Antibiotics Without MICs
Feasible or Fantasy
Cons

Challenges

- Adjuvants (anti-resistance, activity enhancers)
  - Mutational pathways to resistance still exist
  - Large variation mechanisms that may need to be overcome
- Inhibitors of biofilm formation
  - Likely early or preventative application necessary
- Monoclonal antibodies
  - Costs will likely limit applications
- Manipulation of microbiotia (probiotics)
- Immunomodulatory agents
  - Complexity, balance, and timing

Challenges

- Conversion of a pathogen to a commensal
  - Persistence could be a source of clinical relapse once therapy is stopped
  - Many pathogens already have resistance genes, the reservoir for which could remain
- Effectiveness may be highly dependent on early use
  - e.g., anti-adherence agents, anti-toxins

Challenges

- Pathogen virulence strategies are diverse and multiple
  - Specificity of action may require heavy reliance on rapid diagnostics
  - Single anti-virulence targeting may not be sufficient
    - e.g., difficulty with efforts to develop *S. aureus* vaccines

Challenges

- Anti-virulence strategies are not necessarily immune to resistance selection
  - Bacteria have multiple efflux pumps with broad spectrum substrate profiles that extend beyond their natural substrates and could include small molecule anti-virulence agents
  - Mutations in regulatory genes can produce constitutive pump overexpression and resistance
  - Mutant target molecules with lower drug affinity do not necessarily lose virulence potential
  - Mutants resistant to anti-virulence agents could be enriched since their replication would likely exceed that of temporarily avirulent parental strains in the host

Challenges

- Conventional antimicrobials will still be needed for many patients
  - Infections occurring in immunocompromised hosts
  - Infections at body sites where host defenses are limited (endocarditis, meningitis)
- Clinical development will require more complex and as yet undefined protocols for combination therapies
- For preventative strategies need for key decisions about the target populations because of variation in risk-benefit-cost relationships