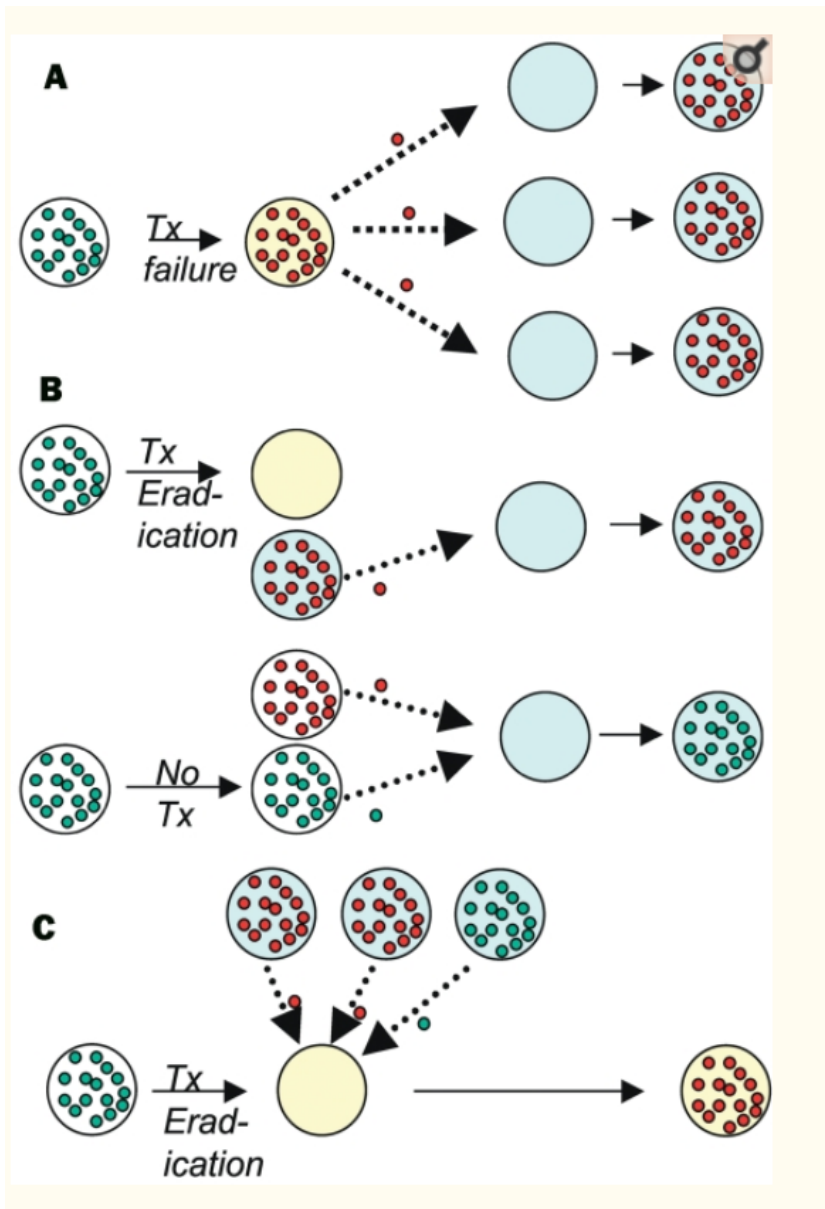


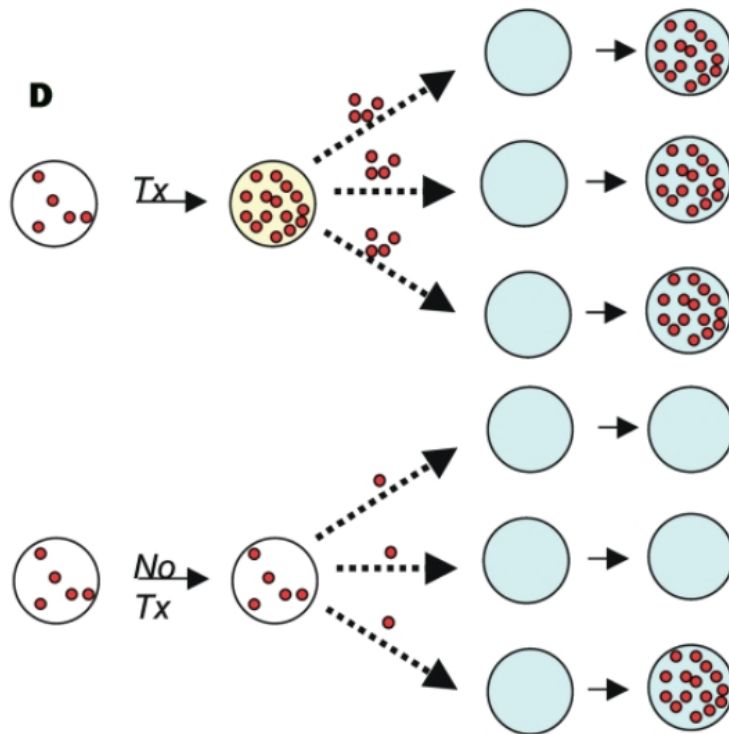
evolution of parasite countermeasures

23 March 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)
-





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

Bacteria

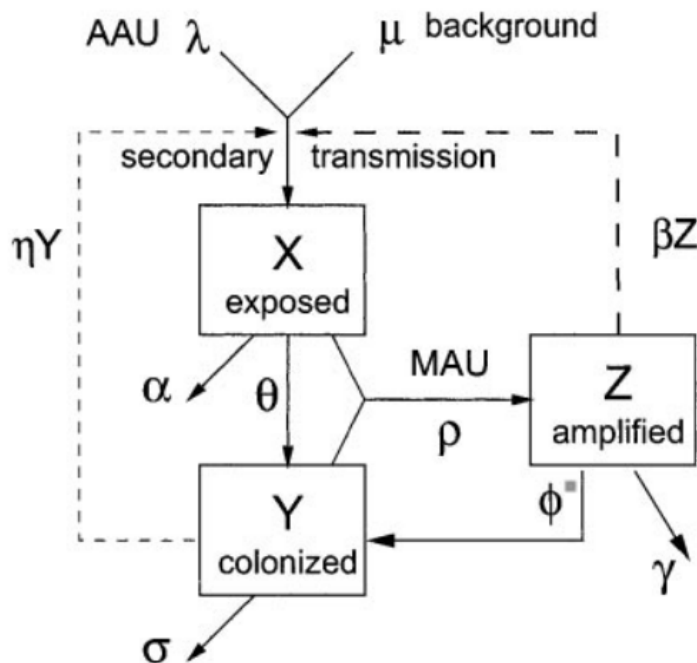
Mechanisms

- 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)

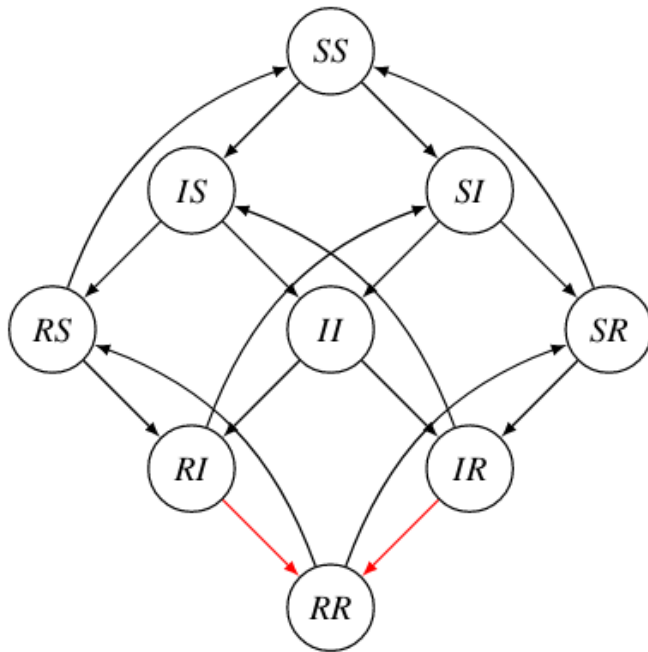


- but regulation still helps with spillover infections (Lipsitch et al., 2002)
- “the long-term benefit of single drug treatment from introduction of the antibiotic until a high frequency of resistance precludes its use is almost independent of the pattern of antibiotic use” (Bonhoeffer et al., 1997b)
- “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 et al., 1997a)
- 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:

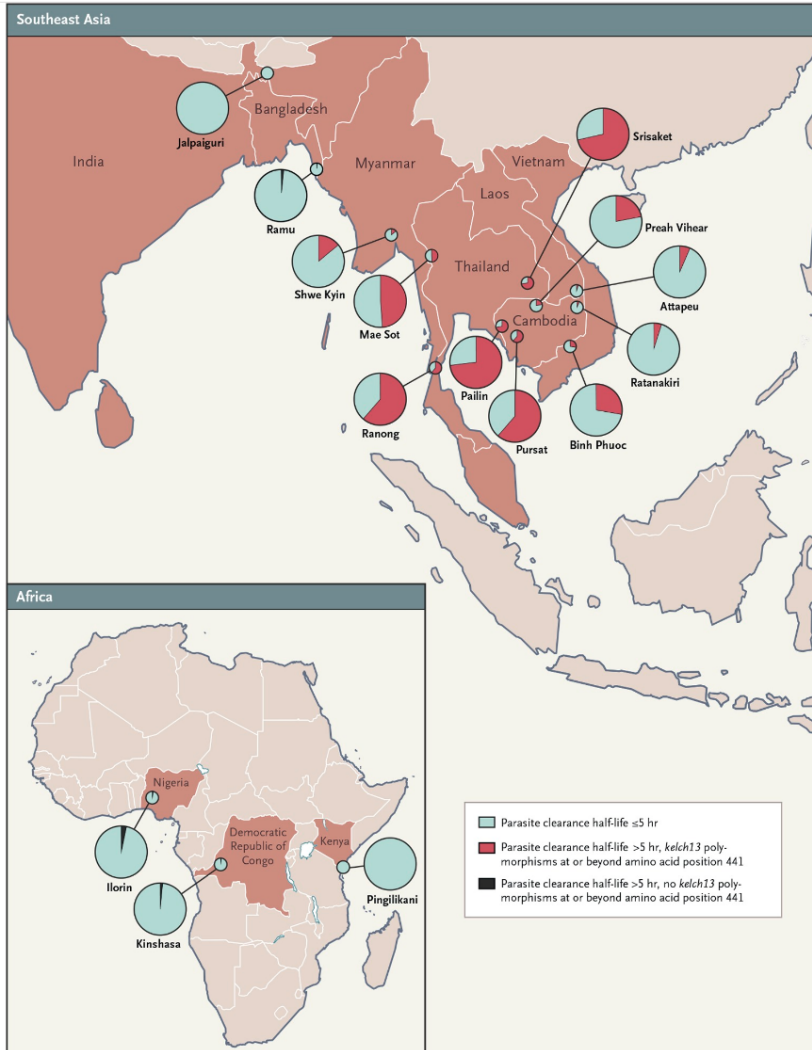
reading various malaria documents that discuss having endemic malaria today despite spending ~\$4.1B/yr, I always want to insert the comment, “Well, WTF did you expect? No one who understands malaria believes elimination would be possible without spending at least \$10B/yr”

Main components:

- antimalarial drugs
- vaccine (children only, max effectiveness $\approx 40\%$, 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)



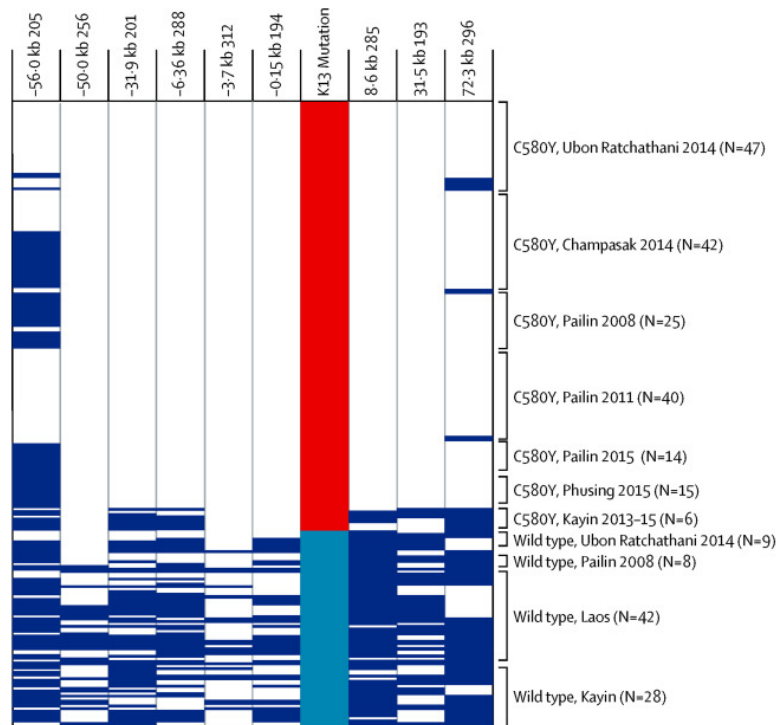


Figure 1 Microsatellite haplotypes of the *PfKelch13* flanking regions

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 (Dennis 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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