Custom Antibiotic Cycles Reinforced by Selective Pressures

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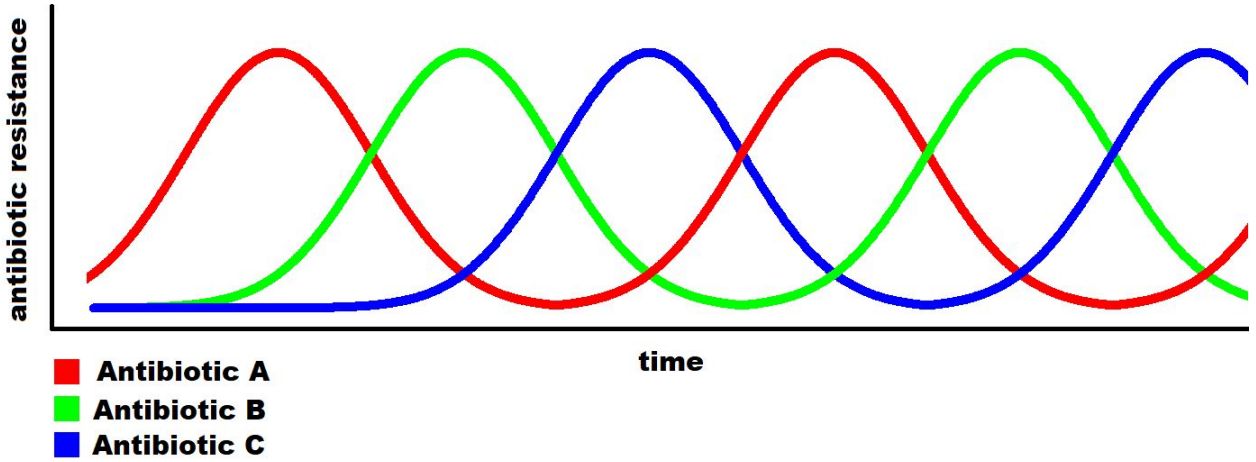
What is the problem?

- Antimicrobial resistance (AMR) - Resistance to multiple antibiotics emerging at once in a population
- Our solution provides a tool to addresses the resistance problem on a community level
- What would it look like if hospitals could plan and create custom antibiotic cycles to fight resistance?
- What would it look like if public officials had easy access to the information they needed?

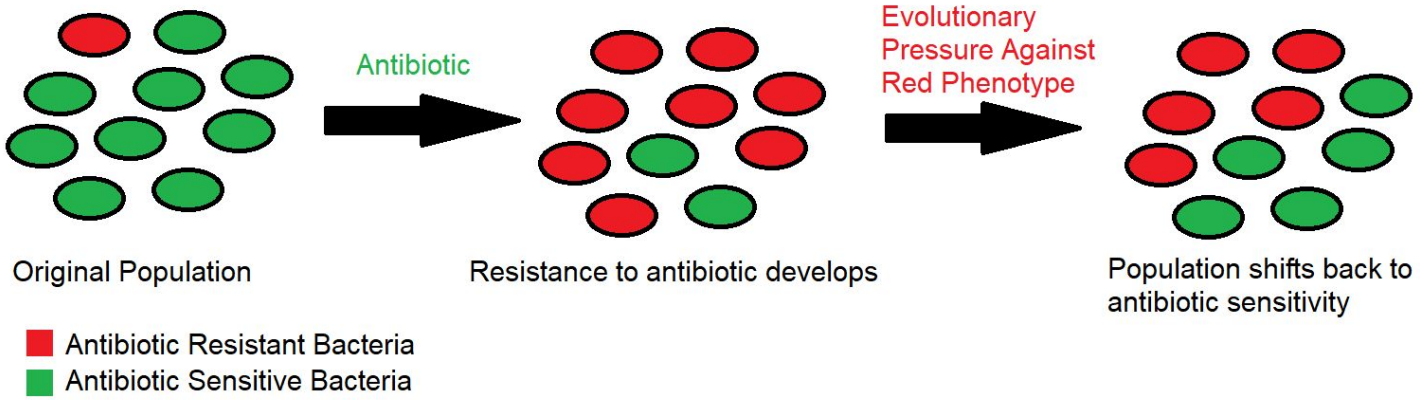
What is our solution?

- Allows users to create optimized antibiotic cycles designed to combat resistance, specific to the needs of a population
- Uses collateral resistance: the idea that resistance to one antibiotic can increase sensitivity or resistance to another antibiotic



How Do Selective Pressures Work?

- Based on a resistance pathway, stress the cells to select for the antibiotic-susceptible phenotype.
- Prevents deviation from the cycle into other forms of antibiotic resistance.
- Slows down the cycle, allowing resistance to a given antibiotic to dissipate before it comes back into use.

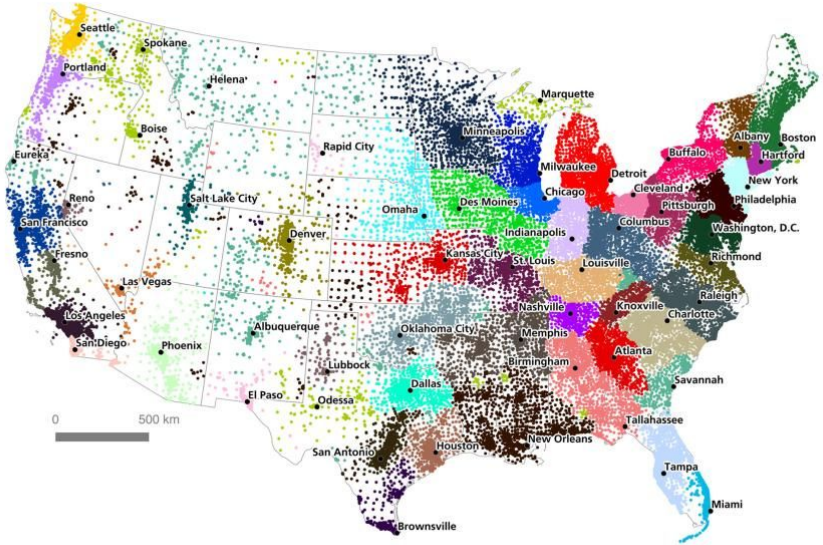


Responses to Resistance Pathways

Antibiotic Target	Resistance Pathway	Selective Pressure
Protein Synthesis	Mutations affecting antibiotic-ribosome interactions	Use directed phages to insert a plasmid with an expensive protein
Cell Wall Disruption	Destroying the antibiotic with a beta-lactamase	Introduce a chemical that becomes toxic when the beta-lactam ring is cleaved
DNA Gyrase	Mutations affecting antibiotic-DNA Gyrase interactions	Use directed phages to insert a large plasmid with a long replication
Lipopolysaccharide (LPS)	Mutations in *arnBCADTEF* operon, *prmA*, and *prmB* that modify Lipid A	High Magnesium diet to limit expression of mutated genes
RNA Polymerase	Mutations affecting RNA Polymerase-antibiotic interactions	Use directed phages to insert a plasmid with a highly transcribed gene.

Who is it for?

- Targeted towards hospital and public health administrators, at a regional level
- Keeps hospitals in a single region on the same cyclic regimen
- For example, all hospitals in the Salt Lake City area would prioritize a certain antibiotic as their first line of defense
- The first line of defense changes over time, through the cycle, to limit resistance building up in a population



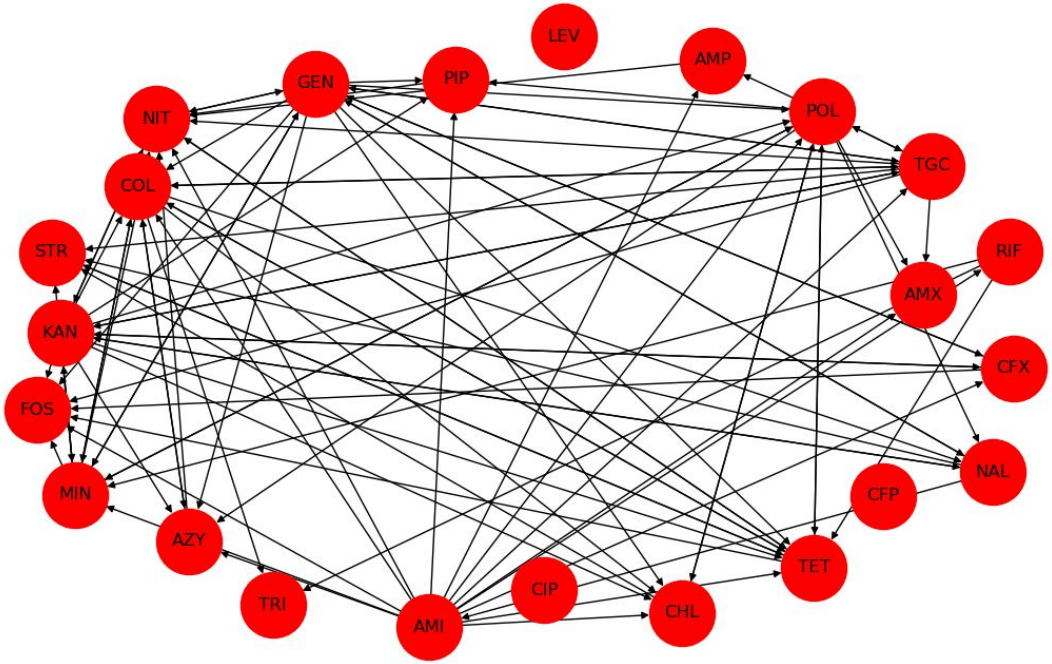
This map shows the megaregions of the U.S. (represented by colors) based on an algorithmic analysis of four million commutes (represented as lines). - Garrett Dash Nelson, Alasdair Rae

How do they use it?

- Tool built based on collateral sensitivity network data
  - Measure antibiotic resistance of various resistant strains against antibiotic panels
  - Look for examples of collateral resistance
- Input antibiotic resistance data
  - An algorithm converts the data to a heatmap and creates a sensitivity matrix
- Output a cycle specific to the needs of the population
  - Ideally, infections that are resistant to each antibiotic in the cycle will be susceptible to the next antibiotic in the cycle (leverage collateral resistance)
  - Prioritizes cycles with higher levels of sensitivity and an average of six antibiotics
- Additional treatment to slow development of resistance, and allow the use of the current antibiotic for as long as possible
- Shift to the next antibiotic in the cycle when population reaches a threshold of resistance to current antibiotic

Collateral Sensitivity Network

- Used recent *E. coli* data to create a directed graph fully modeling sensitivity network
- Created an algorithm capable of traversing the network to develop drug cycles with scoring based on sensitivities and cycle sizes
- Remodeled best cycles for potential medical use
- Algorithm designed for possible weighting of the antibiotics based on availability and the relative costs of different cycles



Citations

Imamovic L, et al. (2018) *Drug-Driven Phenotypic Convergence Supports Rational Treatment Strategies of Chronic Infections*. Cell. 2018 Jan 11;172(1-2):121-134.e14. doi: 10.1016/j.cell.2017.12.012. Epub 2018 Jan 4

Imamovic L, et al. (2013) *Use of collateral sensitivity networks to design drug cycling protocols that avoid resistance development*. Sci Transl Med. 2013 Sep 25;5(204):204ra132. doi: 10.1126/scitranslmed.3006609.