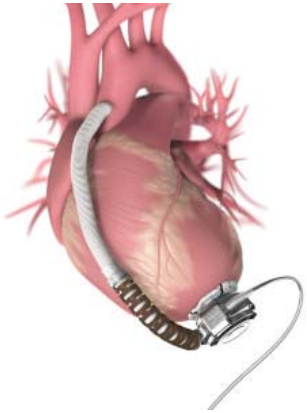
Woods & Read (2015) *Evolution, Medicine and Public Health*

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Options for resistance management:

1. Impact origin (transmission, mutation, HGT)

2. Impact expansion

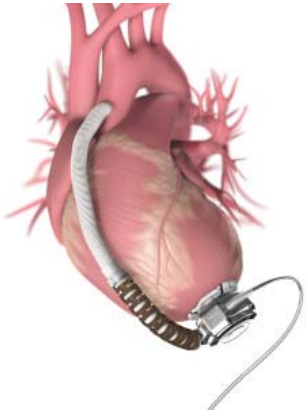


What now?

Choice of drug

1. Continue meropenem until that fails, switch to cefepime
2. Switch back to cefepime until that fails, then switch to meropenem
3. Combination therapy, meropenem and cefepime
4. Combination therapy, meropenem or cefepime + levo or cipro
5. Short duration with gentamicin or colistin

Option 1 is standard practice, so.....

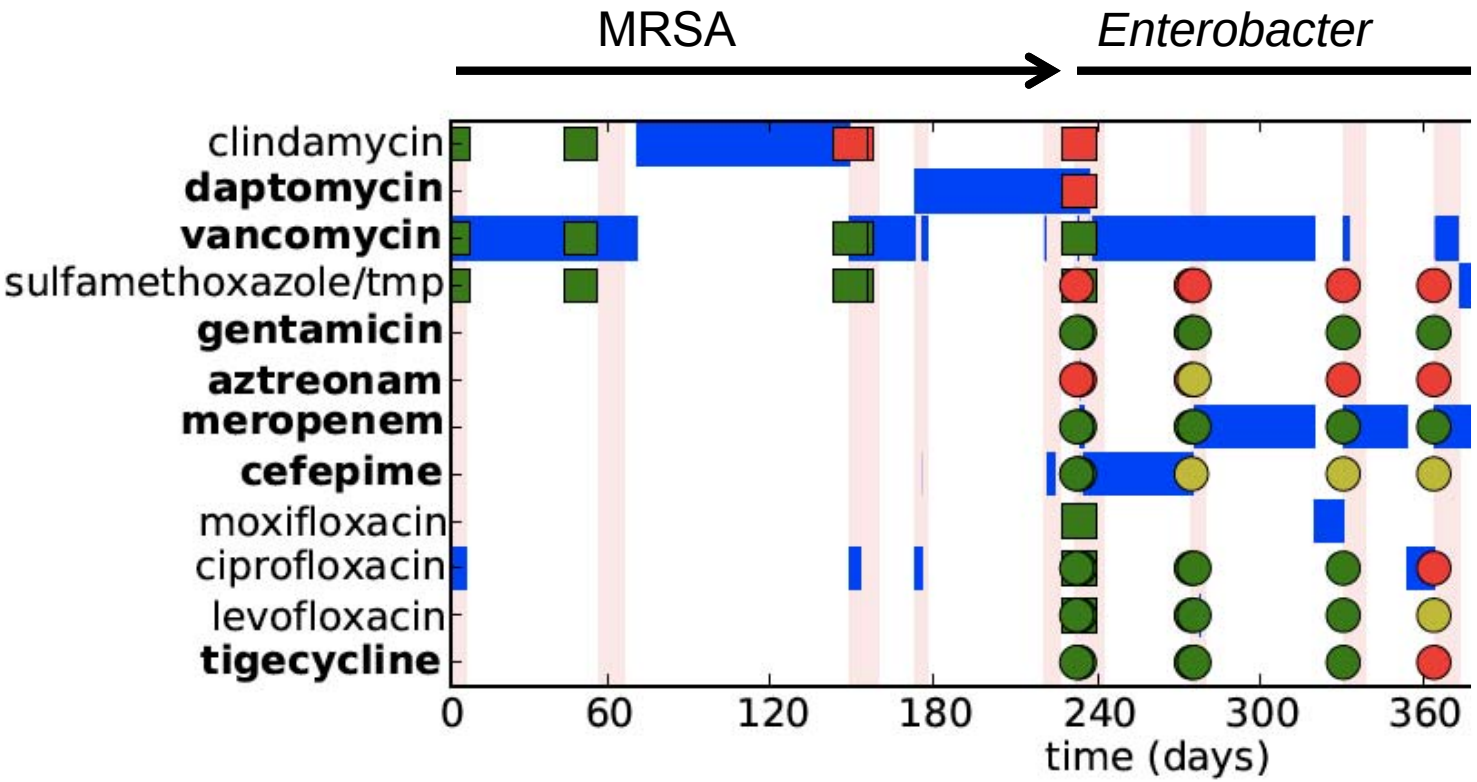


= hospitalized

= drug used

Resistance phenotype

	sensitive	intermediate	resistant
MRSA	■	■	■
Enterobactera	●	●	●



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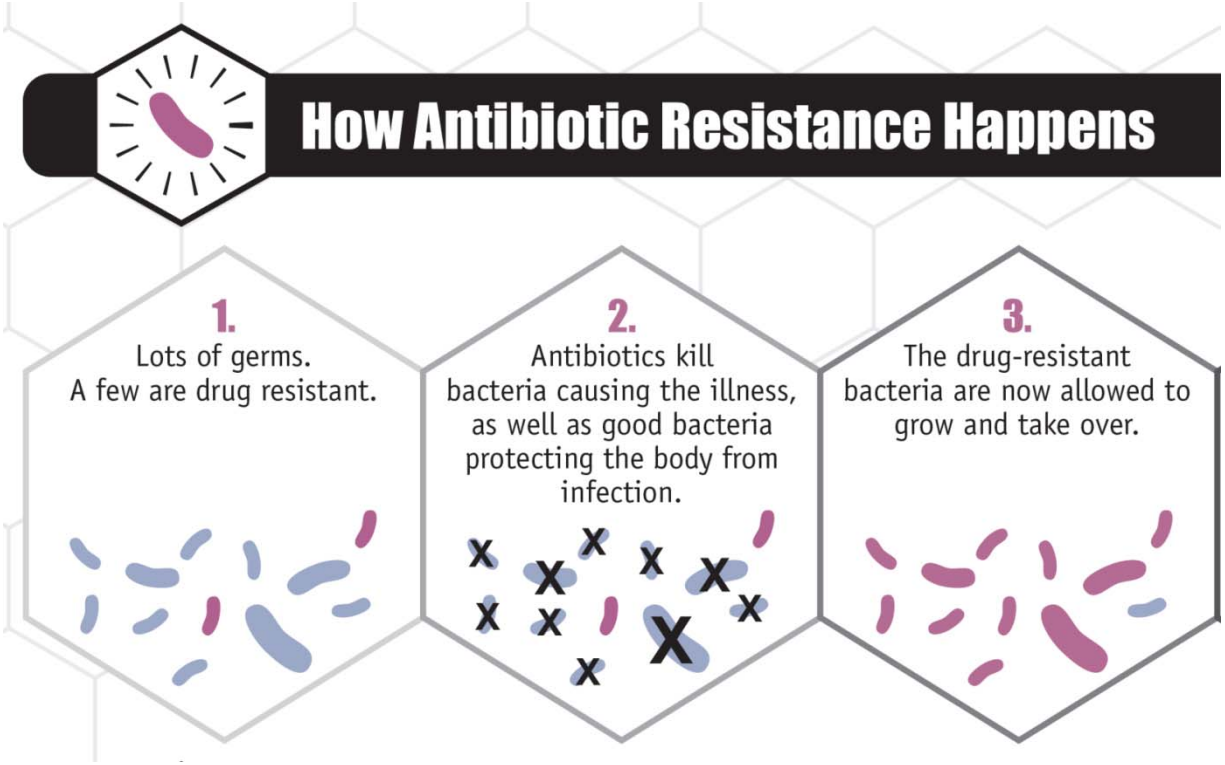
How to treat patients when patient treatment causes resistance?

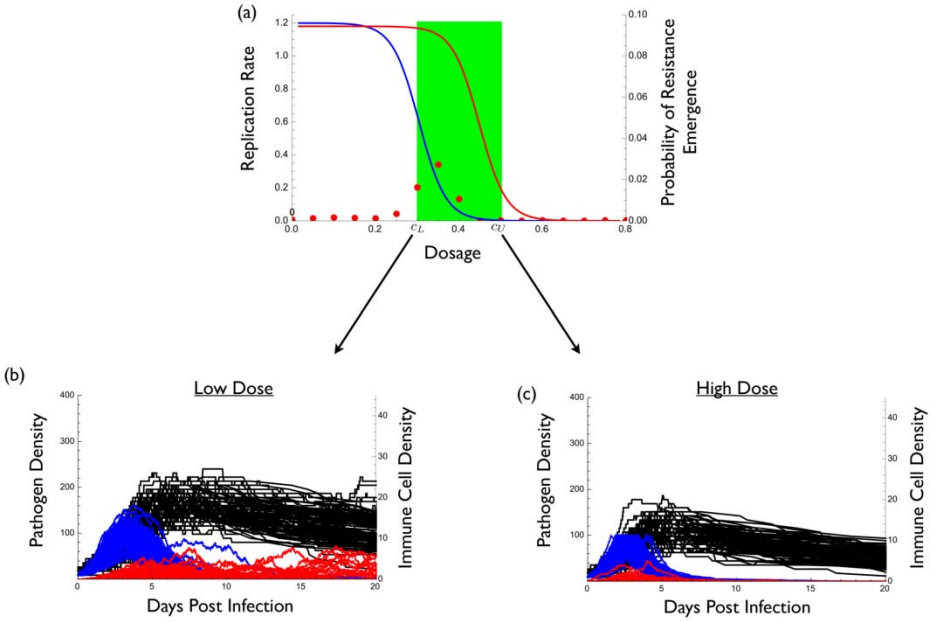


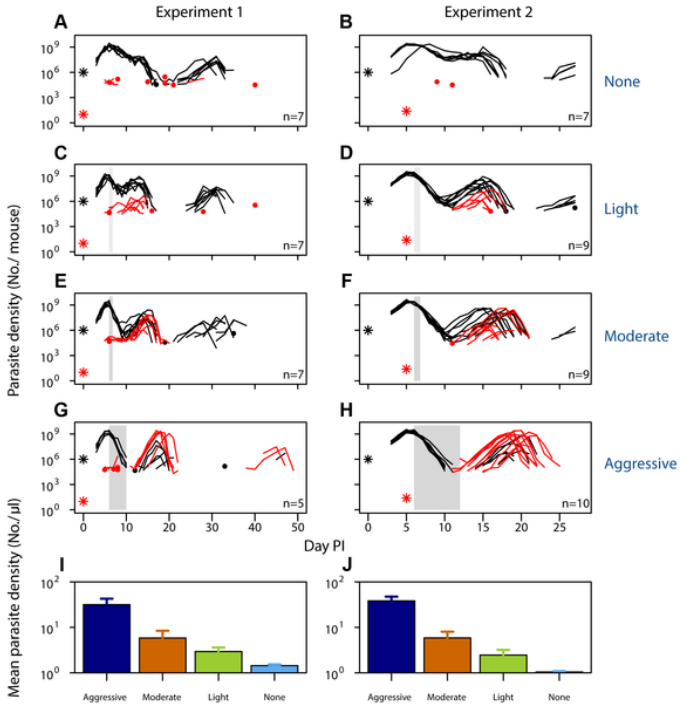
Options for resistance management:

1. Impact origin (transmission, mutation, HGT)

2. Impact expansion

$$\frac{dH}{dc} = \overbrace{\int_0^a \pi \left(\frac{\partial \lambda}{\partial p}\frac{\partial p}{\partial c} + \frac{\partial \lambda}{\partial c} \right) \mathrm{d}s}^{\text{mutation}} + \overbrace{\int_0^a \lambda \left(\nabla_x \pi \cdot x_c + \frac{\partial \pi}{\partial c} \right) \mathrm{d}s}^{\text{de novo hazard}} + \overbrace{\frac{n}{1-\pi} \left(\nabla_x \pi^0 \cdot x_c^0 + \frac{\partial \pi^0}{\partial c} \right)}^{\text{standing hazard}}$$



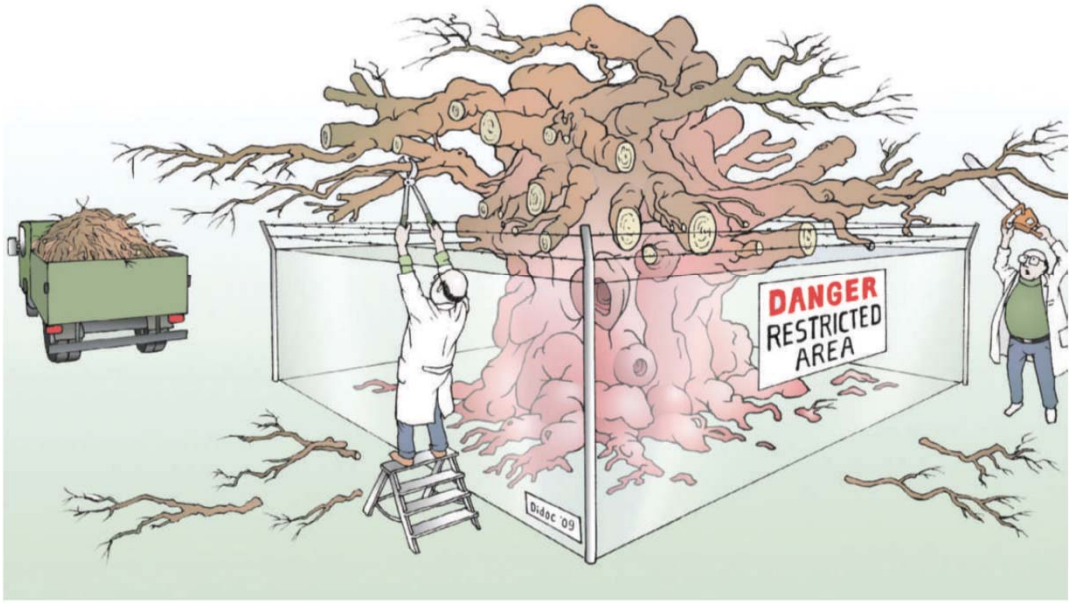


Read, Huijben, Day 2011 *PNAS*, Huijben et al. *PLoS Pathogens* 2013, Day, Read *PLoS Comp Biol* 2016

Cure or containment?

OPINION NATURE|Vol 459|28 May 2009

ESSAY



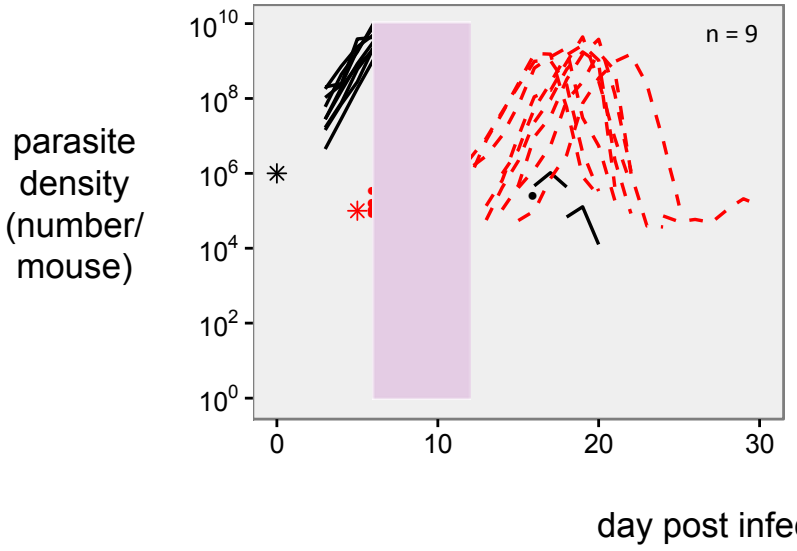
A change of strategy in the war on cancer

Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.

Evolution-proofing existing antibiotics

pABA abundant

pABA depleted



Susceptible +
Resistant

✳ Susceptible Inoculum

✳ Resistant Inoculum

Pyrimethamine Treatment

Wale, Sim, Jones, Salathe, Day, Read in prep.

Take home messages

The problem is big, but we don't really know how big

Science of antibiotic stewardship is just beginning

New approaches to patient treatment are coming

New opportunities for pharma
- drugs for containment not cure
- evolution-proofing compounds

Drug resistance is a hard problem.
But it is not the hardest problem facing humanity – so long as we tackle it.