Evolution with Hosts

Jason Andrews

Jeremy Goldhaber-Fiebert

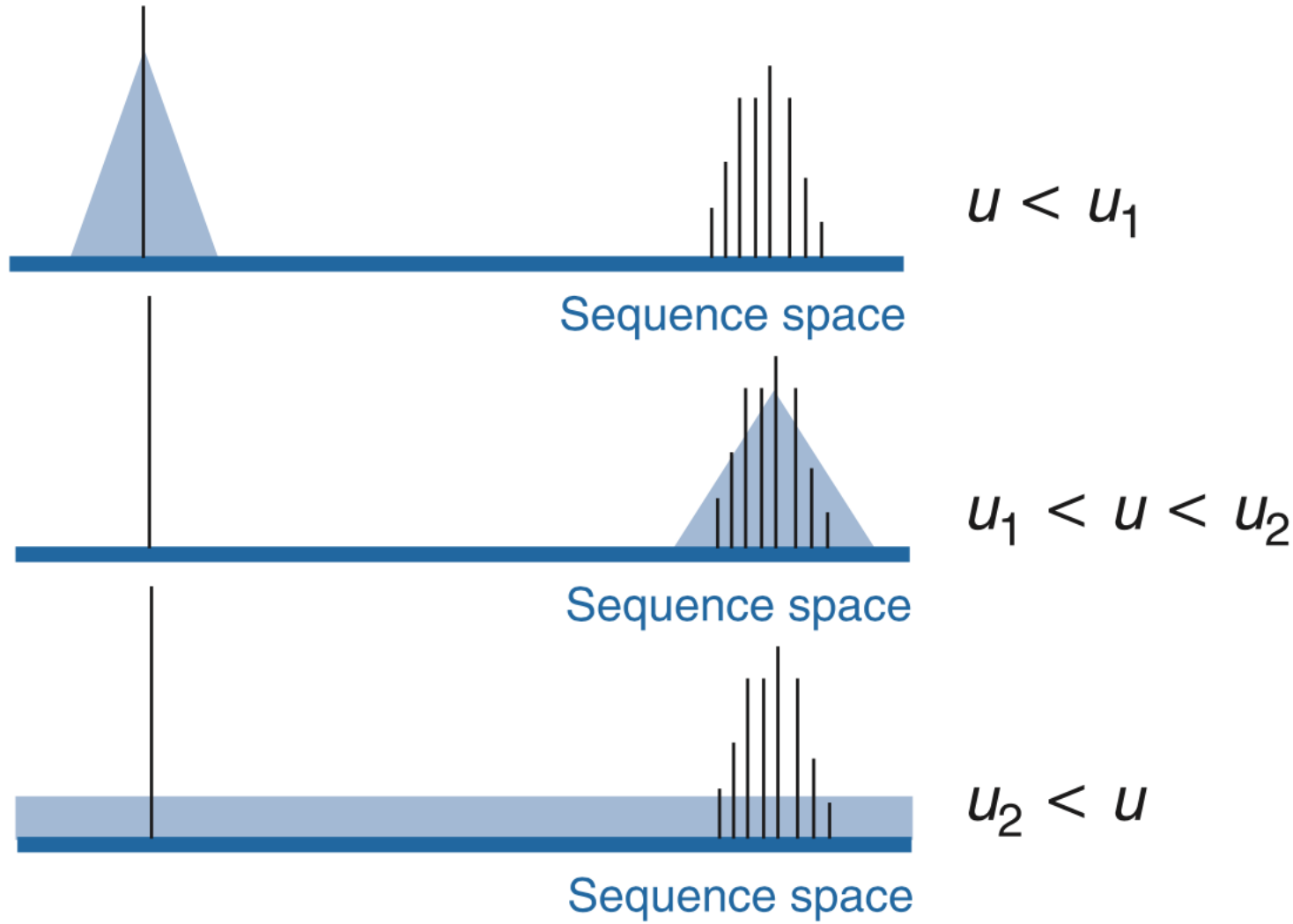
May 21, 2020

Announcements

If mutations lead to a lower equilibrium fitness, why have mutations?

Do faster mutation rates navigate better to fitness maxima?

Selection of the quasispecies



$u < u_1$

$u_1 < u < u_2$

$u_2 < u$

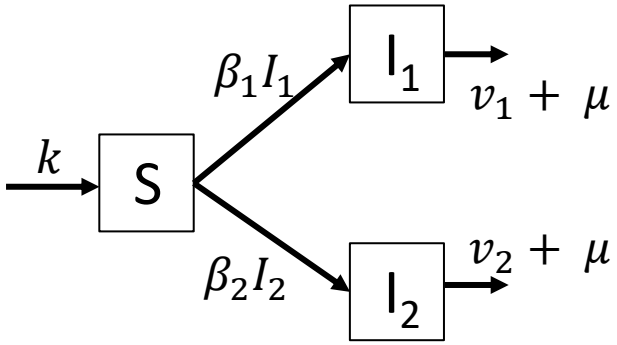
Summary of fitness and adaptation

- Selection occurs when organisms have different rates of reproduction
- When growth is exponential, selection leads to survival of the fittest
- Mutations enable co-existence of strains with different fitness
- Quasispecies are populations of genetically related organisms, formed by mutation and selection
- There is typically one stable equilibrium of quasispecies, it is often not the fittest but rather a distribution around the fittest
- Adaptation cannot occur if mutation rates are too high

This material is covered in Novak Ch 11

Evolution of virulence

Selection when competing for hosts



$$\dot{S} = k - S(\beta_1 I_1 + \beta_2 I_2) - \mu S$$

$$\dot{I}_1 = I_1(\beta_1 S - v_1 - \mu)$$

$$\dot{I}_2 = I_2(\beta_1 S - v_2 - \mu)$$

$$k = birth\ rate$$

$$v = virulence = excess\ mortality\ associated\ with\ infection$$

$$R0_1 = \frac{\beta_1}{\mu + v_1}\frac{k}{\mu}$$

$$R0_2 = \frac{\beta_2}{\mu + v_2}\frac{k}{\mu}$$

Question: Assuming $R0_1 > 1$ and $R_{02} > 1$, can there be an endemic equilibrium for I_1 and I_2?

$$\dot{I}_1 = 0, I_1 > 0$$

$$\dot{I}_1 = I_1(\beta_1 S - v_1 - \mu) = 0$$

$$S = \frac{v_1 + \mu}{\beta_1} = \frac{1}{R0_1}$$

$$S = \frac{v_2 + \mu}{\beta_2} = \frac{1}{R0_2}$$

$$S = \frac{1}{R0_1} = \frac{1}{R0_2}$$

$$R0_1 = R0_2$$

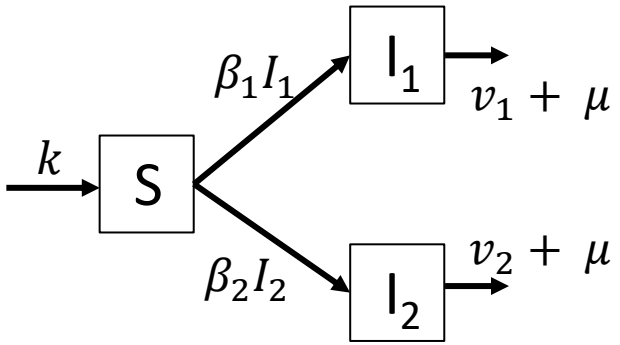
The only way to have coexistence of two species in full competition for hosts is for equal R_0.

Evolution maximizes R_0

$$R_0 = \frac{\beta}{\mu + v}\frac{k}{\mu}$$

Is virulence helpful or harmful to the organism here?
If no constraints, evolution will increase transmission (β) and decrease virulence (v)

harmful for original model - evolution would minimize virulence



What if infectivity is proportionate to virulence?

then virulence is helpful - evolution would maximize virulence

$$\beta = av$$

in this slide, all u's should be mu's

$$R_0 = \frac{av}{\mu + v}\frac{k}{\mu} = \frac{ak}{\mu}\left(\frac{v}{v + \mu}\right)$$

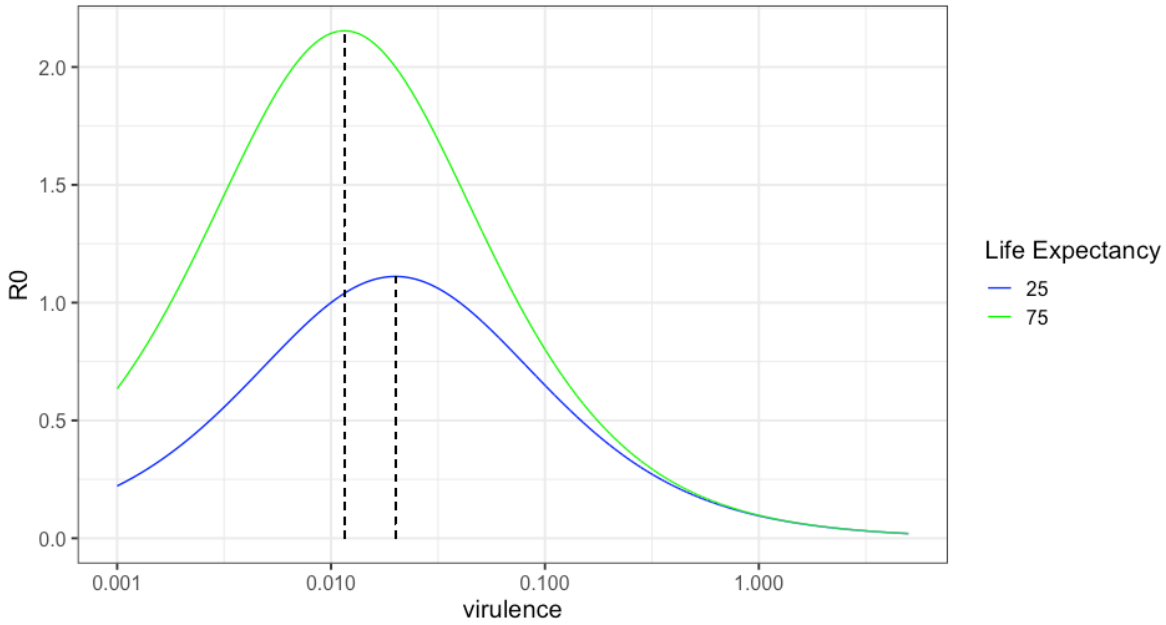
What if infectivity is a saturating function of virulence?

equation just beta is just made up so that it is a saturating function of virulence.
c is a saturation constant: determines how fast (with increasing v) infectivity saturates w/ virulence (sigmoidal)

$$\beta = a\frac{v}{c + v}, \qquad as\ v \to \infty, \beta \to a$$

then R0 is maximized at v=sqrt(cu)

$$R_0 = \left(a\frac{v}{c + v}\right)\left(\frac{k}{\mu}\right)\left(\frac{1}{u + v}\right)$$



should be dv, not dt

$$\frac{dR_0(v)}{dt} = 0\ to\ find\ maximum. Maximum\ at\ v = \sqrt{cu}$$

Virulence Summary

- When there is competition for hosts, evolution generally maximizes R_0
- If virulence and infectivity scale linearly, organisms would increase virulence to their maximum
- Usually there are constraints in relationship between virulence and infectivity, such that organisms will evolve towards intermediate virulence to maximize R_0

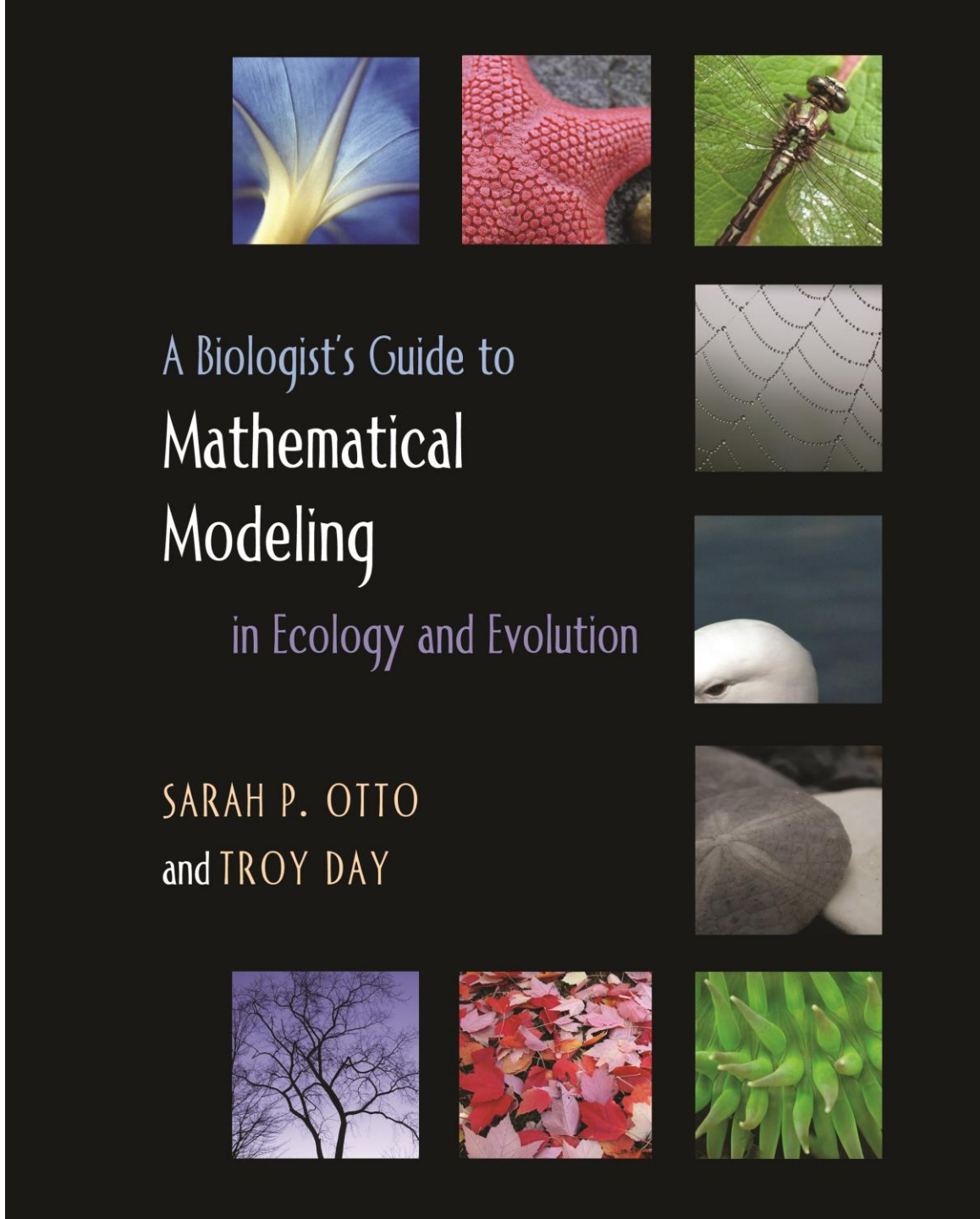
Superinfection

- When a new strain is able to infect a host who is already infected
- Leads to:
  - Higher virulence than optimal for maximizing R0 (than would be optimal for maximizing R0 absent superinfection)
  - Co-existence of strains with range of virulence
  - Fewer infected hosts than without superinfection

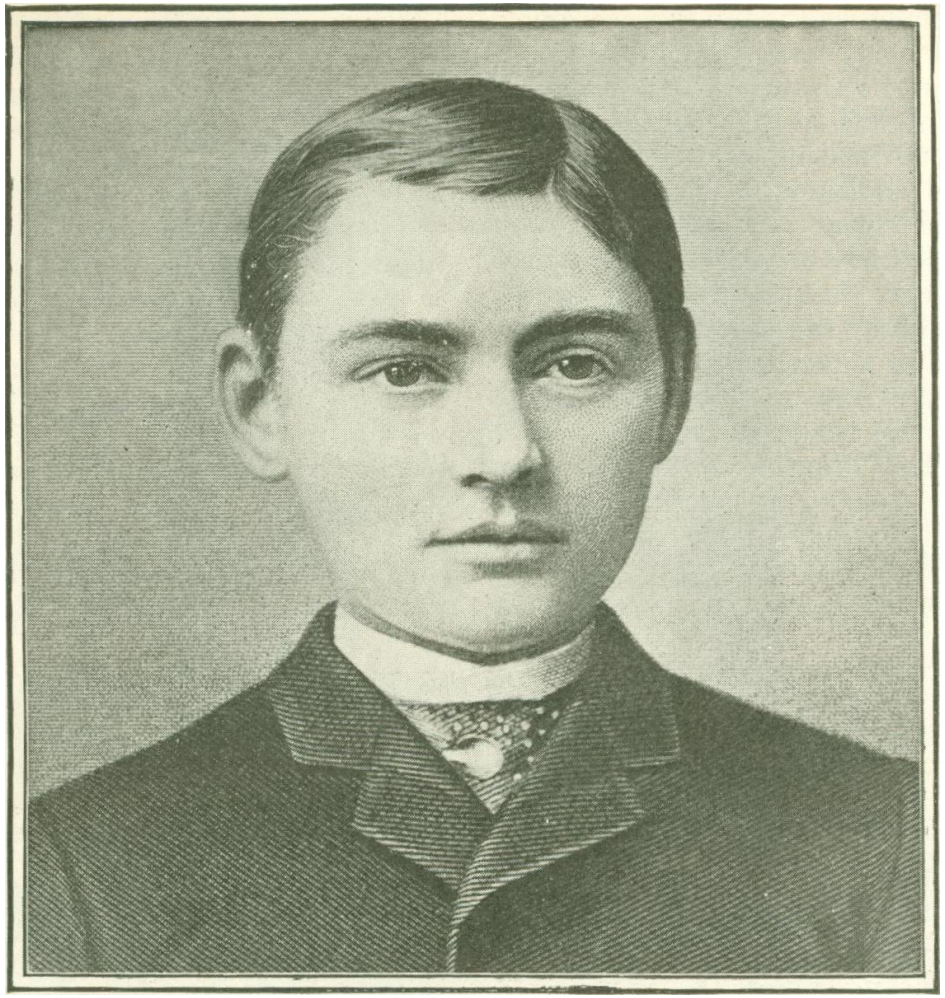
Further Reading

Nowak, *Evolutionary Dynamics,* Chapter 11

Otto and Day, *A Biologists Guide to Mathematical Modeling in Ecology and Evolution,* Chapter 12



Antimicrobial Resistance



Leland Stanford, Jr.
(1868 – 1884)

STANFORD HAS AN EPIDEMIC OF TYPHOID FEVER

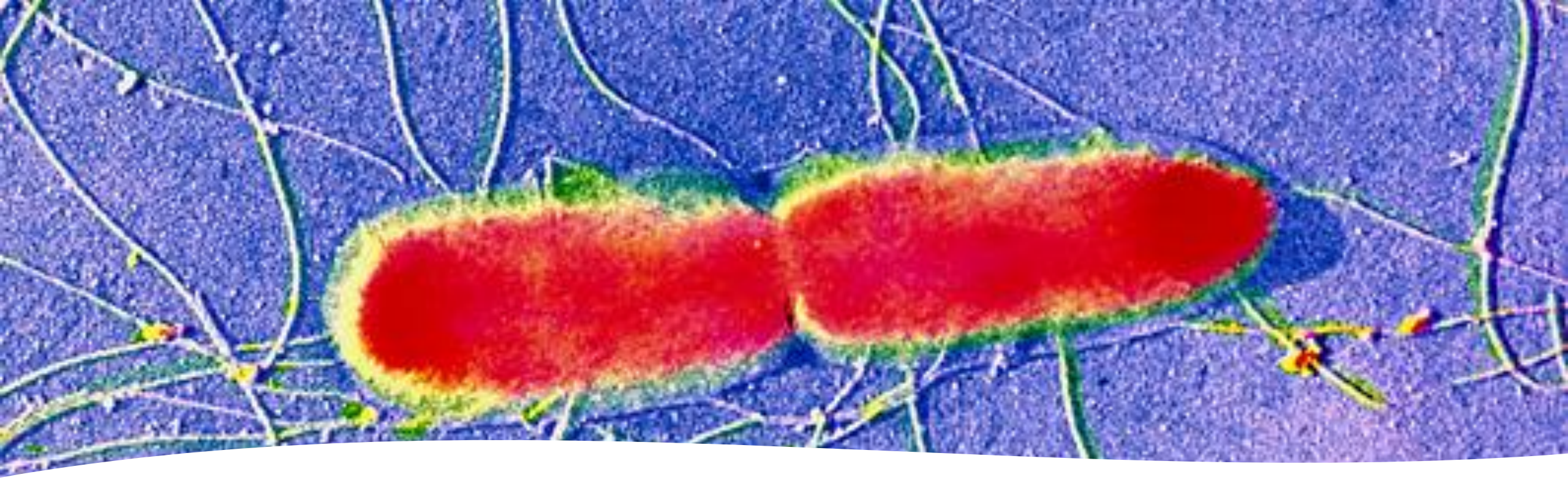
Thirty-Two Cases Appear at the University, Due to Infected Milk Supply.

(ASSOCIATED PRESS CABLEGRAMS.)

STANFORD UNIVERSITY, April 17.—There are thirty-two cases of typhoid fever here due to infected milk.

This is the second instance within three months of a University suffering from an epidemic of typhoid fever. Cornell University at Ithaca, N. Y., has lost a large number of students by death from this malady and several hundred by desertion. In the case of Cornell a polluted water supply was to blame.

About 110 cases have developed among the students of the university, and there have been four deaths, all in Palo Alto. The source of infection was promptly detected. The period of incubation, about three weeks, is now past; every care has been taken to pre-



Typhoid Fever ("enteric fever")

- Bacterial infection caused by *Salmonella* Typhi
- Transmitted by fecal-oral route, person-to-person or via contaminated food or water
- 10-25 million cases annually, vast majority in low or middle income countries
- Untreated, case fatality rate is 15-25%

TECHNICAL PAPERS

Chloromycetin, a New Antibiotic From a Soil Actinomycete

JOHN EHRLICH, QUENTIN R. BARTZ, ROBERT M. SMITH, and DWIGHT A. JOSLYN

The Research Laboratories, Parke, Davis & Company, Detroit

PAUL R. BURKHOLDER

Osborn Botanical Laboratory, Yale University

From a soil sample collected in a mulched field near Caracas, Venezuela, a *Streptomyces* sp. was isolated.[1] Agar streak cultures were found to inhibit adjacent inocula of *Bacillus mycoides*,[1] *B. subtilis*,[1] *Mycobacterium tuberculosis* var. *hominis* (ATCC 607[1] and H37Rv[2]), *Staphylococcus aureus*,[1,3] *Streptococcus pyogenes*,[3] *Brucella abortus*,[3] *Escherichia coli*,[1,3] *Klebsiella pneumoniae*,[3] *Salmonella schottmuelleri*,[3] and *Shigella paradysenteriae* (Sonne).[3] When the organism was grown in liquid media in shaken flasks, filtrates of these submerged aerated cultures proved to possess marked antibacterial activity in broth-dilution assays against several gram-negative bacteria, notably *S. paradysenteriae* (Sonne), and indications of antirickettsial activity. From these filtrates a crystalline antibiotic has been isolated, for which the name Chloromycetin is proposed.

TABLE 1

Vol. medium	Container (capacity)	Yield (μg./ml.)
100 ml.	Erlenmeyer flask (500 ml.)	55
18 l.	Glass fermenter (30 l.)	85
100 gal.	Rotary aluminum drum (200 gal.)	49

The organism has been found to produce Chloromycetin in aerated submerged culture in various media. A satisfactory formula is: maltose, 1.0 per cent; casamino acids (Bacto), 0.5 per cent; distillers' solubles, 0.5 per cent; and sodium chloride, 0.5 per cent. Typical yields with this medium in various containers are given in Table 1. Potency is estimated turbidimetrically in terms of weight of crystalline material from a standard curve for 50 per cent inhibition of *S. paradysenteriae* (Sonne).

It was found that Chloromycetin could be concentrated and purified by extracting acidified culture filtrates with ethyl acetate, removing the solvent by distillation *in vacuo*, extracting the antibiotic with diethyl ether, chromatographing the ether solution over aluminum oxide, removing the solvent by evaporation, extracting the residue with water, extracting the aqueous solution with petroleum ether, and concentrating the aqueous solution. During the course of the concentration the antibiotic crystallized. After three recrystallizations from methylene dichloride, ethylene dichloride, and a mixture of diethyl ether and petroleum ether, colorless needles or elongated plates having the following properties were obtained: m.p., 149.7–150.7°C. (corrected); $(\alpha)_D^{25}$, − 25.5° (ethyl acetate)[4]; solubility in water at 25°C., about 2.5 mg./ml.; very soluble in methanol, ethanol, butanol, propylene glycol, and acetone; analysis: C, 41.11; H, 3.89; N, 8.60; Cl (nonionic), 21.71.[5]

Chloromycetin is a neutral compound and is unique in that it contains both nitrogen and nonionic chlorine. It is furthermore characterized by being stable at room temperature in aqueous solutions over the pH range of 2–9 for more than 24 hours, and in distilled water is unaffected by boiling for 5 hours.

The *in vitro* activity of the crystalline material against several bacteria is shown in Table 2. The test against *Br. abortus* was performed by dissolving varying amounts of the crystals in agar and streaking with *Br. abortus*.[3] *Myco. tuberculosis* was assayed by an end-point broth-dilution method.[2] The other organisms were tested by a turbidimetric method.[3]

TABLE 2

WEIGHT OF CRYSTALLINE CHLOROMYCETIN CAUSING INHIBITION OF TEST ORGANISM

Species	μg./ml.	Inhibition (%)
Brucella abortus	2.0	100
Escherichia coli	0.33	50
Klebsiella pneumoniae	0.33	50
Mycobacterium tuberculosis (H37Rv)	12.5	100
Proteus sp.	0.33	50
Salmonella schottmuelleri	0.33	50
Shigella paradysenteriae (Sonne)	0.2	50
Staphylococcus aureus	1.0	50

The crystalline material showed marked chemotherapeutic activity against *Rickettsia prowazeki* in screening tests using chick embryos[6] and against a number of rickettsiae and one virus when tested in embryonated eggs or in mice (*1*).

The intravenous LD_{50} for 20-gram mice is 3.0 mg./mouse. In contrast to streptomycin, Chloromycetin appears to be well absorbed when administered orally to mice and dogs.[7]

Detailed accounts of these studies are in preparation.

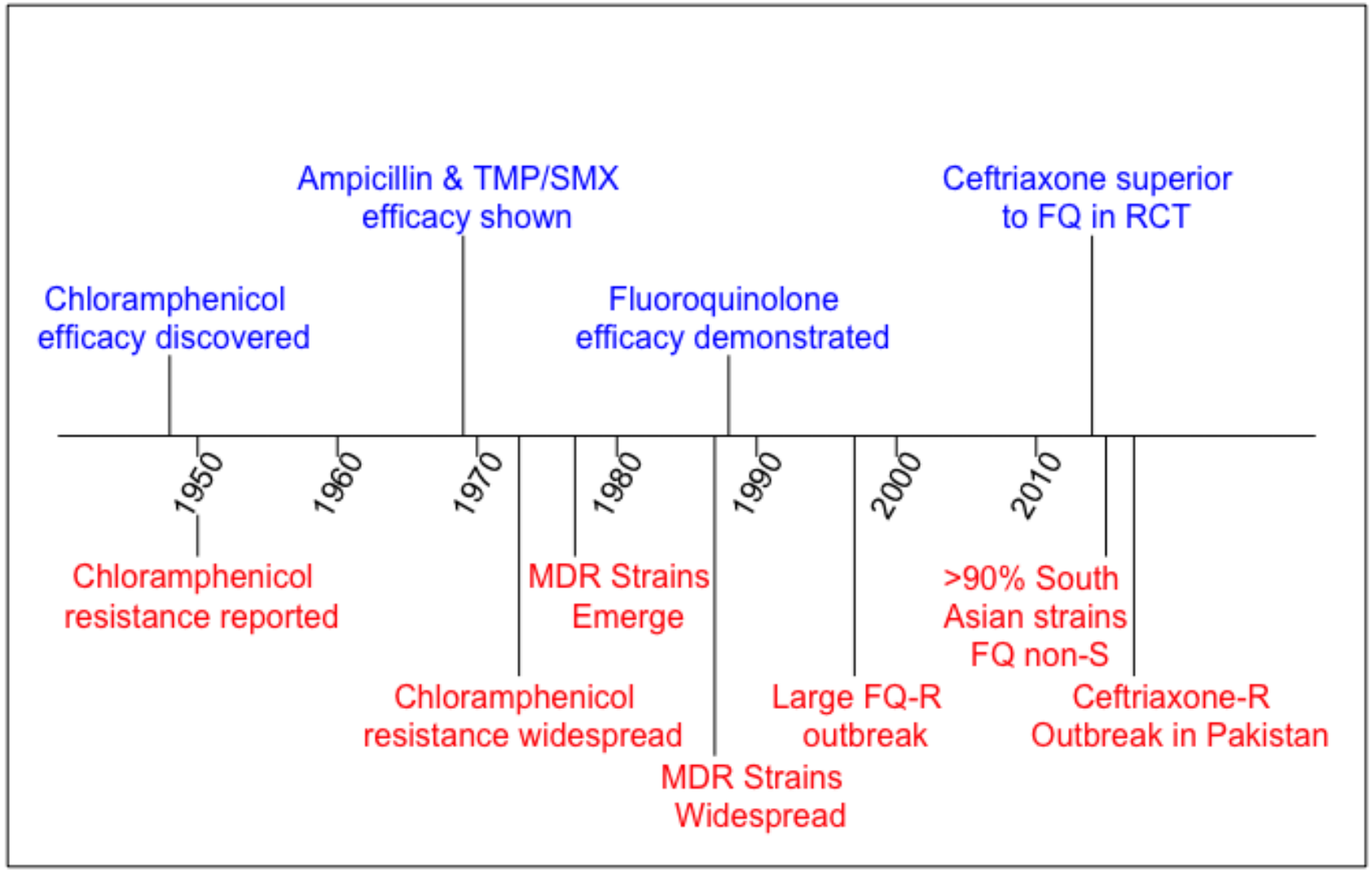
Reference

1. SMADEL, J. E., and JACKSON, E. B. *Science*, 1947, **106**, 418.

[1] In Paul R. Burkholder's laboratory, Yale University.
[2] In Guy P. Youmans' laboratory, Northwestern University.
[3] In the Research Laboratories, Parke, Davis & Company.
[4] Determined by Robert L. Harris, Parke, Davis & Company.
[5] Determined by A. W. Spang, Parke, Davis & Company.
[6] Determined by I. W. McLean, Jr., Parke, Davis & Company.
[7] Determined by O. M. Gruhzit, Parke, Davis & Company.

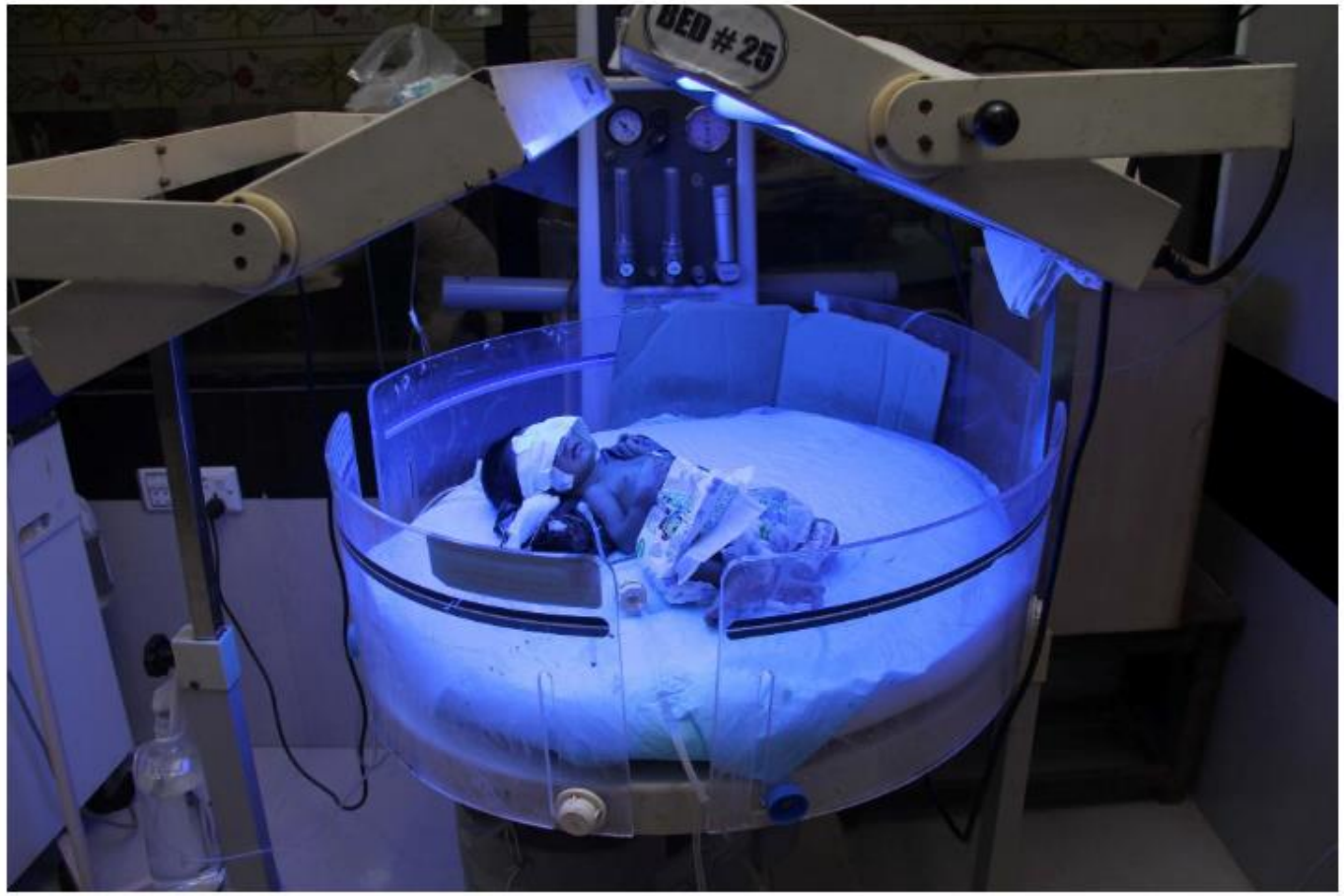
PRELIMINARY REPORT ON THE BENEFICIAL EFFECT OF CHLOROMYCETIN IN THE TREATMENT OF TYPHOID FEVER*

By THEODORE E. WOODWARD, M.D., JOSEPH E. SMADEL, M.D., HERBERT L. LEY, JR., M.D., *Baltimore, Maryland,* and *Washington, D. C.*, RICHARD GREEN, M.D., and D. S. MANKIKAR, M.D., *Kuala Lumpur, Federation of Malaya*


Ampicillin & TMP/SMX
efficacy shown
Ceftriaxone superior
to FQ in RCT
Chloramphenicol
efficacy discovered
Fluoroquinolone
efficacy demonstrated
1950
1960
1970
1980
1990
2000
2010
Chloramphenicol
resistance reported
MDR Strains
Emerge
>90% South
Asian strains
FQ non-S
Chloramphenicol
resistance widespread
Large FQ-R
outbreak
Ceftriaxone-R
Outbreak in Pakistan
MDR Strains
Widespread

GLOBAL HEALTH

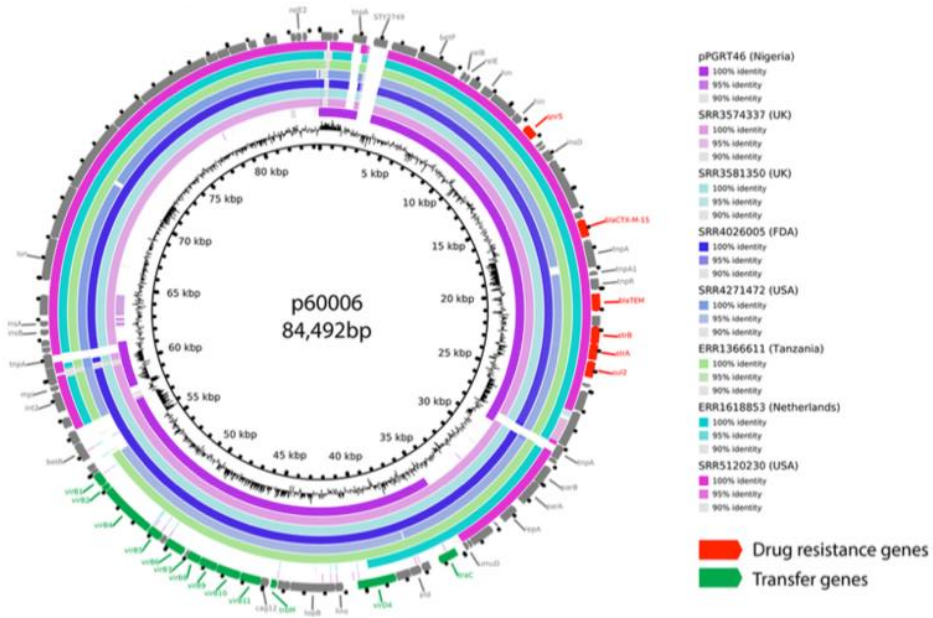
'We're Out of Options': Doctors Battle Drug-Resistant Typhoid Outbreak



A baby believed to have contracted a drug-resistant strain of typhoid, hospitalized in Hyderabad, Pakistan in February. Nadeem Khawer/European Pressphoto Agency

Emergence of an Extensively Drug-Resistant *Salmonella enterica* Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins

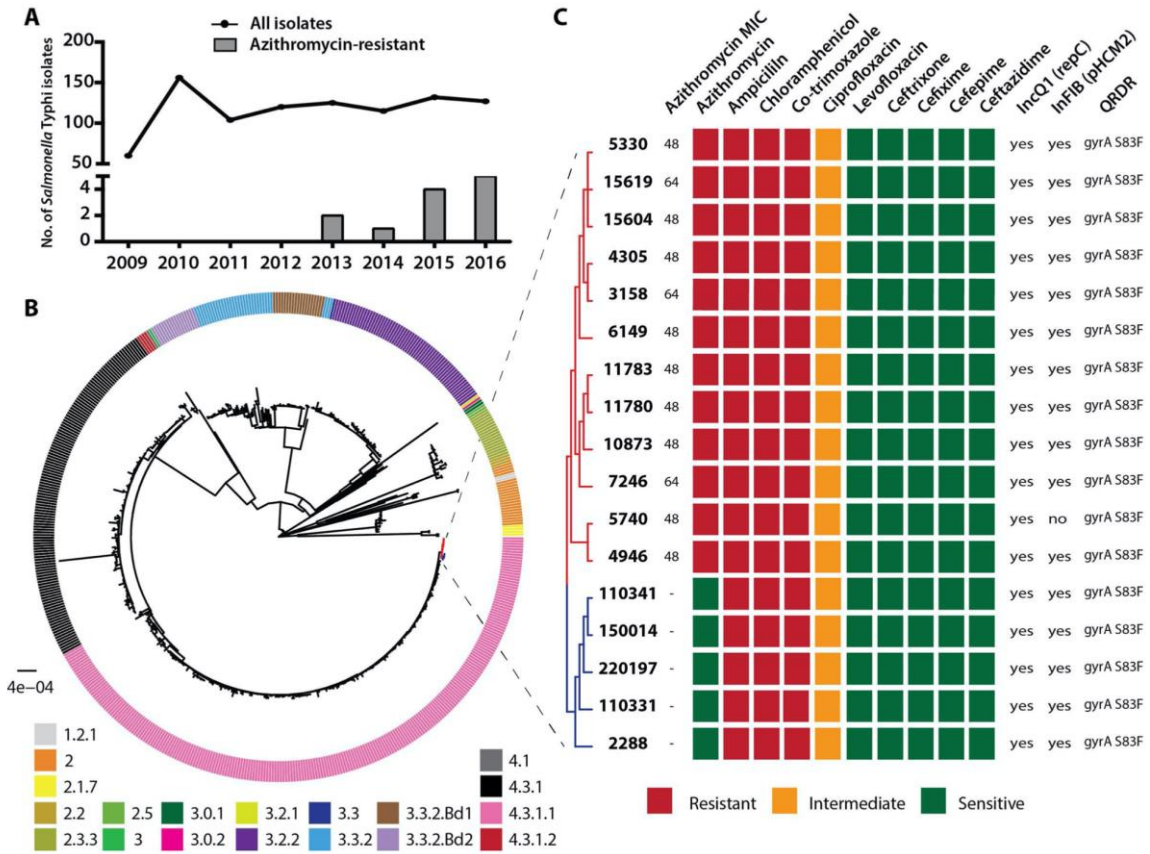
Elizabeth J. Klemm,[a] Sadia Shakoor,[b] Andrew J. Page,[a] Farah Naz Qamar,[b] Kim Judge,[a] Dania K. Saeed,[b] Vanessa K. Wong,[c] Timothy J. Dallman,[d] Satheesh Nair,[d] Stephen Baker,[e,f,g] Ghazala Shaheen,[b] Shahida Qureshi,[b] Mohammad Tahir Yousafzai,[b] Muhammad Khalid Saleem,[b] Zahra Hasan,[b] Gordon Dougan,[a,c] Rumina Hasan[b]



RESEARCH ARTICLE

Molecular mechanism of azithromycin resistance among typhoidal *Salmonella* strains in Bangladesh identified through passive pediatric surveillance

Yogesh Hooda[1,2], Mohammad S. I. Sajib[1], Hafizur Rahman[1], Stephen P. Luby[3], Joseph Bondy-Denomy[4,5], Mathuram Santosham[6], Jason R. Andrews[3], Samir K. Saha[1,7]*, Senjuti Saha[1,6]*



Will AMR bacteria win the arms race?

What favors their selection? What constrains their spread?

Antimicrobial Resistance Exercise

Create a SI model for antimicrobial resistant organisms competing with susceptible organisms. Draw the model, write out the differential equations. Assume that having antimicrobial resistance might alter the fitness of the organism in various ways.

What factors determine whether the resistant organism outcompetes the susceptible one?

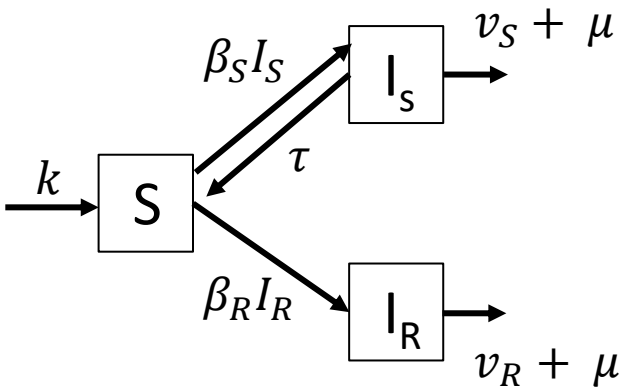
A Model for Antimicrobial Resistance

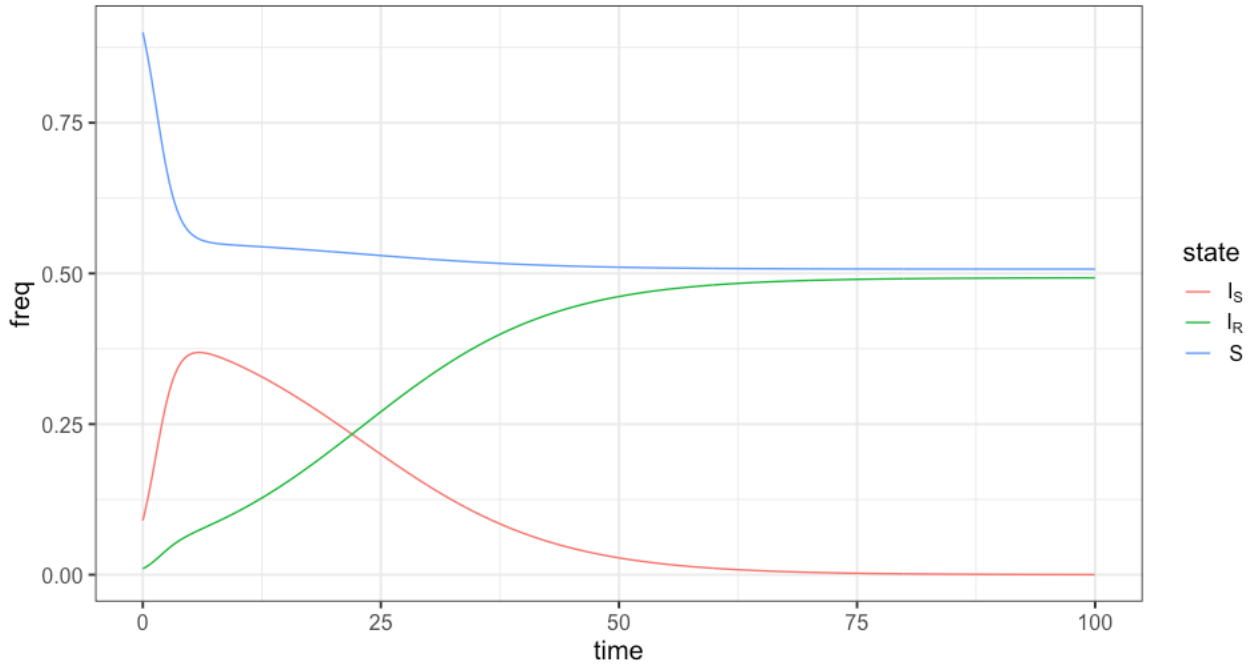
$$\dot{S} = k - S(\beta_S I_S + \beta_R I_R) - \mu S$$

$$\dot{I_S} = I_S(\beta_S S - v_S - \mu - \tau)$$

$$\dot{I_R} = I_R(\beta_R S - v_R - \mu)$$

$$\tau = treatment$$





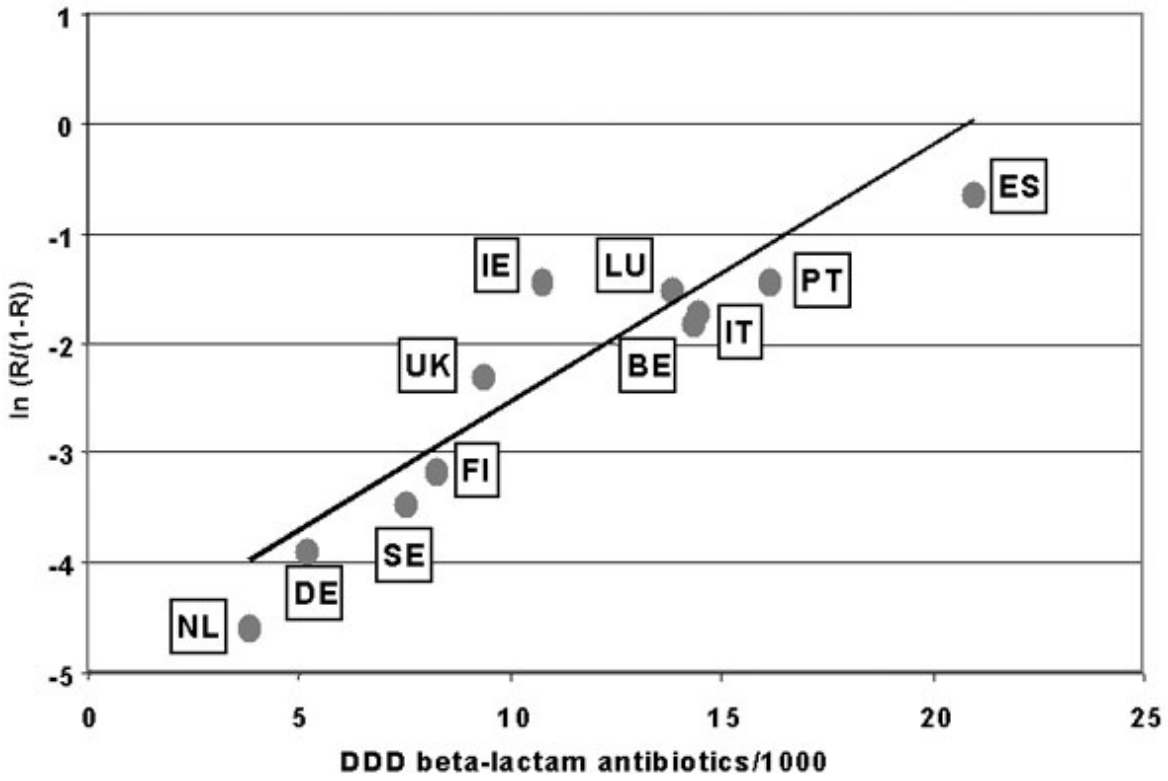
Lipsitch, *Trends in Micro,* 2001

AMR Model Insights

$$\dot{S} = k - S(\beta_S I_S + \beta_R I_R) - \mu S$$

$$\dot{I_S} = I_S(\beta_S S - v_S - \mu - \tau)$$

$$\dot{I_R} = I_R(\beta_R S - v_R - \mu)$$



Bronzwaer et al, *EID* 2002

$$P(t) = \frac{I_R(T)}{I_S(t) + I_R(t)} = proportion\ resistant$$

$$L(t) = logit\left(P(t)\right) = \ln(\frac{p}{1-p}) = \log odds\ of\ resistance$$

$$\frac{dL}{dt} = (\beta_R - \beta_S)S - (v_R - v_S) + \tau$$

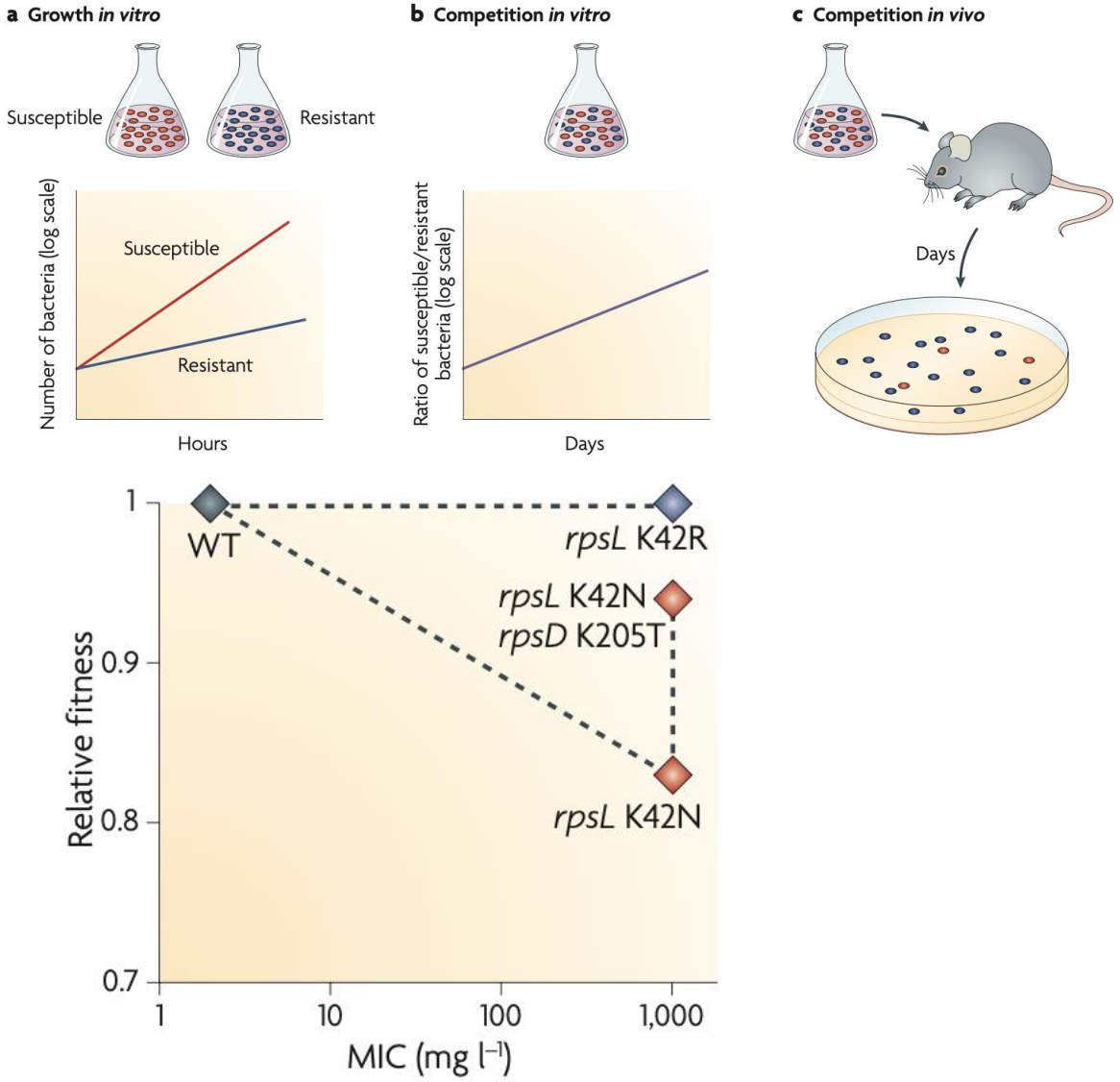
Implications:

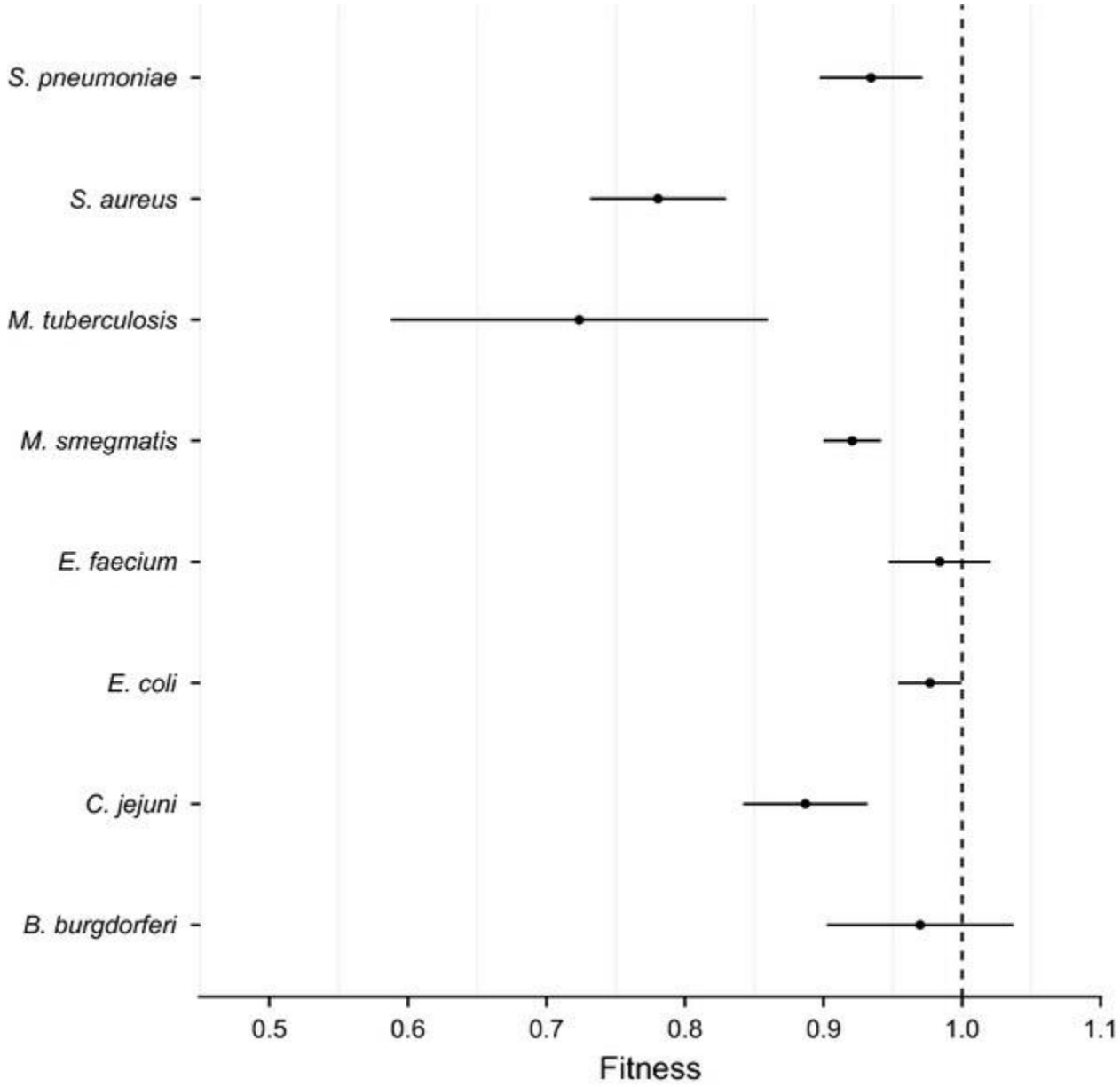
- Log odds of resistance rises linearly with antibiotic use
- Resistant organisms can be less transmissible and more virulent and still spread, in presence of antibiotics

$$(\beta_R - \beta_S)S - (v_R - v_S) + \tau > 0$$

$$\tau > \underbrace{(v_R - v_S)}_{\text{More virulent}} + \underbrace{(\beta_S - \beta_R)S}_{\text{Less Transmissible}}$$

AMR and fitness





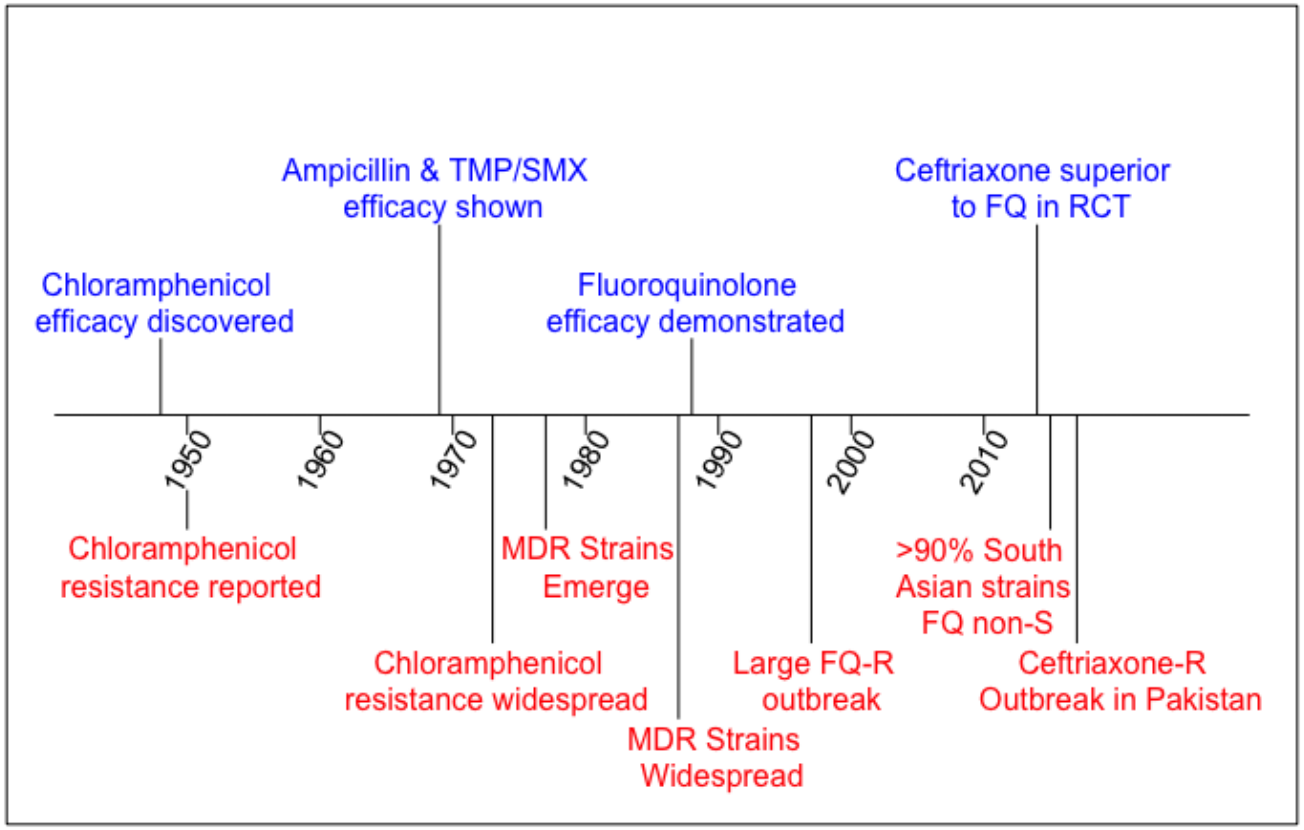
Andersson and Hughes, *Nat Micro* 2010

Melnyk et al, *Evol Appl,* 2015

Exploiting fitness deficits for therapy

- In medicine, we sometimes intentionally give an antimicrobial to which an organism is resistant, in order to maintain that variant that is less fit, and then treat with a second antimicrobial to kill that population of organisms
- Examples:
  - M184V mutation in HIV confers resistance to lamivudine, but decrease replication fitness by 4-8%, increases reverse transcriptase fidelity, decreasing further spontaneous mutagenesis, and increases susceptibility to other ARVs.
  - MRSA with VanA-type resistance to Vancomycin have 20-38% reduction in fitness, but only in the presence of Vancomycin.

Cycling and Steering



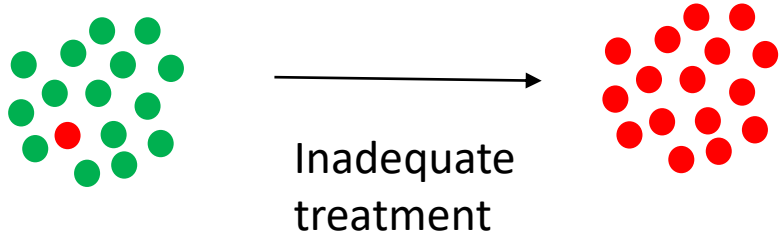
RESEARCH ARTICLE

Steering Evolution with Sequential Therapy to Prevent the Emergence of Bacterial Antibiotic Resistance

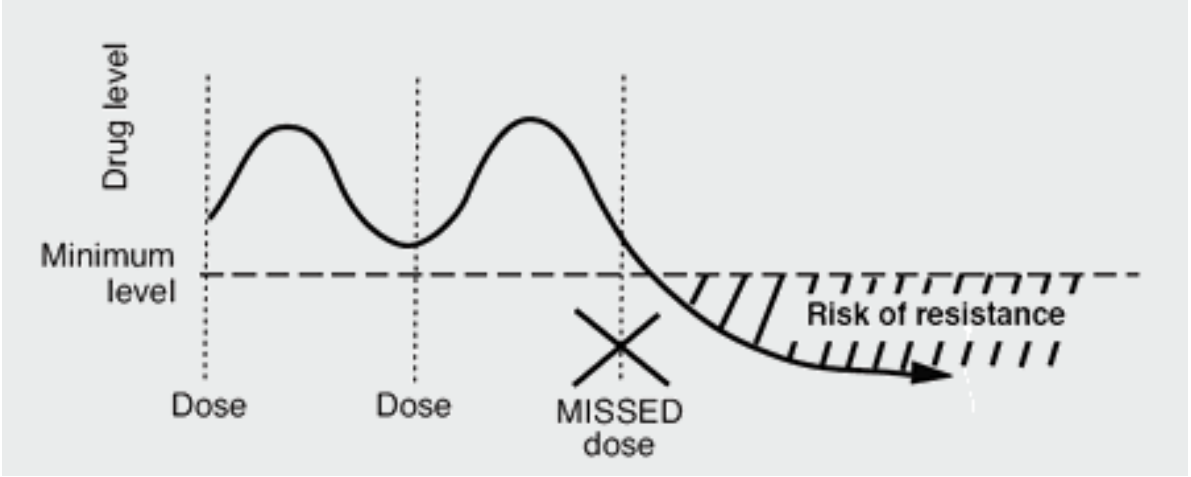
Daniel Nichol[1,2]*, Peter Jeavons[1], Alexander G. Fletcher[3], Robert A. Bonomo[4], Philip K. Maini[3], Jerome L. Paul[5], Robert A. Gatenby[2], Alexander R.A. Anderson[2], Jacob G. Scott[2,3]*

Are more antibiotics bad or good for AMR?

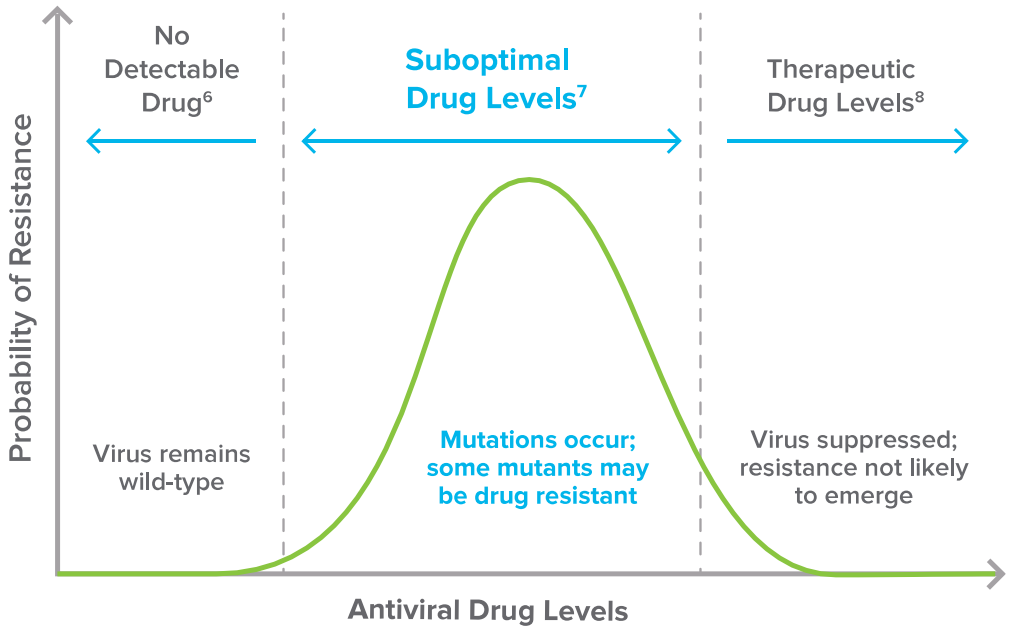
"Always complete the full prescription, even if you feel better, because stopping treatment early promotes the growth of drug-resistant bacteria" – World Health Organization, 2016

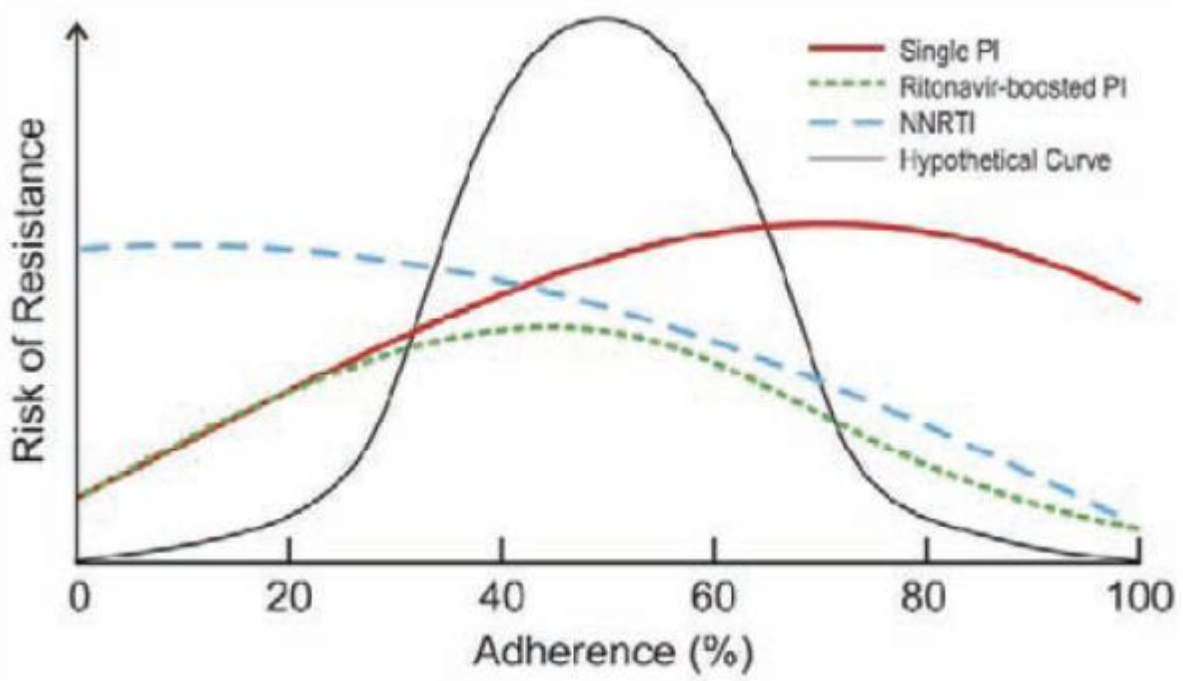


"Hit hard and hit fast"
-Paul Ehrlich, 1913



Antimicrobial and AMR relationship complex at individual level





Nachega et al, *Infect Disord Drug Targets* 2011

Antibiotics in the environment

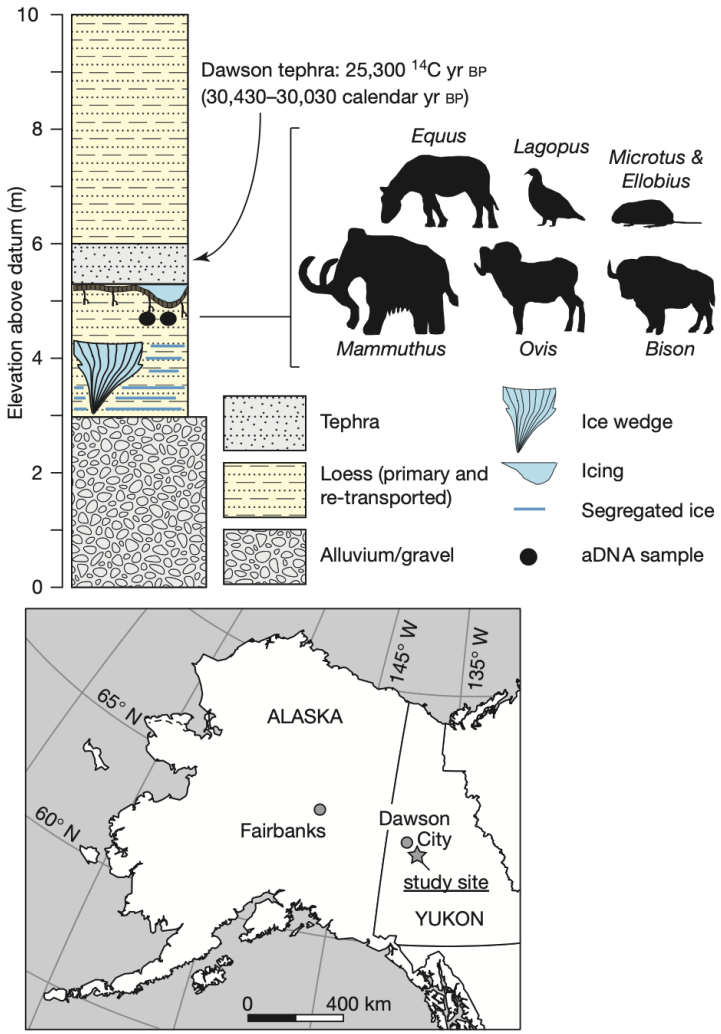
>70% of antibiotics used are used in livestock

Pathways

- Highly resistant bacteria observed in animals, may directly infect humans
- Runoff of antibiotics into environment creating selective pressure in environmental bacteria or when ingested by humans

Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]



are highly susceptible to antibiotics[3]. Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

Summary of AMR Dynamics

- Antibiotic use creates selective pressure for emergence of resistance
- Within the individual, the risk of AMR emergence is complex and might be optimized at intermediate use of antimicrobials
- At population level, greater use of antimicrobials selects for AMR strains by reducing the presence of susceptible strains
- AMR acquisition often comes at an initial fitness cost to organisms, though sometimes organisms can further evolve to compensate (at least partially) for fitness
- The amount of fitness deficit possible (decreased transmissibility, increased virulence) depends on the antimicrobial pressure
- Antimicrobial exposures from environment, human-made or natural, may be important drivers of AMR

Further Readings of Models of AMR

The rise and fall of antimicrobial resistance

Marc Lipsitch

Antimicrobial resistance is a growing problem in nearly every infectious disease, but the extent and rate of increase of the problem varies widely with different pathogen–drug combinations. The rate of increase of resistance depends primarily on the availability of resistant variants and the intensity of selection imposed by antimicrobial treatment (appropriately measured). Declines in resistance following antimicrobial control measures are typically faster in hospital-acquired infections than in community-acquired ones, probably owing to the dependence in the latter case on the fitness cost of resistance. Open questions and approaches for testing the hypotheses proposed here are outlined.

The rise of antimicrobial resistance in human pathogens poses a growing challenge to medicine and public health. Increasing resistance to preferred therapies has limited the options for treating such diverse infections as HIV infection and malaria, as well as a variety of hospital- and community-acquired bacterial infections[1,2]. Preserving the effectiveness of existing therapies is an increasingly urgent consideration in the choice of treatment for these infections. However, apart from avoiding unnecessary use of antimicrobial agents, the best way to extend the life of these drugs at the population level is not well understood. Resistance not only makes treatment of individual patients more complicated and more expensive; it also compromises the effectiveness of disease control programs for those infections where effective case detection and treatment are central to the prevention of disease transmission [notably tuberculosis (TB) and some sexually transmitted infections][3].

Although the problem of antimicrobial resistance is almost ubiquitous in infectious diseases, the scale of the problem, and the rate at which resistance becomes a problem, is highly variable, depending on the antimicrobial agent, the pathogen and the setting in which transmission occurs. For example, resistance to single anti-infective agents used for treatment of both TB and HIV infection was documented almost immediately after these agents became available, and the development of effective combination therapy regimens has provided only a partial solution to these problems[2,3]. The result has been not only treatment failures in individual patients, but also the transmission of resistant infections to others. At the other extreme is the use of penicillin to treat infections with group A streptococci; despite >50 years of use, no case of penicillin resistance has been documented in this organism[4]. Most pathogen–drug combinations fall between these two extremes[5].

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Just as the rate of increase in resistance is highly variable, the rate at which resistance declines in response to interventions also differs considerably in different pathogen–drug combinations, ranging from dramatic reductions in a few months to equivocal results or small declines after several years of control measures. In designing and evaluating efforts to control antimicrobial resistance, it is crucial to understand the factors that determine whether resistance spreads rapidly or slowly in a population, and whether measures to reduce resistance are likely to show results over a span of months, years, or longer. In this review, I will describe some of what is known on this topic from both empirical and theoretical studies, and also attempt to highlight key areas of present ignorance. The discussion will concentrate on human uses of antimicrobial agents; this omission is for the sake of space and is not intended to minimize the importance of agricultural and veterinary uses of antibiotics.

The rise of resistance

The appearance and growth of antimicrobial resistance as a clinical problem requires several distinct steps. Any one of these steps can be 'rate-limiting'; the span of time between the first use of a particular drug and the appearance of resistance to that drug as a clinical problem for a given pathogen depends on the rates at which these steps are accomplished.

First, resistance must be genetically and physiologically possible for the infectious agent. In some infections, such as TB, creation of a resistant organism requires only a single point mutation; these mutations occur so frequently that at least one bacterium with a mutation is present in nearly every host with active disease. In other cases, the appearance of the first viable resistant organism can take much longer, for any of several reasons. Resistance can be genetically and biochemically complex, requiring the assembly of several genes that work together to create the resistant phenotype, as in the case of vancomycin resistance in *Enterococcus*[6]. A related phenomenon is the requirement for multiple mutations in the same or different genes to confer high-level resistance to certain drugs; in this case, resistance can be delayed because bacteria containing only one mutation are not sufficiently resistant to gain an advantage in the face of clinically achievable drug concentrations, and double mutants are

http://tim.trends.com 0966-842X/01/$ – see front matter PII: S0966-842X(01)02130-8

Antimicrobial Use and Antimicrobial Resistance: A Population Perspective

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The need to stem the growing problem of antimicrobial resistance has prompted multiple, sometimes conflicting, calls for changes in the use of antimicrobial agents. One source of disagreement concerns the major mechanisms by which antibiotics select resistant strains. For infections like tuberculosis, in which resistance can emerge in treated hosts through mutation, prevention of antimicrobial resistance in individual hosts is a primary method of preventing the spread of resistant organisms in the community. By contrast, for many other important resistant pathogens, such as penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus faecium* resistance is mediated by the acquisition of genes or gene fragments by horizontal transfer; resistance in the treated host is a relatively rare event. For these organisms, indirect, population-level mechanisms of selection account for the increase in the prevalence of resistance. These mechanisms can operate even when treatment has a modest, or even negative, effect on an individual host's colonization with resistant organisms.

The growth of antimicrobial resistance has prompted calls to reduce unnecessary antibiotic use and to improve treatment protocols to maximize the lifespan of these drugs. These calls rest on the well-supported idea that the use of antimicrobial agents is a powerful selective force that promotes the emergence of resistant strains.

To reduce antimicrobial resistance, multiple, and often conflicting recommendations, have been made. For example, strategies to minimize the burden of resistance in hospitals have included reduction of all antimicrobial classes, increased use of prophylactic antimicrobials to reduce colonization, rotation of different antibiotic classes in a temporal sequence, and simultaneous use of different antimicrobials for different patients (1-6).

Underlying these often varying recommendations for improving antimicrobial use is frequently conflicting evidence about the relationship between antibiotic treatment and antibiotic resistance. In some pathogens, showing that antibiotic treatment puts treated persons at a greater risk for acquiring resistant organisms has been difficult (7-8); nonetheless, the cumulative effect of using these antibiotics has clearly been to increase the prevalence of resistance in the population as a whole.

For many pathogens of current concern, especially organisms for which asymptomatic colonization typically precedes infection (e.g., *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus* spp., and the gram-negative enteric bacteria), the relationship between antimicrobial use and resistance differs in fundamental ways from the relationship found in *Mycobacterium tuberculosis*, for which many modern principles of chemotherapy were developed. Furthermore, we argue that the selective effects of antibiotic use on these organisms are poorly understood, and we make specific suggestions for studies that could improve understanding of the mechanisms by which antibiotics exert natural selection on these organisms. Such an understanding will be crucial for the design of rational policies of antibiotic use to maximize the lifespan of existing drugs and to minimize the impact of resistant infections.

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Resistance in People and Populations

Ehrlich's advice that treatment of infections should "hit hard and hit early," formulated in the earliest days of antimicrobial chemotherapy, presciently summarized the principles of treatment for infections such as tuberculosis (TB) (9). These principles are embodied in modern protocols of directly observed, short-course chemotherapy, where the goal is to treat with adequate concentrations of multiple drugs and maintain treatment until the bacterial population is extinct. Resistance to each of the major antituberculosis drugs is mediated by single point mutation; therefore tuberculosis treatment is designed to prevent the ascent of subpopulations of mutant bacilli that are resistant to any one of the drugs. Similar principles have been suggested for other infections in which resistance can arise by simple mutation, most notably HIV (9), although there has been some controversy on this topic (11). In these infections, the relationship between treatment, resistance in the treated person, and resistance in the community at large is relatively clear. Inadequate therapy (owing to subtherapeutic drug concentrations, too few drugs, or poor adherence to therapy) results in the emergence of resistance, and possibly treatment failure, in the treated host. Following the emergence of resistance in the treated host, resistant infections may be transmitted to others. (Figure, A; Table).

For many pathogens, both the genetics and the epidemiology of resistance differ from those of TB in important ways.

Mutations across the genome

x(t=0)= 1011

x(t=1)= 1011

u = probability of mutation in each position

L = length of genome

q= probability of making exact copy with no mutants = $(1-u)^L$

x_0 = master sequence, with $f_0>1$

x_1 = all other mutants, with f = 1

$x_0 + x_1 = 1$

$$\dot{x}_0 = x_0(f_0 q - \phi)$$
$$\dot{x}_1 = x_0 f_0 (1-q) + x_1 - \phi x_1$$

Constraints on mutation rates

$$\dot{x}_0 = x_0(f_0 q - \phi)$$
$$\dot{x}_1 = x_0 f_0 (1-q) + x_1 - \phi x_1$$

$$\phi = f_0 x_0 + x_1$$

Rewrite as:

$$\dot{x_0} = x_0(f_0 q - 1 - x_0(f_0 - 1))$$

At equilibrium:

$$\dot{x_0} = 0$$

$$x_0^* = \frac{f_0 q - 1}{f_0 - 1}$$

$$for\ x_0^*\ to\ be > 0:$$
$$f_0 q > 1$$

$$f_0 q > 1$$

$$q = (1-u)^L$$

$$f_0 (1-u)^L > 1$$

$$\log(f_0 (1-u)^L) > 0$$

$$\log(f_0) + L\log(1-u) > 0$$

$$L\log(1-u) > -\log(f_0)$$

for small u, $\log(1-u) \approx -u$

$\log(f_0) \approx 1$

So:

$$u < \frac{1}{L}$$

Mutation rates and adaptation

$$u < \frac{1}{L}$$

$$uL < 1$$

Mutations per genome < 1 in order to adapt

Table 3.1 Genome length (in bases), mutation rate per base, and mutation rate per genome for organisms ranging from DNA viruses to humans

Organism	Genome length in bases	Mutation rate per base	Mutation rate per genome
RNA viruses			
Lytic viruses			
Qβ	4.2×10^3	1.5×10^{-3}	6.5
Polio	7.4×10^3	1.1×10^{-4}	0.84
VSV	1.1×10^4	3.2×10^{-4}	3.5
Flu A	1.4×10^4	7.3×10^{-6}	0.99
Retroviruses			
SNV	7.8×10^3	2.0×10^{-5}	0.16
MuLV	8.3×10^3	3.5×10^{-6}	0.029
RSV	9.3×10^3	4.6×10^{-5}	0.43
Bacteriophages			
M13	6.4×10^3	7.2×10^{-7}	0.0046
λ	4.9×10^4	7.7×10^{-8}	0.0038
T2 and T4	1.7×10^5	2.4×10^{-8}	0.0040
E. coli	4.6×10^6	5.4×10^{-10}	0.0025
Yeast *(S. cerevisiae)*	1.2×10^7	2.2×10^{-10}	0.0027
Drosophila	1.7×10^8	3.4×10^{-10}	0.058
Mouse	2.7×10^9	1.8×10^{-10}	0.49
Human *(H. sapiens)*	3.5×10^9	5.0×10^{-11}	0.16

Sources: Drake (1991, 1993) and Drake et al. (1998).

Note: Most organisms have a mutation rate per genome which is less than one, as predicted by the error threshold theory. Why Qβ and VSV have such a high mutation rate is at present unexplained.

Nowak, *Evolutionary Dynamics*