Modeling the Emergence of Multidrug Antibiotic Resistance

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Abstract

One of the most worrisome aspects of the worldwide growth of antibiotic resistance is the emergence of bacterial strains (or "clones") that are resistant to multiple classes of antibiotics. Such multidrug resistance has made some life-threatening diseases more difficult and more expensive to treat, and has contributed to an increase in mortality from formerly well-controlled diseases such as tuberculosis. It has also led to increasing reliance on the newest and most powerful antibiotics, sparking concerns that resistance will soon reduce their effectiveness as well, and eliminate all options for treatment in some cases.

We have previously presented a small system dynamics model, drawing upon a case study of pneumococcal resistance to the beta-lactams, that portrays the development of resistance within a bacterial population to a single class of antibiotics. This model is now extended to consider growth in resistance to two different classes of antibiotics, with special application to pneumococcal resistance to the beta-lactams and the macrolides.

The extended model shows how selective pressure from antibiotics may cause multidrug resistant clones to become dominant over both non-resistant and single-class resistant strains, even when the microbiological mechanisms of resistance for the two antibiotic classes are unrelated. The implications for policy are explored. In particular, how can the growth of two-class resistance best be reversed? Does it require very large reductions in the use of both contributing antibiotic classes, or is there a less difficult way?
Background on multidrug resistance (MDR)

- MDR makes infections more difficult and expensive to treat, and has emerged in the last two decades in a variety of pathogens, including:
  - *S. aureus*: many strains resistant to all antibiotics except expensive vancomycin
  - *M. tuberculosis*: some strains now evade all treatment
  - *N. gonorrhoeae*: treatment now limited to cephalosporins
  - *S. dysentaria*: some strains treatable only by expensive fluoroquinolones, often unavailable in developing countries
  - *E. faecalis*: some strains now evade all treatment
  - *E. coli*: MDR found in strains causing urinary tract infections
  - *P. aeruginosa*: some strains now evade all treatment
  - *S. pneumoniae*: some strains resistant to six different classes of antibiotics

Background on multidrug resistance (MDR), continued

• MDR may result from mutations affecting single or multiple biochemical mechanisms
  
  – Single mechanism
    
    • Within a drug class (due to chemical relatedness)
      
      – ex. altered penicillin-binding proteins (PBPs) affect all beta-lactam drugs (penicillins, cephalosporins, carbapenems)
    
    • Across multiple drug classes (due to target overlap or active efflux)
      
      – ex. one altered ribosomal enzyme confers common resistance to macrolides, lincosamides, and streptogramins (“MLS resistance”)

  – Multiple mechanisms
    
    • Each mechanism confers resistance to a corresponding drug class
    
    • Multiple resistance genes often physically adjacent and transferred together in chromosomal “cassettes” or “integrons”
    
    • Multiply-resistant bacterial clones may gain reproductive advantage when multiple drug classes are used excessively
MDR in *S. pneumoniae* (Pneumococcus)  
Data from the USA and Spain

<table>
<thead>
<tr>
<th>Resistance number*</th>
<th>USA 1995/8</th>
<th></th>
<th>Spain 1990-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>2183</td>
<td>69.8%</td>
<td>3703</td>
</tr>
<tr>
<td>1</td>
<td>293</td>
<td>9.4%</td>
<td>1732</td>
</tr>
<tr>
<td>2</td>
<td>252</td>
<td>8.1%</td>
<td>840</td>
</tr>
<tr>
<td>3</td>
<td>164</td>
<td>5.2%</td>
<td>1817</td>
</tr>
<tr>
<td>4</td>
<td>122</td>
<td>3.9%</td>
<td>1151</td>
</tr>
<tr>
<td>5</td>
<td>114</td>
<td>3.6%</td>
<td>N/A</td>
</tr>
<tr>
<td>All</td>
<td>3128</td>
<td>100.0%</td>
<td>9243</td>
</tr>
<tr>
<td>1 or more</td>
<td>945</td>
<td>30.2%</td>
<td>5540</td>
</tr>
<tr>
<td>2 or more</td>
<td>652</td>
<td>20.8%</td>
<td>3808</td>
</tr>
</tbody>
</table>

* Resistance number: Number of specified drugs to which an isolate is resistant (includes both intermediately and highly resistant isolates.)
For USA, the five drugs include: penicillin, erythromycin, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP/SMP).
For Spain, the first four of these drugs are reported but not TMP/SMP.

Sources:
**USA**: Doern 1996 (N=1527 in 1995 sample), Doern 1999 (N=1601 in 1998 sample);
**Spain**: Fenoll et al. 1998 (continuous sampling 1990-1996).
Where we started: Modeling resistance to one drug class

- Initial focus on pneumococcal resistance to penicillin (PRP) and other beta-lactams
  - Three-state model is a simplification of the *near-continuum* of resistance states in PRP
    - Extensive use of beta-lactams has given mutant resistant pneumococci a reproductive advantage they would not otherwise have
    - The one-class model can reproduce historical PRP growth in USA, Spain, South Africa, and Hungary

- Subsequent focus on pneumococcal resistance to erythromycin (PRE) and other macrolides
  - Two-state model reflects *essentially binary* situation in PRE
    - PRE emerged more recently than PRP, but has caught up in western countries, as macrolide use grew while beta-lactam use declined
    - The one-class model can reproduce historical PRE growth in USA, Spain, France, and Hungary
One-class resistance model used for studying PRP and PRE*

* For PRE, only 2 (rather than 3) states required: Susceptible and Resistant

**Diagram:**
- **Susceptible bacterial density**
- **Intermediately resistant bacterial density**
- **Resistant bacterial density**
- **Highly resistant bacterial density**
- **Total bacterial density**
- **Antibiotic use**
- **Mutation to intermediate resistance**
- **Mutation to high resistance**
- **Effect of niche saturation on growth**
- **Effect of niche saturation on resistance**
- **Effect of serotype variation on high resistance**
- **Effect of serotype variation on resistance**

Effects:
- \(\text{Antibiotic use} \rightarrow \text{Highly resistant bacterial density}\) (strong effect)
- \(\text{Highly resistant bacterial density} \rightarrow \text{Susceptible bacterial density}\) (moderate effect)
- \(\text{Susceptible bacterial density} \rightarrow \text{Resistant bacterial density}\) (weak effect)

* For PRE, only 2 (rather than 3) states required: Susceptible and Resistant
Modeling two-class resistance

• Purpose: To investigate how MDR clones may become dominant even when resistance mechanisms differ
  • To avoid undue complexity, modeled co-resistance to two drug classes only; anticipated that lessons learned for two-class MDR would apply to higher-order MDR as well
  • To represent PRP/PRE co-resistance, need 6 clone types
    – 3 PRP resistance states x 2 PRE resistance states
  • Initial version of MDR model assumed largely independent transfer of PRP and PRE genes
    – This model able to show how two-class resistant clones may develop from single-class resistant clones, through change in a single gene; but unable to show emerging dominance of these new MDR clones
  • Subsequent version assumes mostly co-transfer of PRP and PRE genes
    – This model able to show emerging MDR clone dominance given sufficient use of both drug classes
Two-class resistance model used for studying PRP/PRE (P: penicillin/beta-lactams; E: erythromycin/macrolides)

<table>
<thead>
<tr>
<th>Type of Antibiotic</th>
<th>Resistance Model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P antibiotic use</td>
<td>Ps-Es clone</td>
<td>Ps: susceptible to P</td>
</tr>
<tr>
<td></td>
<td>Pi-Es clone</td>
<td>Pi: intermediately resistant to P</td>
</tr>
<tr>
<td></td>
<td>Pr-Es clone</td>
<td>Pr: highly resistant to P</td>
</tr>
<tr>
<td>E antibiotic use</td>
<td>Ps-Er clone</td>
<td>Es: susceptible to E</td>
</tr>
<tr>
<td></td>
<td>Pi-Er clone</td>
<td>Er: resistant to E</td>
</tr>
</tbody>
</table>

**Effect of niche saturation on bacterial growth**

**Total bacterial density**

**Resistance to P**

**Resistance to E**

**Effect of serotype on growth in P resistance**

**Effect of serotype on growth in E resistance**

**Mutation to**

- PsEr
- PiEr
- PrEr

**KEY**

- Ps: susceptible to P
- Pi: intermediately resistant to P
- Pr: highly resistant to P
- Es: susceptible to E
- Er: resistant to E

**PRP only**

- Ps-Es clone density
- Pi-Es clone density
- Pr-Es clone density

**PRP+PRE**

- Ps-Er clone density
- Pi-Er clone density
- Pr-Er clone density

**Ps-Es clone density**

**Pi-Es clone density**

**Pr-Es clone density**

**Ps-Er clone density**

**Pi-Er clone density**

**Pr-Er clone density**

**Ps-Es clone density**

**Pi-Es clone density**

**Pr-Es clone density**

**Ps-Er clone density**

**Pi-Er clone density**

**Pr-Er clone density**

**Ps-Er clone density**

**Pi-Er clone density**

**Pr-Er clone density**

**Ps-Es clone density**

**Pi-Es clone density**

**Pr-Es clone density**

**Ps-Er clone density**

**Pi-Er clone density**

**Pr-Er clone density**
Pneumococcal resistance to penicillin (PRP): One- and two-class model simulations vs. history

PRP here includes both intermediate (MIC ≥ 0.12 µg/mL) and high resistance (MIC ≥ 2 µg/mL) in isolates from normally sterile sites.

MIC: Minimum inhibitory concentration

Beta-lactam use data and assumptions

Pneumococcal resistance to erythromycin (PRE): One- and two-class model simulations vs. history

PRE here includes both intermediate (MIC $\geq 1$ $\mu$g/mL) and high resistance (MIC $\geq 4$ $\mu$g/mL) in isolates from normally sterile sites.

Macrolide use data and assumptions

# Key parameter values in one-class and two-class models

<table>
<thead>
<tr>
<th></th>
<th>One-class</th>
<th>Two-class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative reproductive fitness [$f$]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f(Ps)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>f(Pi)</td>
<td>0.942</td>
<td>0.942</td>
</tr>
<tr>
<td>f(Pr)</td>
<td>0.936</td>
<td>0.936</td>
</tr>
<tr>
<td>f(Es)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>f(Er)</td>
<td>0.942</td>
<td>0.942</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic inhibition factors [$b$]</th>
<th>One-class</th>
<th>Two-class</th>
</tr>
</thead>
<tbody>
<tr>
<td>b(Ps)</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>b(Pi)</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>b(Pr)</td>
<td>0.0040</td>
<td>0.0055</td>
</tr>
<tr>
<td>b(Es)</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>b(Er)</td>
<td>0.0150</td>
<td>0.0165</td>
</tr>
</tbody>
</table>

* In the two-class model, relative reproductive fitness of a clone type is found by multiplying the $f$-values of its component P and E genes; ex., $f(PrEr) = f(Pr)f(Er) = (.936)(.942) = .8817$.

** These $b$ factors describe inhibition effect at a normalizing level of antibiotic use (ABn), expressed in prescriptions per thousand population per year. For beta-lactams (BL), ABn = 200; for macrolides (M), ABn = 70. Given these normalizing levels, the effect of BL use on proliferation = $(1-b)^{BL/200}$; the effect of M use on proliferation = $(1-b)^{M/70}$.

In the two-class model, the effect of antibiotic use on proliferation of a clone type is found by multiplying the beta-lactam and macrolide effects on its component P and E genes; ex., the effect of antibiotic use on proliferation of PrEr = $(1 - 0.0055)^{BL/200}(1 - 0.0165)^{M/70}$.
### Initial (1979) values in one-class and two-class models

#### Resistance percentages, initial (1979)

**Resistance types**

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One-class</td>
<td>Two-class</td>
</tr>
<tr>
<td>Ps</td>
<td>98.5%</td>
<td>98.5%</td>
</tr>
<tr>
<td>Pi</td>
<td>1.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Pr</td>
<td>0%</td>
<td>0.02%</td>
</tr>
<tr>
<td>Es</td>
<td>99.7%</td>
<td>99.7%</td>
</tr>
<tr>
<td>Er</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

#### Clone types (two-class model)

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsEs</td>
<td>98.3%</td>
<td>94.3%</td>
</tr>
<tr>
<td>PsEr</td>
<td>0.23%</td>
<td>0.29%</td>
</tr>
<tr>
<td>PiEs</td>
<td>1.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>PiEr</td>
<td>0.03%</td>
<td>0.09%</td>
</tr>
<tr>
<td>PrEs</td>
<td>0.02%</td>
<td>0.44%</td>
</tr>
<tr>
<td>PrEr</td>
<td>0.001%</td>
<td>0.04%</td>
</tr>
<tr>
<td>total</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Prevalence of pneumococcal clones with PRP ($\text{Pir}: \text{Pi or Pr}$) and/or PRE ($\text{Er}$) in the USA

PRP/PRE (red) clones gain dominance after 1999. PRP-only (blue) clones decline after 1997, while PRE-only (green) clones are still on the rise.

Prevalence of pneumococcal clones with PRP (Pir: Pi or Pr) and/or PRE (Er) in Spain

PRP/PRE (red) clones gain dominance after 1997. PRP-only (blue) clones decline after 1990, while PRE-only (green) clones are still on the rise.
The great majority of clones with PRE also have PRP. Until the late 1990s in the USA and the late 1980s in Spain, PRP/PRE clones had a significant reproductive advantage over those with PRE alone. With the decline in beta-lactam use in both countries, the fastest-growing clone type is now PRE-only, followed by PRP/PRE.

Testing impacts of antibiotic use reduction

• Questions
  – How much reduction in use does it take to reverse the growth of two-drug resistance (PRP/PRE)?
  – Does it require large reductions in both drug classes sufficient to drive out all resistance, or is there an easier way?

• Procedure
  – In USA-calibrated model, assume constant use levels from 2002 onward; test various use reduction combinations
    • Base run: Continue use forward at assumed 1999-2001 levels
      – Beta-lactams = 190 Rxs/1000/year
      – Macrolides = 68 Rxs/1000/year
    • Test use above and below thresholds for resistance elimination
      – Beta-lactams for PRP elimination $\simeq 140$ [historical low: 160.1 (1998)]
      – Macrolides for PRE elimination $\simeq 50$ [historical low: 50.2 (1991)]
Reducing use of one class only: Prevalence of two-class resistant (PRP/PRE) clones

If use of either drug class is reduced below its elimination threshold (as in P125 and E45), two-class resistance is ultimately eliminated. Otherwise, reduction in use of one class only may allow two-class resistance to grow further (E55) or to decline but only partially and with a delay (P150).
Reducing use of both classes:
Prevalence of two-class resistant (PRP/PRE) clones

Two-class resistance may be more effectively reversed when use of both drug classes is reduced. Quick reversal may be achieved even when use of both classes remains somewhat above their respective elimination thresholds (as in P150E55). However, ultimate *elimination* of two-class resistance still requires that use of at least one drug class be reduced below its threshold.
Reducing use of one class only: Prevalence of one-class and two-class resistant (PRP and/or PRE) clones

If use is reduced for one drug class only, resistance to the other class will persist. The reduction in use may, however, take away the reproductive advantage of two-class resistant clones. If use of the one class is reduced below the elimination threshold (as in P125 and E45), resistance to the other class will ultimately be all one-class resistance.
Reducing use of both classes: Prevalence of one-class and two-class resistant (PRP and/or PRE) clones

When use of both drug classes is reduced, the growth of both one-class and two-class resistance may be quickly reversed. This holds true even when use of both classes remains somewhat above their respective elimination thresholds (as in P150E55).
Conclusions and Next Steps

• Conclusions
  • The two-class model is able to reproduce historical growth patterns of one-class and two-class pneumococcal resistance
    – The two-class model is a straightforward extension of the one-class model, with emphasis on reproductive advantage rather than mutation, including co-transfer of resistance genes
  • Reversal and ultimate elimination of two-class resistance can be achieved by reducing use of either of the two drug classes below its respective elimination threshold
    – But reducing use of the other drug class as well, even if not below the elimination threshold, can significantly speed that process

• Possible next steps
  • Seek more recent US data on resistance by clone type
  • Publish results in medical journal
  • Apply model to growing fluoroquinolone class
  • Apply model to a different pathogen
References


References, continued


