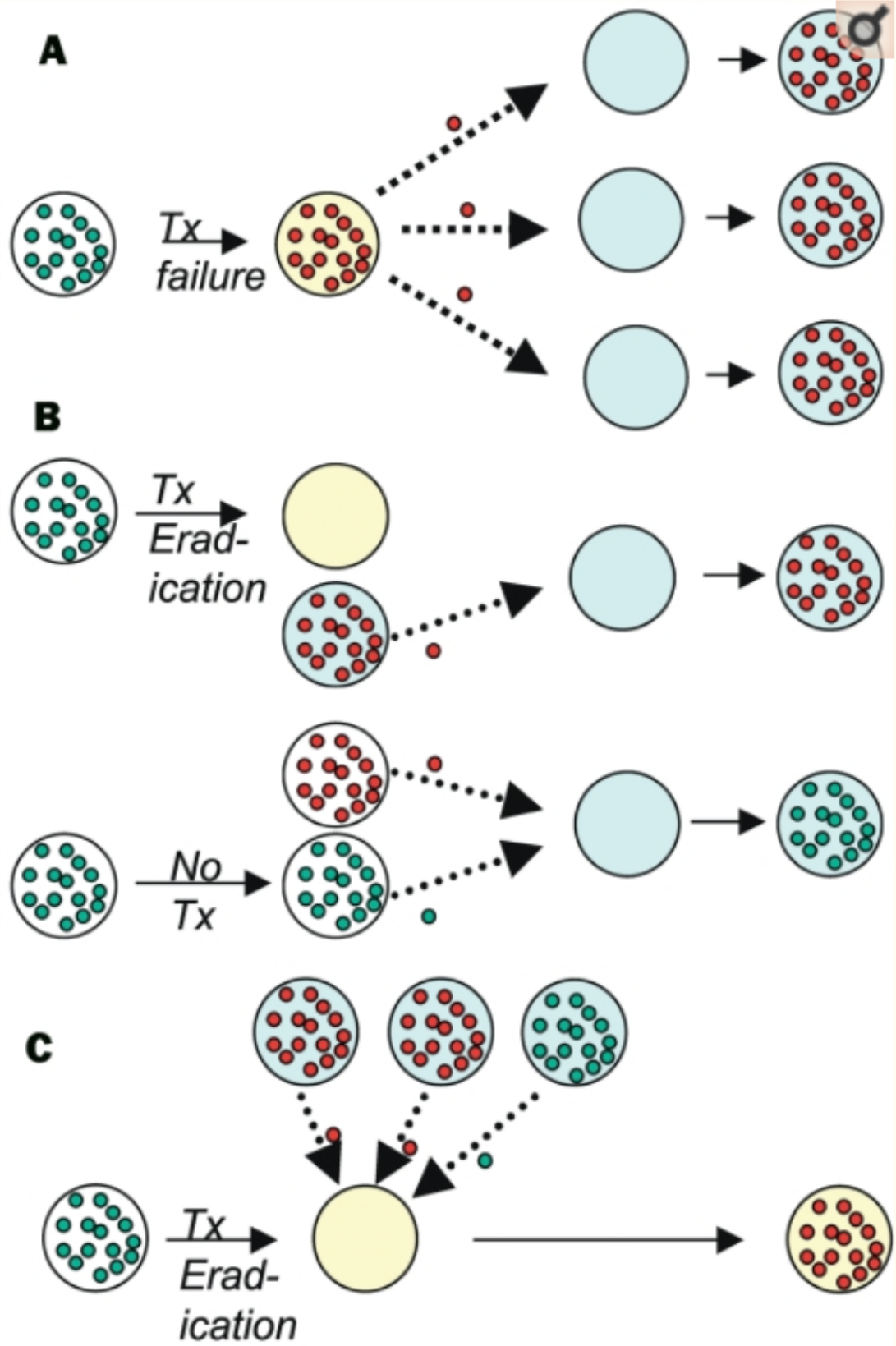
evolution of parasite countermeasures

6 Nov 2023

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 & Samore, 2002)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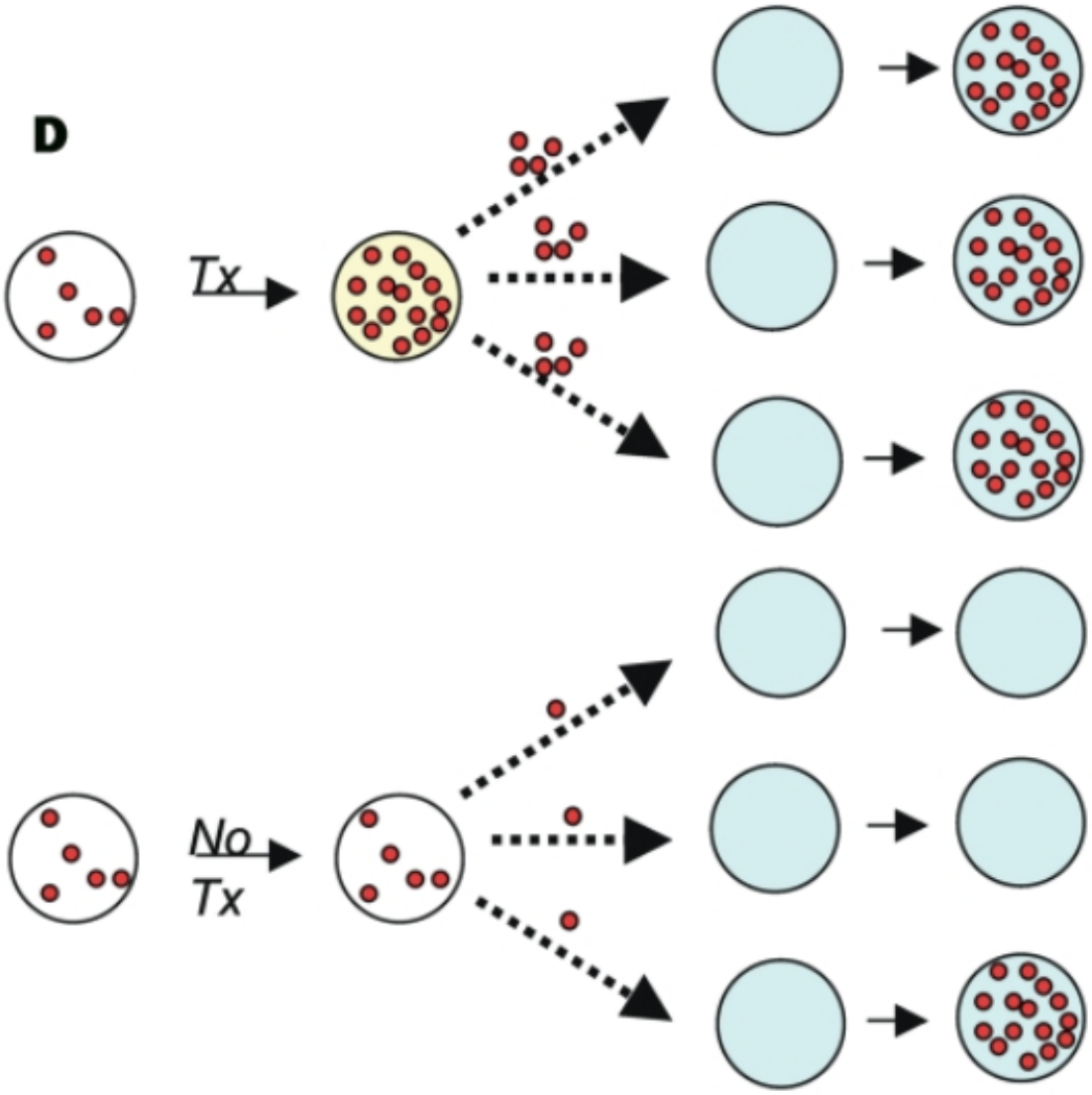


a. resistant bacteria take over during treatment failure (within-host competition)
b. resistant bacteria take advantage of reduced transmission by treated hosts (between-host)
c. resistant bacteria colonize a treated host (empty patch)
d. resistant bacteria take advantage of side effects (bystander effects)

Bacteria

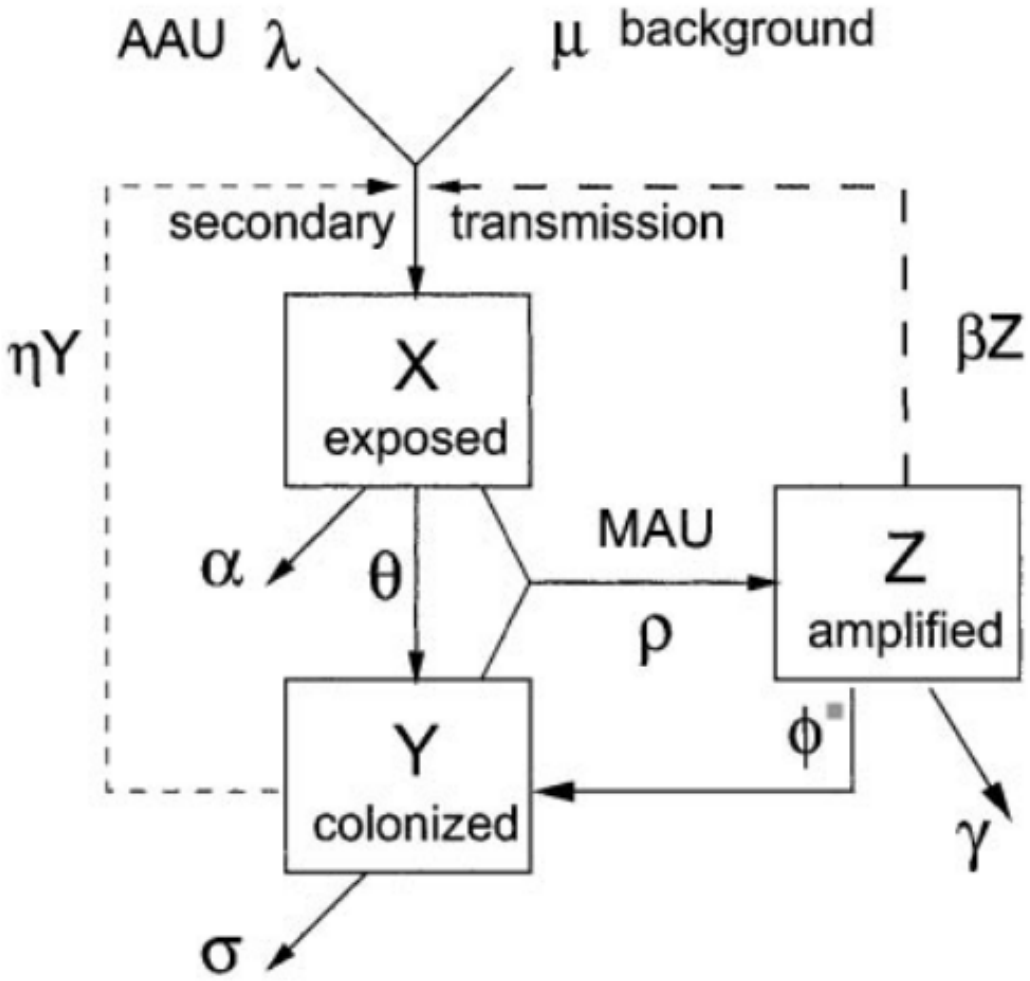
Mechanisms

- because bacteria and animals are biochemically different, can use substances that disrupt bacterial but not animal metabolic processes
- many biologically derived
  - fungi (penicillin!) (Karwehl & 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 et al., 2021)

  - often present in antibiotic *producers* (Benveniste & Davies, 1973)
- huge problem, e.g. mdrMRSA ([multi-drug resistant], methicillin-resistant *Staphylococcus aureus*), extensively drug-resistant (XDR) tuberculosis (Centers for 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 et al., 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)

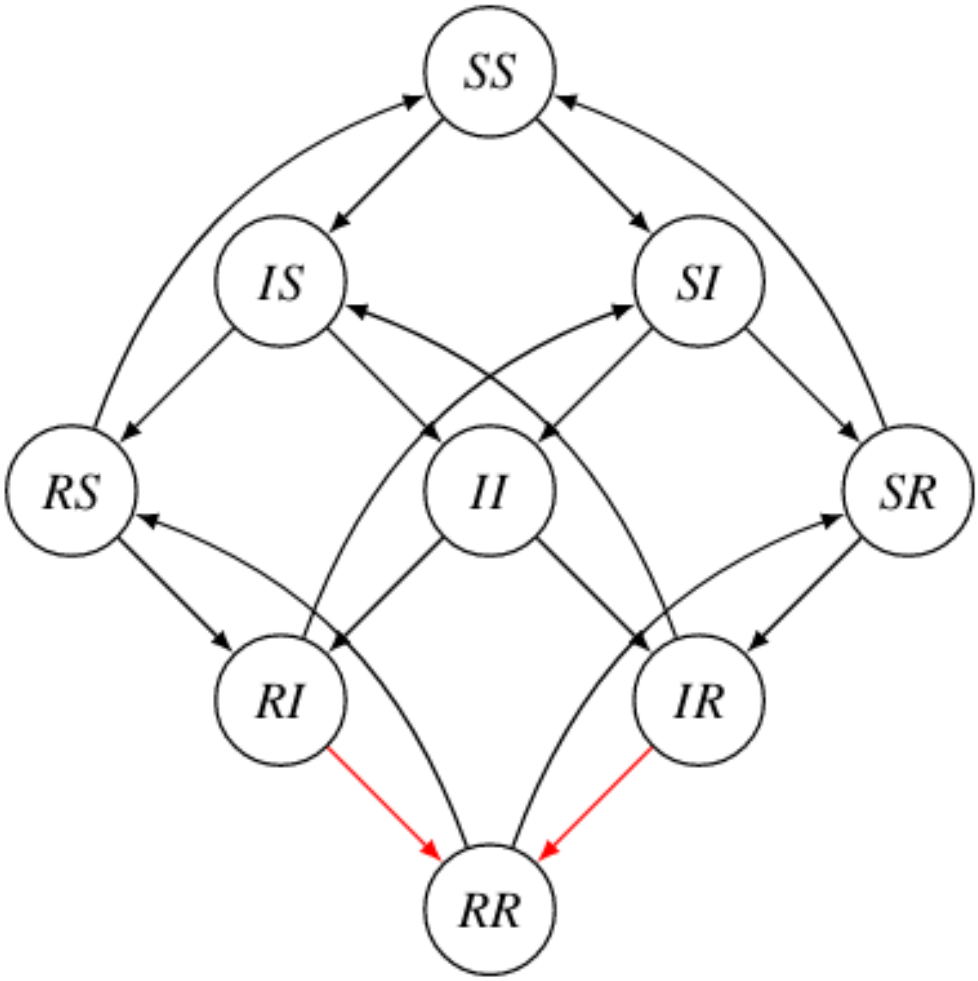


  - but regulation still helps with spillover infections (Lipsitch et al., 2002)
- "the long-term benefit of single drug treatment from introduction of the antibiotic until a high frequency of resistance precludes its use is almost independent of the pattern of antibiotic use" (Bonhoeffer, Lipsitch, et al., 1997)
- "cocktails" may be best; varying treatments in space is better than cycling (Bergstrom et al., 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 (Bonhoeffer, Coffin, et al., 1997)
  - target non-host-like biochemistry: nucleoside and non-nucleoside resistance transcriptase inhibitors; protease, integrase inhibitors

  - HAART (Eggleton & 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 control

Twitter:

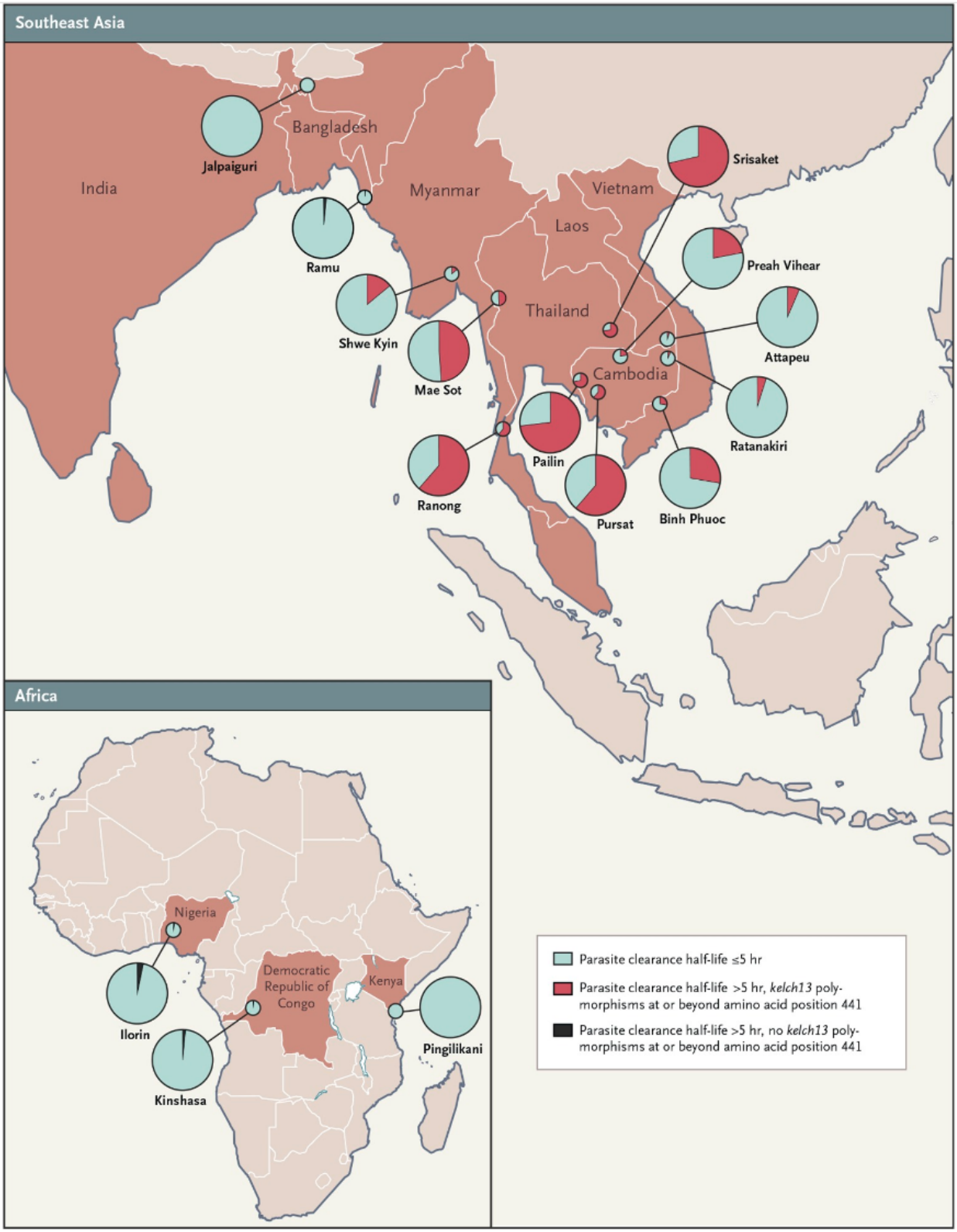
reading various malaria documents that discuss having endemic malaria today despite spending ~$4.1B/yr, I always want to insert the comment, "Well, WTF did you expect? No one who understands malaria believes elimination would be possible without spending at least $10B/yr"

Main components:

- antimalarial drugs
- vaccine (children only, max effectiveness ≈ 40%, safety concerns ...) (Jarry, 2021; Seo et al., 2014)
- vector control
  - indoor residual spraying (lethality + avoidance)
  - treated bednets (lethality + avoidance)
  - biocontrol (e.g. *Gambusia*, "mosquito fish")
  - improved housing? (Musiime et al., 2022)

malaria resistance to antimalarial drugs

- protozoan parasite
- quinine, chloroquine (Achan et al., 2011; Ashley et al., 2014)
- artemisinin (and combination therapy, ACT)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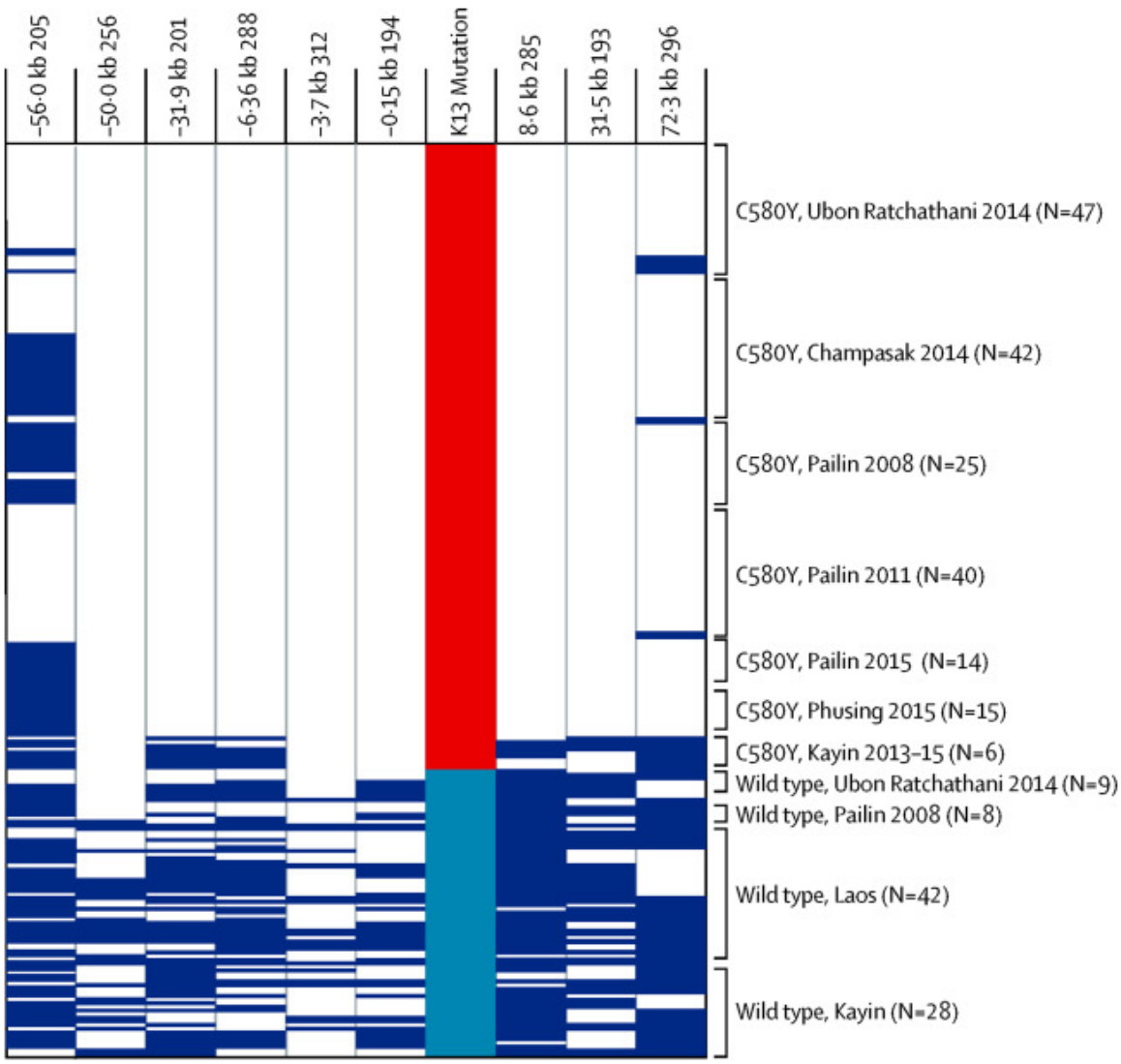

Figure 1 Microsatellite haplotypes of the *PfKelch13* flanking regions

containment strategies: eliminate *falciparum* malaria from Greater Mekong region or "firewall"?

vectors and resistance to insecticides

- DDT Wikipedia
  - environmental side effects
    - fast evolution of resistance: 6-7 years (Gladwell, 2001)
- other methods?
  - sterile male release (irradiation, *Wolbachia*) (Atyame et al., 2016)
  - **gene drive** (Burt et al., 2018) and/or bacterial infection (Dennison et al., 2014)
    - reduce vector competence
    - shift sex ratios toward males
  - evolution-resistant insecticides: shorten host life span (Koella et al., 2009; McMeniman et al., 2009)
    - weak selection against late-acting processes (Medawar, 2019)
    - late-acting insecticides (W. or fungal)

* larvicides: resistant phenotypes are smaller/short-lived

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