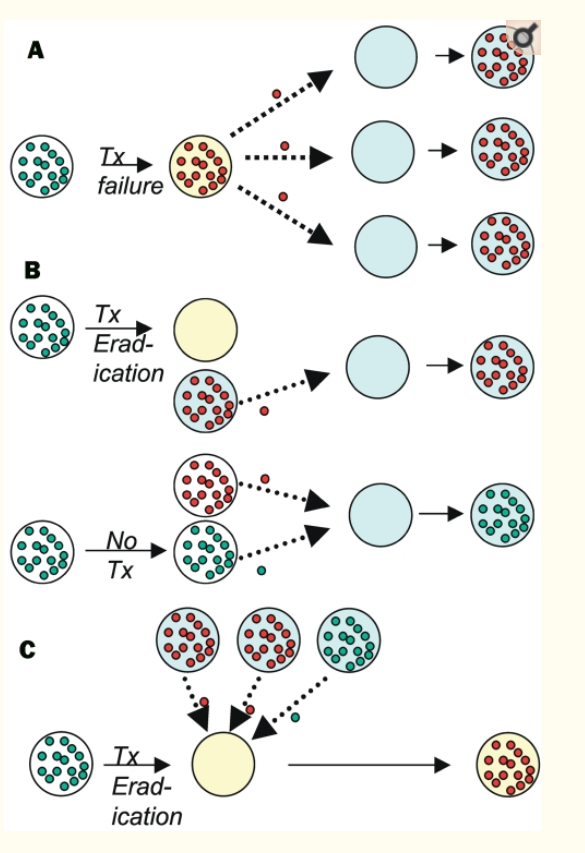
evolution of parasite countermeasures

14 March 2022

# General principles

* two stages of evolution: *de novo* mutation and selection
* limiting factors in *de novo* mutation
  + mutation rate (per locus/per genome)
  + population size
  + generation time
  + rate appearance of new mutations = (mutation rate × pop size)/(generation time)
  + mutational **spectrum**: what can mutations achieve?
* limiting factors in selection:
  + selection differential
    - benefits (= prob of encountering antibiotic × benefit of resistance)
    - costs [metabolic/energetic; reduced efficiency]
      * **compensatory** mutations (reduce cost)
  + pop size (drift vs selection; bottlenecks in between-host transmission)
  + variation in selection (within- vs between-host)
  + recombination and/or horizontal transmission via mobile elements (plasmids etc.)
* competition between susceptible and resistant strains (Lipsitch and Samore 2002)

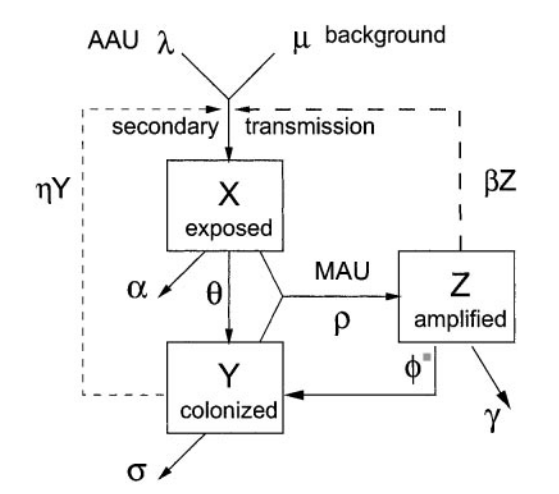


# Bacteria

## Mechanisms

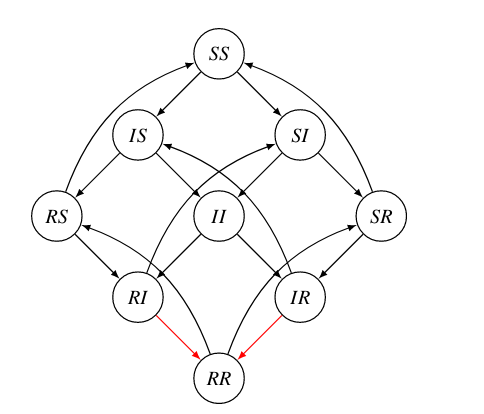
* because bacteria and animals are biochemically different, can use substances that disrupt bacterial but not animal metabolic processes
* many biologically derived
  + fungi (penicillin!) (Karwehl and Stadler 2016)
  + soil bacteria (esp *Streptomyces*; streptomycin, tetracycline)
  + (also chemical/synthetic, e.g. derived from dyes - *sulfa drugs*)
* because antibiotics have been around “forever”, so has antibiotic resistance (D’Costa et al. 2011)
  + but presence **as mobile elements** may be recent, human/animal derived (Ebmeyer, Kristiansson, and Larsson 2021)
  + often present in antibiotic *producers* (Benveniste and Davies 1973)
* huge problem, e.g. MRSA (multi-resistant *Staphylococcus aureus*), extensively drug-resistant (XDR) tuberculosis (Disease Control 2020)
  + threatens to wipe out disease cures …
* horizontal transfer is rampant
  + resistance gene can be anywhere in the microbiome …
  + **collateral** or **non-target selection** (Llewelyn et al. 2017)
  + also makes it easier to lose resistance when no longer required
  + thus resistance is usually/often pre-existing
* mechanisms of action:
  + pumps (“efflux system”: remove toxic substances from the cell)
  + inactivation or degradation/detoxification
  + altered pathways?
* antibiotics are *effectors* (not recognizers)
* cost of resistance; are resistance alleles lost or compensated in the absence of antibiotics? (Bjorkholm et al. 2001; Levin, Perrot, and Walker 2000)

## Implications for antibiotic use

* avoid overuse! “antibiotic conservation”
* regulate agricultural use
  + for human-to-human transmission, regulating agriculture may be too late once resistance is already established in humans (Smith et al. 2002) 
  + but regulation still helps with spillover infections (Lipsitch, Singer, and Levin 2002)
* “the long-term benefit of single drug treatment from introduction of the antibiotic until a high frequency of resistance precludes its use is almost independent of the pattern of antibiotic use” (Sebastian Bonhoeffer, Lipsitch, and Levin 1997)
* “cocktails” may be best; varying treatments in space is better than cycling (Bergstrom, Lo, and Lipsitch 2004)
* treating for longer increases collateral selection (Llewelyn et al. 2017)
* contrast: Tb (chronic disease, resistance from point mutations)

# Viruses

* similar biochemistry to hosts
  + often fought by priming immune system, i.e. *vaccination*
  + resistance via **recognition escape** rather than disabling effectors
  + usually **strain replacement** rather than within-lineage selection on escape alleles
* very high mutation rate
  + *de novo* mutation is a bigger problem
* HIV
  + single-drug resistance evolves quickly (S Bonhoeffer, Coffin, and Nowak 1997)
  + target non-host-like biochemistry: nucleoside and non-nucleoside resistance transcriptase inhibitors; protease, integrase inhibitors
  + HAART (Eggleton and Nagalli 2022); e.g. standard South African regimen includes tenofovir, lamivudine (nucleotide analog), dolutegravir (integrase inhibitor) (South Africa National Department of Health 2019)
  + keeping load low reduces transmission *and* within-host evolution of resistance
  + between-host transmission maybe less important because of early infectivity
* strain replacement
  + COVID-19! alpha, delta, omicron (Ferguson et al. 2021)
  + influenza, every year (*antigenic drift*)/pandemic (*antigenic shift*)
  + other examples: *Haemophilus influenzae B* (Adam et al. 2010)
  + human papilloma virus: maybe not? (Covert et al. 2019; Man et al. 2021)
  + **not**: smallpox (gone), rinderpest, chickenpox, measles, rubella

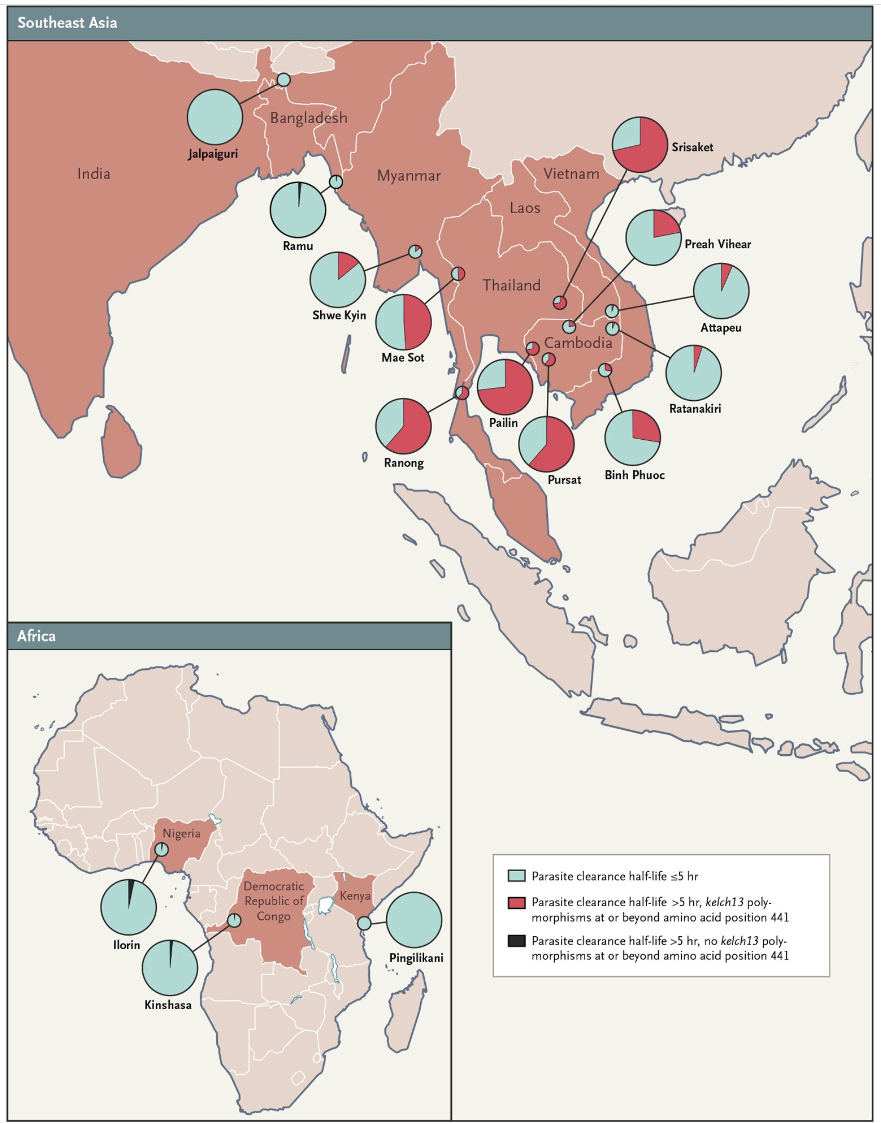


* back to bacteria: vaccine-preventable *Bordetella pertussis*, resurgence and evolution of immune evasion (?) (Gent et al. 2012)

(**to be added, maybe**)

## malaria resistance

* protozoan parasite
* quinine, chloroquine (Achan et al. 2011; Ashley et al. 2014)
* artemisinin



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