Evaluating treatment protocols to prevent antibiotic resistance

Sebastian Bonhoeffer, Marc Lipsitch, Bruce R. Levine
PNAS 1997

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Overview

• Introduction
• Single antibiotic therapy
• Multiple antibiotic therapy
• Discussion
• Review Paper by B. Levin
Antibiotic resistance – Public Health Problem?

• Appearance and spread of antibiotic resistance increases

• Resistant organisms means:
  - compromised treatment success
  - higher treatment costs
  - epidemic spread of antibiotic-resistant infections

• Several measures against antibiotic-resistance with varying success
Single Antibiotic Therapy

A) Single antibiotic treatment

\[ \frac{dx}{dt} = \lambda - dx - bx(y_w+y_r) + r wy_w + r r y_r + fh(1-s)y_w \]

\[ \frac{dy_w}{dt} = (bx-c-rw-fh)y_w \]

\[ \frac{dy_r}{dt} = (bx-c-rr)y_r + fh s y_w \]

- \( \lambda \) rate of uninfected hosts entering population
- \( d \) rate of uninfected hosts removed from population
- \( b \) transmission rate
- \( c \) death rate infected hosts
- \( r \) recover rate
- \( fh \) removal from sensitive infected fraction
- \( s \) wt-infected developing resistance during treatment
Single Antibiotic Therapy

• Assumptions:
  - Fitness cost of resistance = higher clearance rate of infection by host and lower transmission rate
    \[ r_r > r_w \]
  - life-long/temporary immunity neglected
  - no superinfection of wt-infectants by resistant bacteria
  - «acquired resistance» only in treated hosts
Single Antibiotic Therapy – Long-term Consequences of Treatment

- $fh > \Delta r = r_r - r_w$:
  - resistant infections prevail
  - sensitive infections disappear

- $fh < \Delta r = r_r - r_w$:
  - sensitive infections prevail
  - resistant infections coexist at low levels
Single Antibiotic Therapy - Results

- No cost of resistance ($r_w=r_r$)
  - Independent of $f h$
  - no difference in treatment protocols
- Cost of resistance ($r_w<r_r$)
  - influence of $f h$ negligible
  - no difference in treatment protocols
Multiple Antibiotics

B) Treatment with two antibiotics

- 50-50 therapy
- Cycling therapy
- Combination therapy
Multiple Antibiotics –
Case I: Infectious Transmission of Resistance

• Large fraction of patients infected by resistant bacteria before treatment $\rightarrow$
  
  primary resistance $> aquired$ resistance

• Comparable to single antibiotic therapy

Result:

• Benefit of treatment indepent of the treatment protocol
Multiple Antibiotics – Case II: Acquired Resistance

- Resistant infections rare
- \( q \) host become resistant when treated with both drugs simultaneously
- \( s \) host become resistant when treated with single drug

Results:
- Cost to resistance:
  - \( r_w < r_a = r_b < r_{ab} \)
  - 50-50 treatment
- No cost to resistance
  - \( r_w = r_a = r_b = r_{ab} \)
  - 50-50 treatment = cycling = \( G \)
  - if \( q < s^2 \) : combination therapy
  - If \( q > s^2 \) : 50-50 treatment
Multiple Antibiotics –
Case III: Abscence of Multiple Resistant Bacteria

- Result:
  Combination therapy

  ↓

  Give NO advantage to singly resistant strains
Multiple antibiotics - Results

Epidemic transmission

Acquired resistance

No AB resistance

Cycling

50-50

Combination

A

G = 789.3
T_{1/2} = 10.5
G_{1/2} = 547.4

B

G = 789.3
T_{1/2} = 10.5
G_{1/2} = 554.5

C

G = 789.3
T_{1/2} = 17.3
G_{1/2} = 529.3

D

G = -729.4
T_{1/2} = 17.9
G_{1/2} = 474.3

E

G = -735.2
T_{1/2} = 17.5
G_{1/2} = 486.9

F

G = 750.2
T_{1/2} = 18.0
G_{1/2} = 440.6

G

G = -699.4
T_{1/2} = 13.8
G_{1/2} = -4.46

H

G = 2179.8

I

G = 2190.2

J

G = 3295.8
Discussion

• Multiple drug use better than single drug use
• «Combination» in general most successful treatment protocol
• Support of the findings:
  - *Mycobacterium tuberculosis* (Combination therapy → low resistance)
  - *Neisseria gonorrhoeae* (single drug therapy → high resistance)
• Future research:
  – Adaption/specification of model for other organisms/courses of disease
  – Effect of proportion of people treated, reduction of antibiotics, and external resistant/sensitive bacteria?
A model-guided analysis and perspective on the evolution and epidemiology of antibiotic resistance and its future

Bruce R Levin, Fernando Baquero, Pål Johnsen
Current Opinion in Microbiology 2014
Frequency of resistance – Patients treated

- $T_{max} =$ frequency of patients treated:
  - $T_{max, red} = 0.05$
  - $T_{max, blue} = 0.01$
  - $T_{max, green} = 0.02$

Results:
- Frequency of resistance proportional to the rate of antibiotic use
Frequency of resistance – Reductions in antibiotics use and acquired resistance

$k_R$ Frequency of resistance

$\mu$ Rate at which treated host acquires resistance

Purple: $t_{max}=0.1$, $k_R=0.15$, $\mu=0.01$

Red: $t_{max}=0.05$, $k_R=0.15$, $\mu=0.01$

Blue: $t_{max}=0.05$, $k_R=0.15$, $\mu=0.0001$

Green: $t_{max}=0.05$, $k_R=0.05$, $\mu=0.0001$

Results:

- Reduction in antibiotic use & rates of acquired resistance
  - $\rightarrow$ decline in frequency of resistance
Frequency of resistance – external input

- $x_s$ input susceptible bacteria
- $x_r$ input resistant bacteria

**Red:** $x_s=x_r=0$
**Blue:** $x_s=x_r=1E-3$
**Green:** $x_s=x_r=1E-4$

**Results:**
- Equilibrium frequency of resistance increases proportional to input
Antibiotics tragedy of the commons

Individual benefit  Problem for society