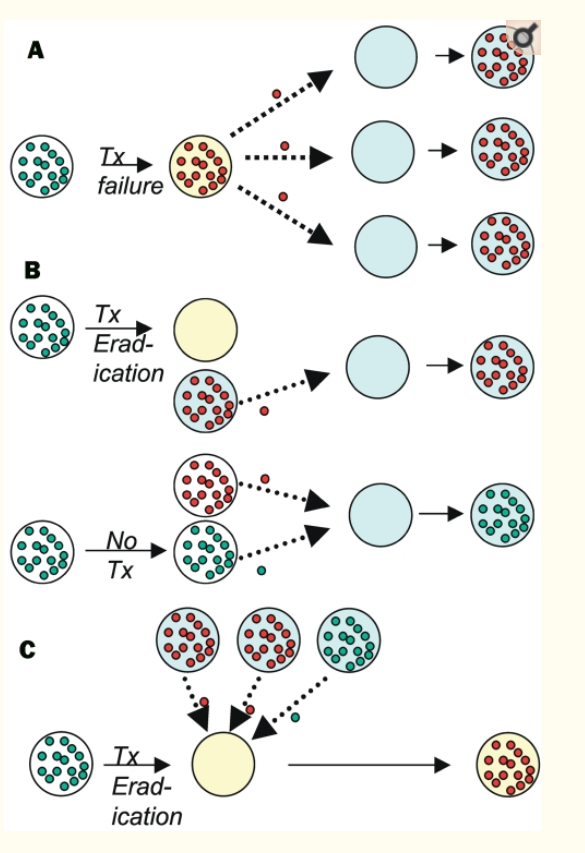
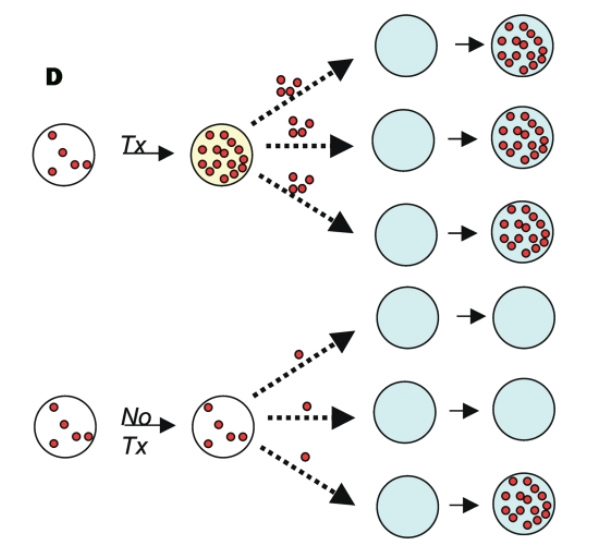
evolution of parasite countermeasures

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)

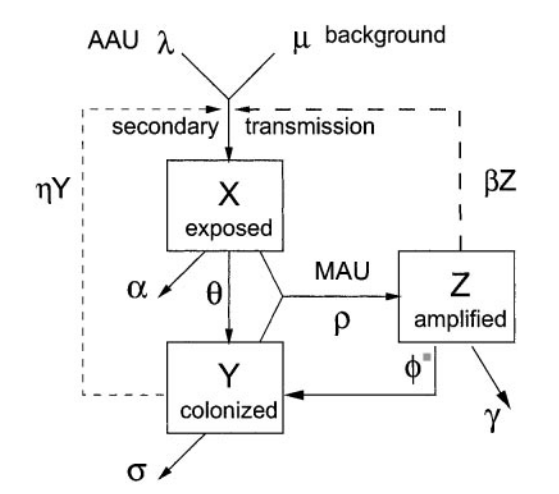
1. resistant bacteria take over during treatment failure (within-host competition)
2. resistant bacteria take advantage of reduced transmission by treated hosts (between-host)
3. resistant bacteria colonize a treated host (empty patch)
4. resistant bacteria take advantage of side effects (bystander effects)

# 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
    - horizontal transfer/lineage-mixing does happen via recombination (especially influenza, phages), but less typical (Mavrich & Hatfull, 2017; Wu et al., 2023)
* 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
  + importance of focusing on **conserved** viral **epitopes**; universal flu vaccine? (Wang et al., 2022) (back to the *mutational spectrum*)
* back to bacteria: vaccine-preventable *Bordetella pertussis*, resurgence and evolution of immune evasion (?) (van Gent et al., 2012)

(**to be added, maybe**)

## malaria control

[Twitter](https://twitter.com/ProfDavidLSmith/status/1504110201875562504):

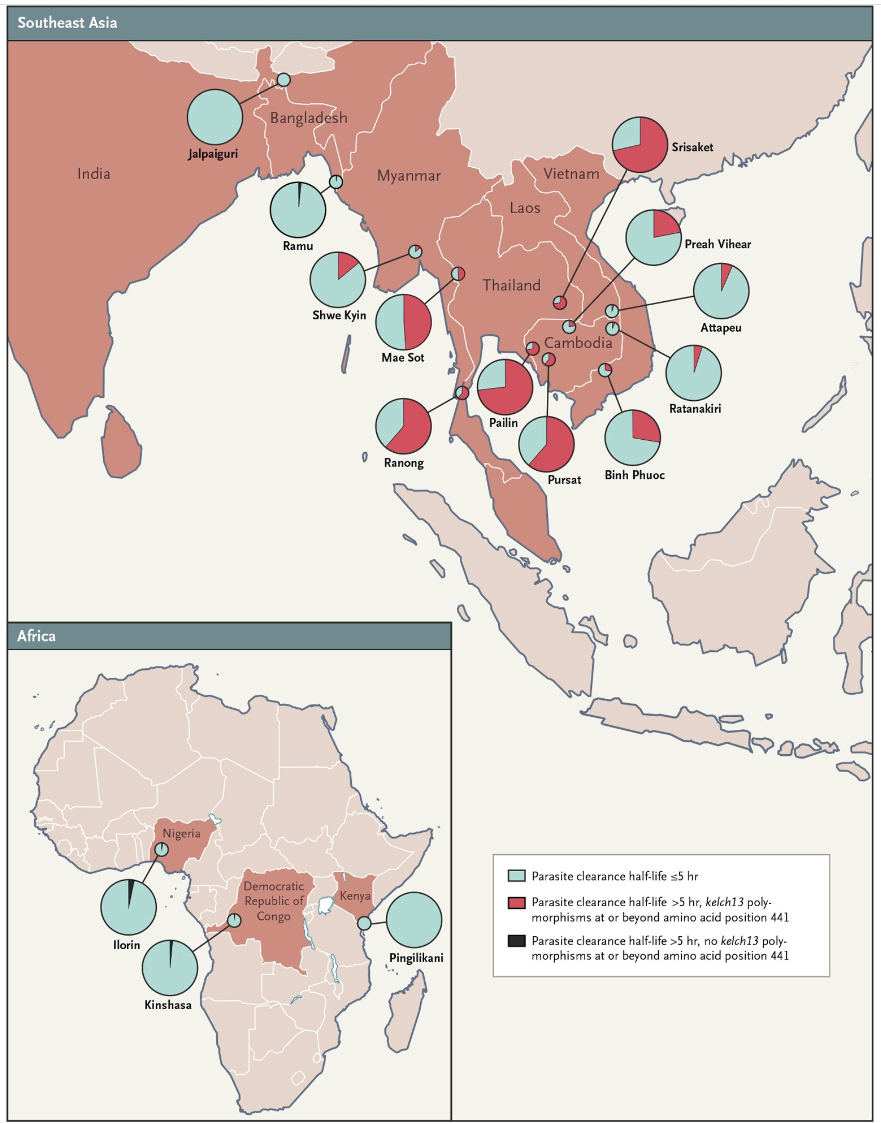
reading various malaria documents that discuss having endemic malaria today despite spending ~$4.1B/yr, I always want to insert the comment, “Well, WTF did you expect? No one who understands malaria believes elimination would be possible without spending at least $10B/yr”

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)

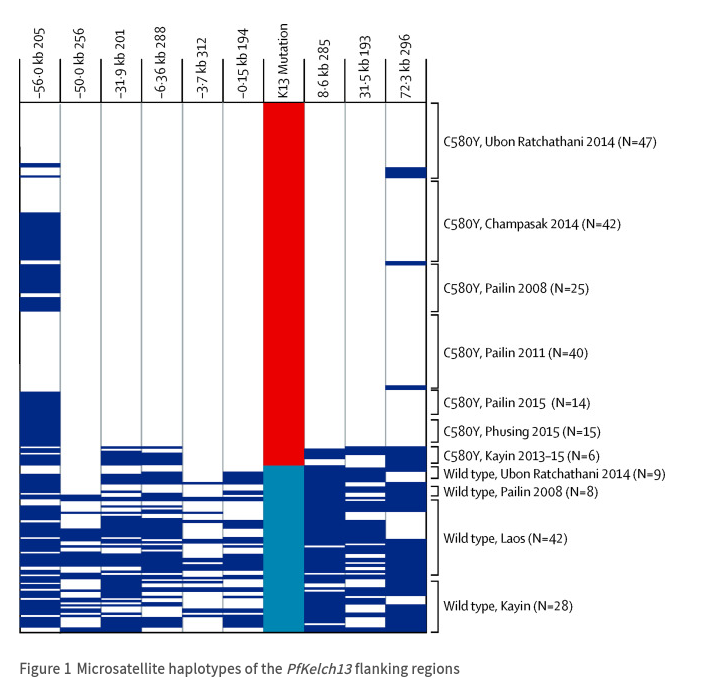
## malaria resistance to antimalarial drugs

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



From Ashley et al. (2014)

Rosenthal (2021): “Recent data suggest that we are on the verge of clinically meaningful artemisinin-resistance in Africa”



From Imwong et al. (2017). Red box=C580Y. Light blue box=wild type. Each row represents one parasite isolate; white cells indicate identical microsatellite alleles compared with the most frequent allele and dark blue cells indicate differences. containment strategies: eliminate *falciparum* malaria from Greater Mekong region or “firewall”?

## vectors and resistance to insecticides

* DDT [Wikipedia](https://en.wikipedia.org/wiki/DDT#Mosquito_resistance)
  + 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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