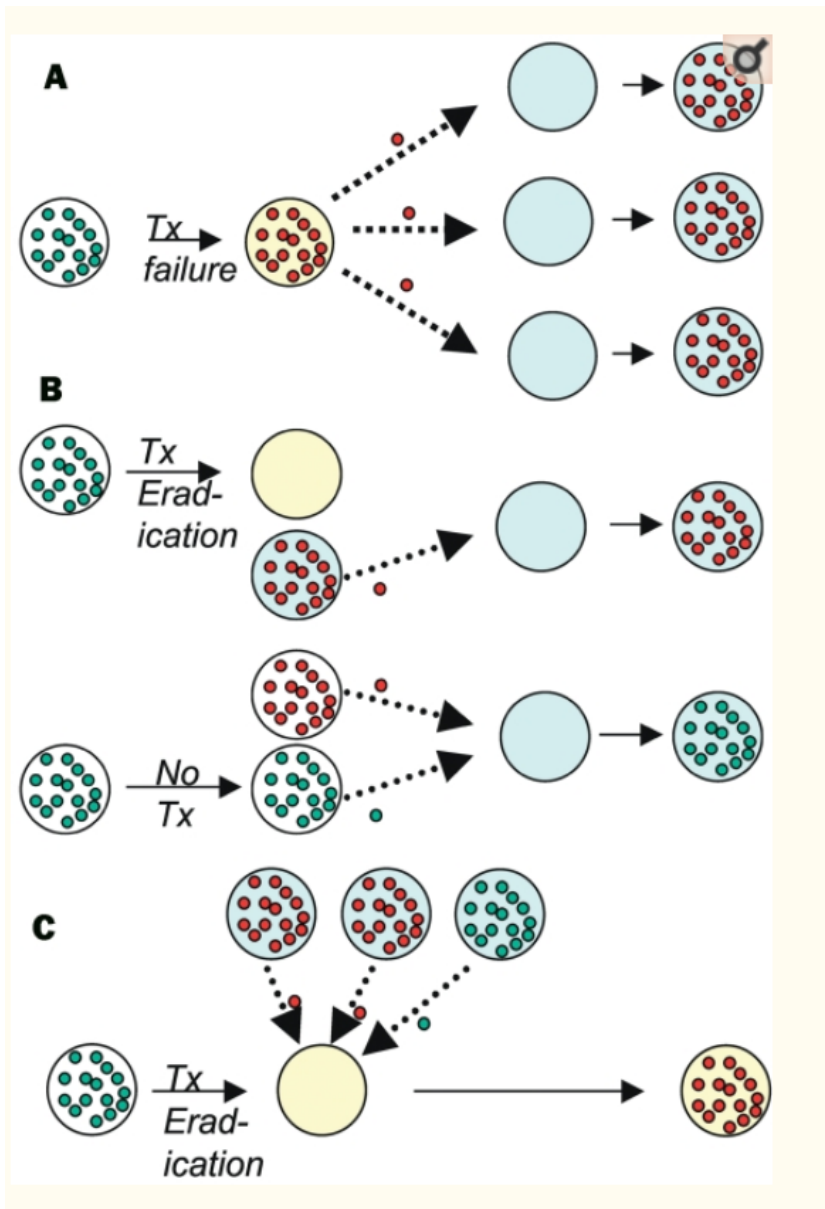


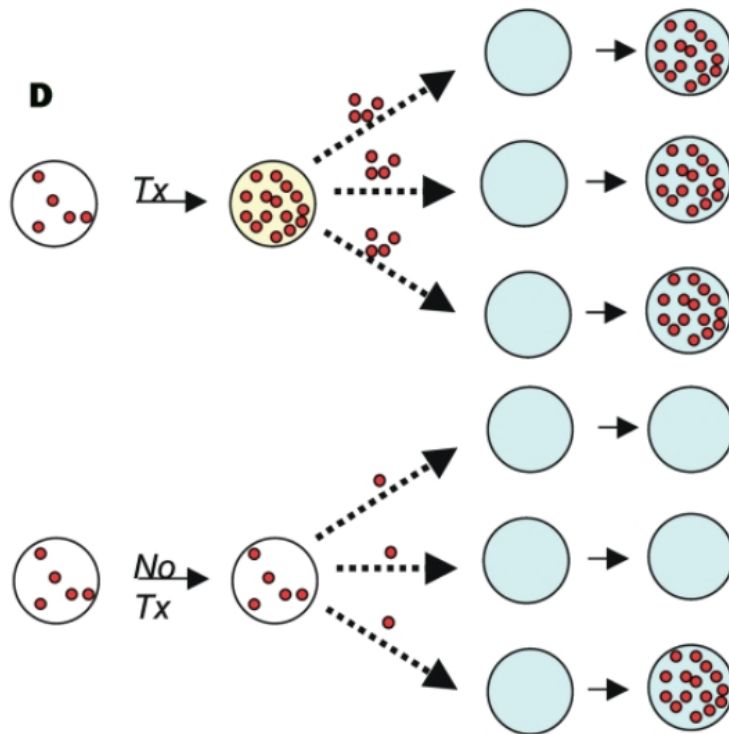
evolution of parasite countermeasures

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 & Samore, 2002)
-





Bacteria

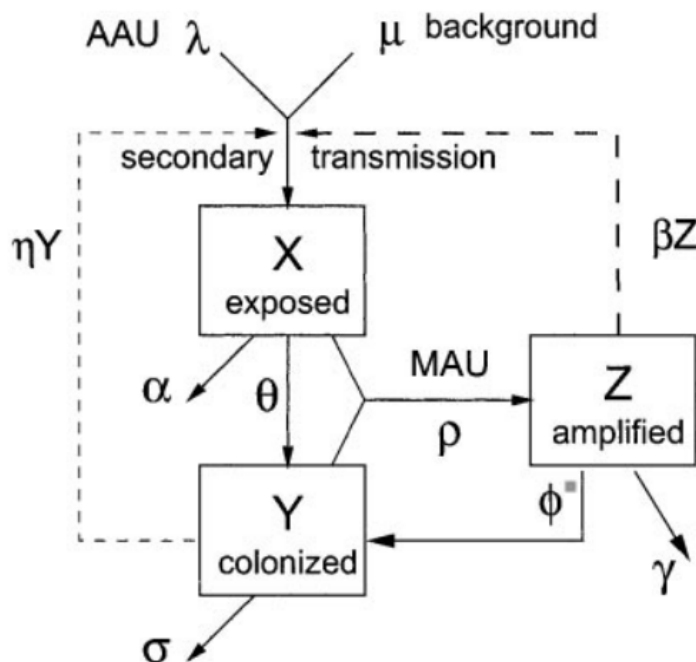
Mechanisms

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

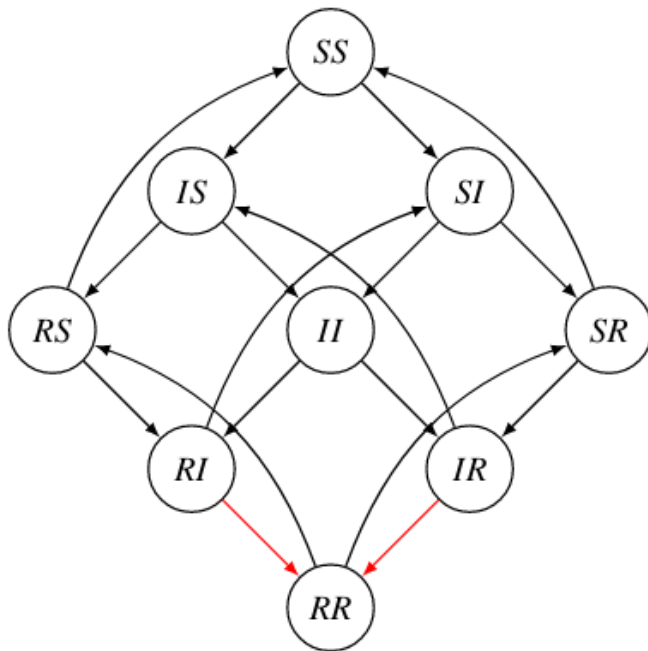


- but regulation still helps with spillover infections (Lipsitch et al., 2002)

- “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 (Eggleston & 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:

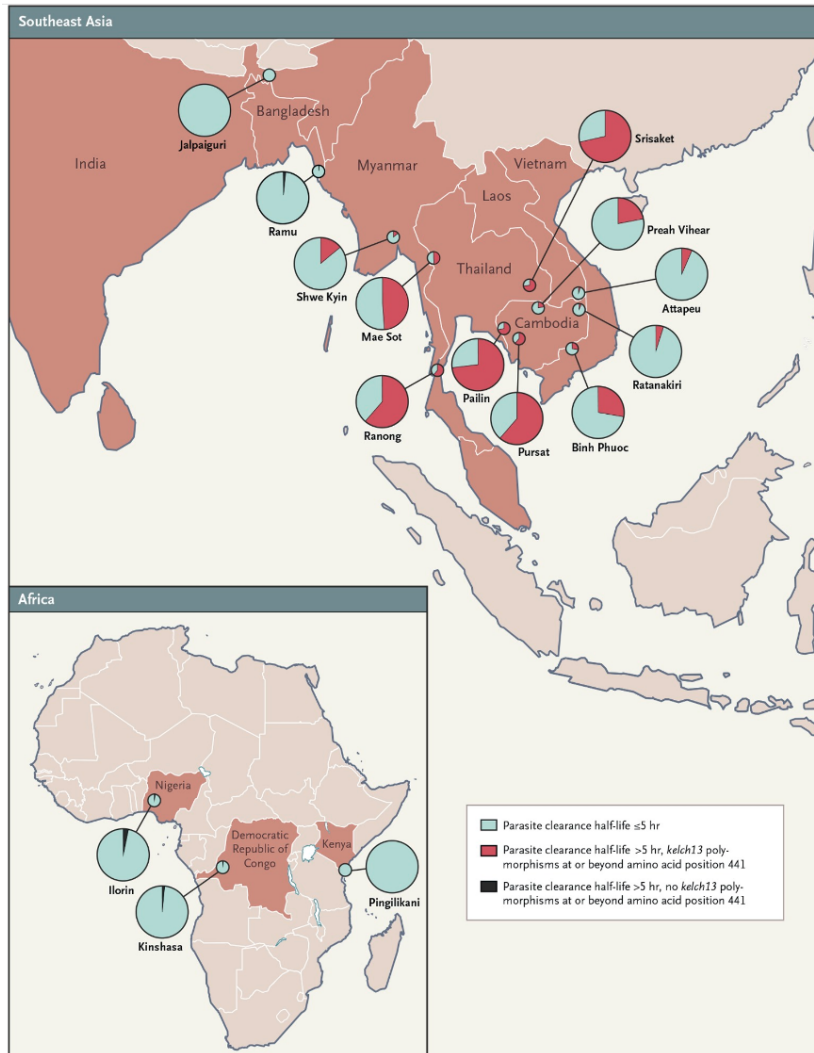
reading various malaria documents that discuss having endemic malaria today despite spending ~\$4.1B/yr, I always want to insert the comment, “Well, WTF did you expect? No one who understands malaria believes elimination would be possible without spending at least \$10B/yr”

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)



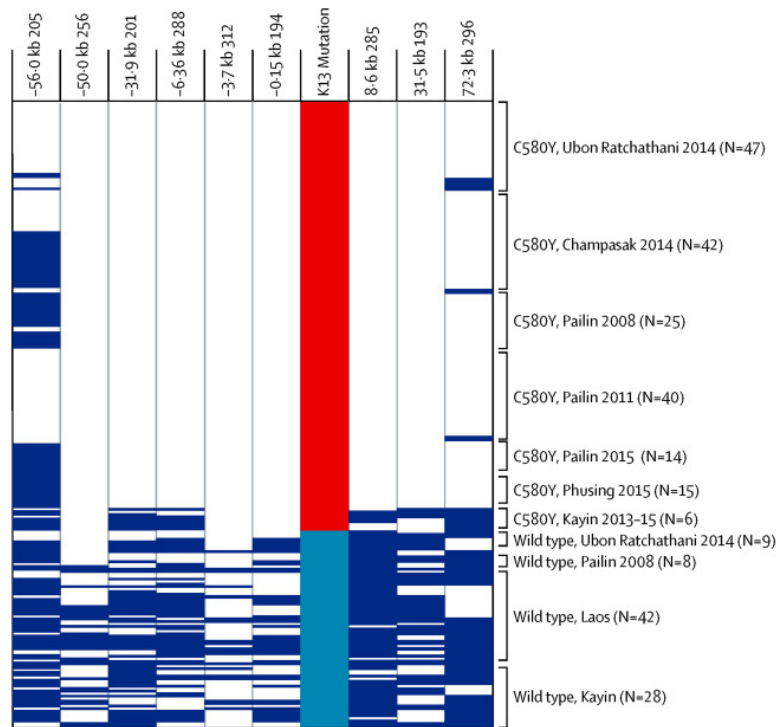


Figure 1 Microsatellite haplotypes of the *PfKelch13* flanking regions

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 (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

References

- Achan, J., Talisuna, A. O., Erhart, A., Yeka, A., Tibenderana, J. K., Baliraine, F. N., Rosenthal, P. J., & D'Alessandro, U. (2011). Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. *Malaria Journal*, 10(1), 144. <https://doi.org/10.1186/1475-2875-10-144>
- Adam, H. J., Richardson, S. E., Jamieson, F. B., Rawte, P., Low, D. E., & Fisman, D. N. (2010). Changing epidemiology of invasive *Haemophilus influenzae* in Ontario, Canada: Evidence for herd effects and strain replacement due to Hib vaccination. *Vaccine*, 28(24), 4073–4078. <https://doi.org/10.1016/j.vaccine.2010.03.075>
- Ashley, E. A., Dhorda, M., Fairhurst, R. M., Amaratunga, C., Lim, P., Suon, S., Sreng, S., Anderson, J. M., Mao, S., Sam, B., Sopha, C., Chuor, C. M., Nguon, C., Sovannaroeth, S., Pukrittayakamee, S., Jittamala, P., Chotivanich, K., Chutasmit, K., Suchatsoonthorn, C., ... White, N. J. (2014). Spread of Artemisinin Resistance in *Plasmodium falciparum* Malaria. *New England Journal of Medicine*, 371(5), 411–423. <https://doi.org/10.1056/NEJMoa1314981>
- Atyame, C. M., Labbé, P., Lebon, C., Weill, M., Moretti, R., Marini, F., Gouagna, L. C., Calvitti, M., & Tortosa, P. (2016). Comparison of irradiation and Wolbachia based approaches for sterile-male strategies targeting *Aedes albopictus*. *PLOS ONE*, 11(1), e0146834. <https://doi.org/10.1371/journal.pone.0146834>
- Benveniste, R., & Davies, J. (1973). Aminoglycoside Antibiotic-Inactivating Enzymes in Actinomycetes Similar to Those Present in Clinical Isolates of Antibiotic-Resistant Bacteria. *Proceedings of the National Academy of Sciences*, 70(8), 2276–2280. <https://doi.org/10.1073/pnas.70.8.2276>
- Bergstrom, C. T., Lo, M., & Lipsitch, M. (2004). Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proceedings of the National Academy of Sciences*, 101(36), 13285–13290. <https://doi.org/10.1073/pnas.0402298101>
- Bjorkholm, B., Sjölund, M., Falk, P. G., Berg, O. G., Engstrand, L., & Andersson, D. I. (2001). Mutation frequency and biological cost of antibiotic resistance in *Helicobacter pylori*. *Proceedings of the National Academy of Sciences of the United States of America*, 98(25), 14607–14612. <https://doi.org/10.1073/pnas.241517298>
- Bonhoeffer, S., Coffin, J. M., & Nowak, M. A. (1997a). Human immunodeficiency virus drug therapy and virus load. *Journal of Virology*, 71(4), 3275–3278. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC191463/>

- Bonhoeffer, S., Lipsitch, M., & Levin, B. R. (1997b). Evaluating treatment protocols to prevent antibiotic resistance. *Proceedings of the National Academy of Sciences*, 94(22), 12106–12111. <https://doi.org/10.1073/pnas.94.22.12106>
- Burt, A., Coulibaly, M., Crisanti, A., Diabate, A., & Kayondo, J. K. (2018). Gene drive to reduce malaria transmission in sub-Saharan Africa. *Journal of Responsible Innovation*, 5(sup1), S66–S80. <https://doi.org/10.1080/23299460.2017.1419410>
- Centers for Disease Control. (2020). *Extensively Drug-Resistant Tuberculosis (XDR TB)*. <https://www.cdc.gov/tb/publications/factsheets/drtb/xdrtb.htm>
- Covert, C., Ding, L., Brown, D., Franco, E. L., Bernstein, D. I., & Kahn, J. A. (2019). Evidence for cross-protection but not type-replacement over the 11 years after human papillomavirus vaccine introduction. *Human Vaccines & Immunotherapeutics*.
- D’Costa, V. M., King, C. E., Kalan, L., Morar, M., Sung, W. W. L., Schwarz, C., Froese, D., Zazula, G., Calmels, F., Debruyne, R., Golding, G. B., Poinar, H. N., & Wright, G. D. (2011). Antibiotic resistance is ancient. *Nature*, 477(7365), 457–461. <https://doi.org/10.1038/nature10388>
- Dennison, N. J., Jupatanakul, N., & Dimopoulos, G. (2014). The mosquito microbiota influences vector competence for human pathogens. *Current Opinion in Insect Science*, 3, 6–13. <https://doi.org/10.1016/j.cois.2014.07.004>
- Ebmeyer, S., Kristiansson, E., & Larsson, D. G. J. (2021). A framework for identifying the recent origins of mobile antibiotic resistance genes. *Communications Biology*, 4(1), 1–10. <https://doi.org/10.1038/s42003-020-01545-5>
- Eggleton, J. S., & Nagalli, S. (2022). Highly Active Antiretroviral Therapy (HAART). In *StatPearls*. StatPearls Publishing. <http://www.ncbi.nlm.nih.gov/books/NBK554533/>
- Ferguson, N., Ghani, A., Cori, A., Hogan, A., Hinsley, W., & Volz, E. (2021). Report 49 - Growth, population distribution and immune escape of Omicron in England. In *Imperial College London*. <http://www.imperial.ac.uk/medicine/departments/school-public-health/infectious-disease-epidemiology/mrc-global-infectious-disease-analysis/covid-19/report-49-omicron/>
- Gent, M. van, Bart, M. J., Heide, H. G. J. van der, Heuvelman, K. J., & Mooi, F. R. (2012). Small Mutations in *Bordetella pertussis* Are Associated with Selective Sweeps. *PLOS ONE*, 7(9), e46407. <https://doi.org/10.1371/journal.pone.0046407>
- Gladwell, M. (2001). The Mosquito Killer. *The New Yorker*. <https://web.archive.org/web/20160416165010/http://gladwell.com/the-mosquito-killer/>

- Jarry, J. (2021). The Malaria Vaccine's Success Story Hides Legitimate Concerns. In *McGill University Office for Science and Society*. <https://www.mcgill.ca/oss/article/health-and-nutrition/malaria-vaccines-success-story-hides-legitimate-concerns>
- Karwehl, S., & Stadler, M. (2016). Exploitation of Fungal Biodiversity for Discovery of Novel Antibiotics. In M. Stadler & P. Dersch (Eds.), *How to Overcome the Antibiotic Crisis : Facts, Challenges, Technologies and Future Perspectives* (pp. 303–338). Springer International Publishing. https://doi.org/10.1007/82_2016_496
- Koella, J. C., Lynch, P. A., Thomas, M. B., & Read, A. F. (2009). Towards evolution-proof malaria control with insecticides. *Evolutionary Applications*, 2(4), 469–480. <https://doi.org/10.1111/j.1752-4571.2009.00072.x>
- Levin, B. R., Perrot, V., & Walker, N. (2000). Compensatory mutations, antibiotic resistance and the population genetics of adaptive evolution in bacteria. *Genetics*, 154(3), 985–997.
- Lipsitch, M., & Samore, M. H. (2002). Antimicrobial Use and Antimicrobial Resistance: A Population Perspective. *Emerging Infectious Diseases*, 8(4), 347–354. <https://doi.org/10.3201/eid0804.010312>
- Lipsitch, M., Singer, R. S., & Levin, B. R. (2002). Antibiotics in agriculture: When is it time to close the barn door? *Proceedings of the National Academy of Sciences of the United States of America*, 99(9), 5752–5754. <https://doi.org/10.1073/pnas.092142499>
- Llewelyn, M. J., Fitzpatrick, J. M., Darwin, E., SarahTonkin-Crine, Gorton, C., Paul, J., Peto, T. E. A., Yardley, L., Hopkins, S., & Walker, A. S. (2017). The antibiotic course has had its day. *BMJ*, 358, j3418. <https://doi.org/10.1136/bmj.j3418>
- Man, I., Vänskä, S., Lehtinen, M., & Bogaards, J. A. (2021). Human papillomavirus genotype replacement: Still too early to tell? *The Journal of Infectious Diseases*, 224(3), 481–491.
- McMeniman, C. J., Lane, R. V., Cass, B. N., Fong, A. W. C., Sidhu, M., Wang, Y.-F., & O'Neill, S. L. (2009). Stable introduction of a life-shortening Wolbachia infection into the mosquito *Aedes aegypti*. *Science*, 323(5910), 141–144. <https://doi.org/10.1126/science.1165326>
- Medawar, P. B. (2019). *The Uniqueness of the Individual*. Routledge. <https://doi.org/10.4324/9780429299759>
- Musiime, A. K., Krezanoski, P. J., Smith, D. L., Kilama, M., Conrad, M. D., Otto, G., Kyagamba, P., Asimwe, J., Rek, J., Nankabirwa, J. I., Arinaitwe, E., Akol, A. M., Kamya, M. R., Staedke, S. G., Drakeley, C., Bousema, T., Lindsay, S. W., Dorsey, G., & Tusting, L. S. (2022). House design and risk of malaria, acute respiratory infection and gastrointestinal illness in Uganda: A cohort study.

PLOS Global Public Health, 2(3), e0000063. <https://doi.org/10.1371/journal.pgph.0000063>

Seo, M. K., Baker, P., & Ngo, K. N.-L. (2014). Cost-effectiveness analysis of vaccinating children in Malawi with RTS,S vaccines in comparison with long-lasting insecticide-treated nets. *Malaria Journal*, 13(1), 66. <https://doi.org/10.1186/1475-2875-13-66>

Smith, D. L., Harris, A. D., Johnson, J. A., Silbergeld, E. K., & Morris, J. G. (2002). Animal antibiotic use has an early but important impact on the emergence of antibiotic resistance in human commensal bacteria. *Proceedings of the National Academy of Sciences of the United States of America*, 99(9), 6434–6439. <https://doi.org/10.1073/pnas.082188899>

South Africa National Department of Health, R. of. (2019). *2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates*. <https://www.nicd.ac.za/wp-content/uploads/2019/11/2019-ART-Clinical-Guidelines-25-Nov.pdf>

Last updated: 2022-03-20 21:21:46