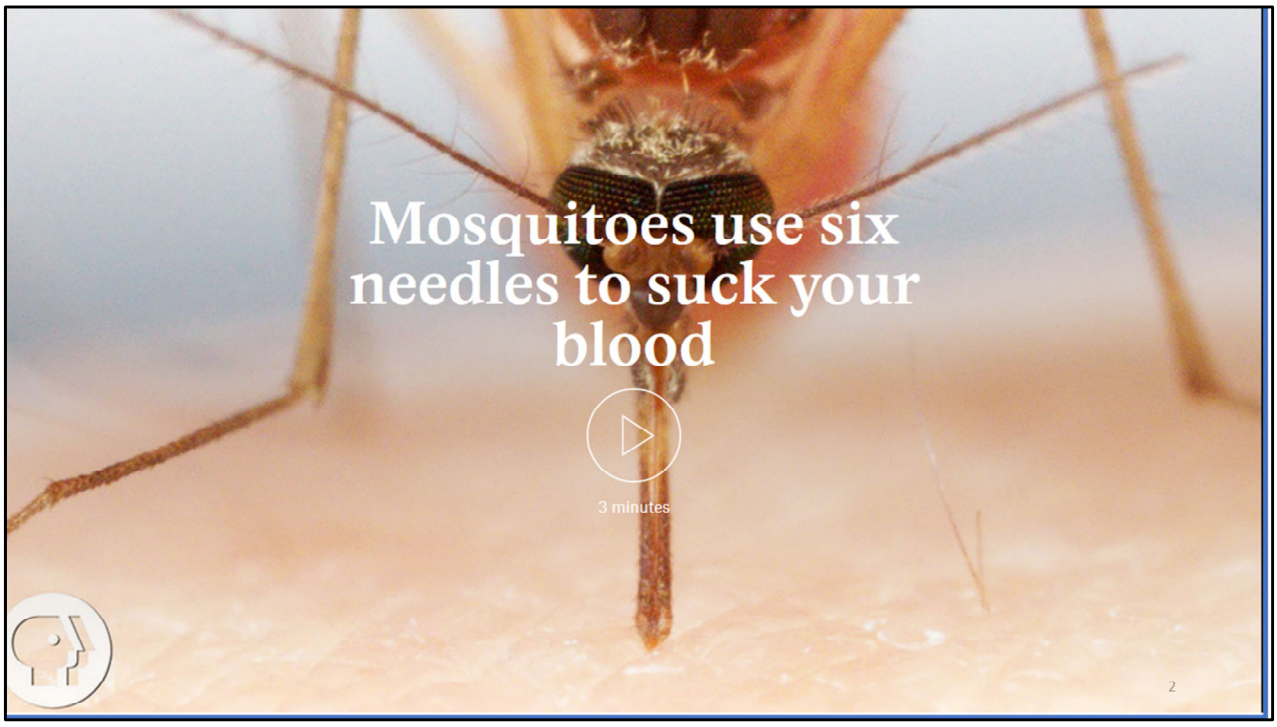
Mosquitoes feed on a wide variety of animals, not just mammals, even some arthropods (caterpillar, left) and reptiles (snake, right). These in the photo are all different species from those that bite us. This reflects the diverse evolutionary histories and ecological roles of mosquitoes.

These images are meant to convey that they are highly successful organisms from an evolutionary and ecological point of view.

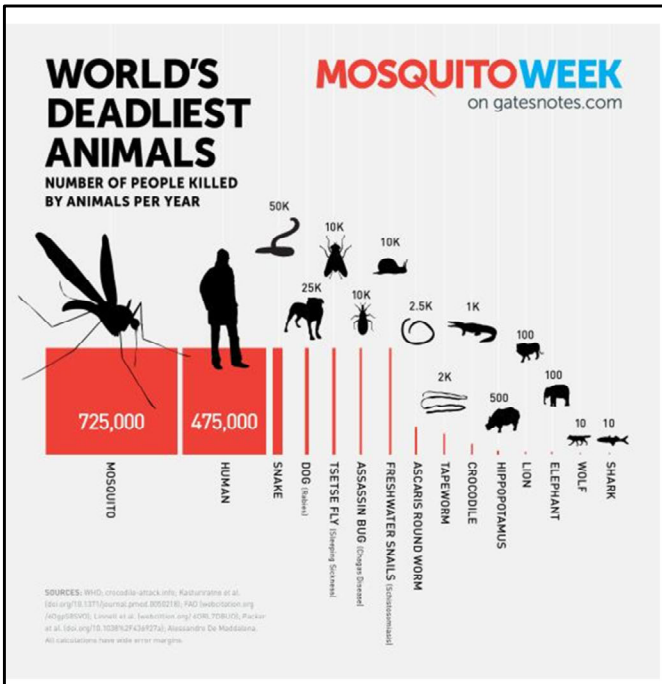


https://aeon.co/videos/what-makes-mosquitoes-so-good-at-getting-under-our-skin

The global mosquito

- Of the millions of insect species, only a tiny fraction of them, less than 1%, are pests.
- A vast majority are beneficial to humans
- 3000 species of mosquito – most feed on nectar of plants
- 100 mosquito species transmit diseases to humans and sicken millions annually
- Half of the global population is at risk of mosquito-born disease

http://www.nytimes.com/2014/08/24/opinion/sunday/bug-love.html




The Mosquitoes Are Coming for Us

They are our apex predator, the deadliest hunters of human beings on the planet.

By Timothy C. Winegard

July 27, 2019

Share unlocked article

https://twitter.com/gatesfoundation/status/461853846458089473

https://www.nytimes.com/2019/07/27/opinion/sunday/mosquitoes-malaria-zika-history.html

Arboviruses transmitted by mosquitoes

- Dengue virus
- Yellow fever virus
- West Nile virus
- La Crosse virus
- St. Louis virus
- Chikungunya virus
- Zika virus
- Oropouche virus – transmitted mainly by midges (gnats)

5

Fang, J. (2010). Ecology: a world without mosquitoes. *Nature News*, *466*(7305), 432-434.

Arboviruses are transmitted by insects

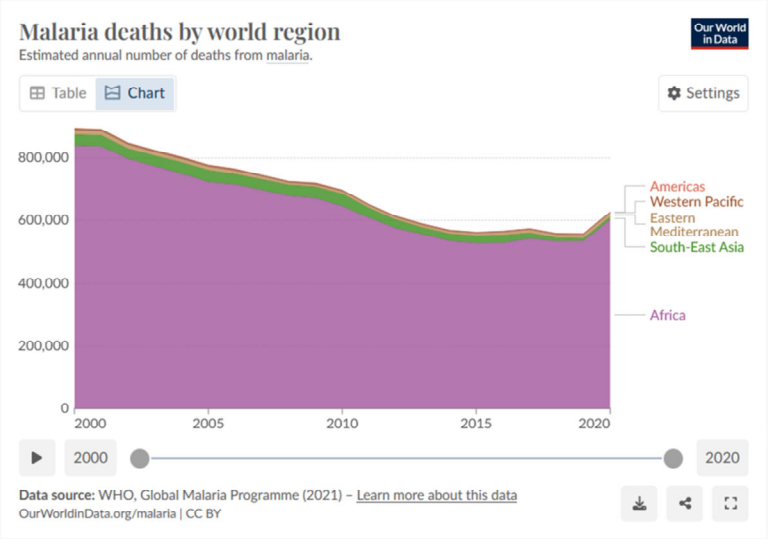
Malaria

- Caused by parasitic protist *Plasmodium* transmitted by the *Anopheles* mosquito
- Globally, 249 million malaria cases in 2022, 608,000 malaria deaths
- Nearly half of the world's population at risk for infection.
- In many of the countries affected by malaria, it is the leading cause of death

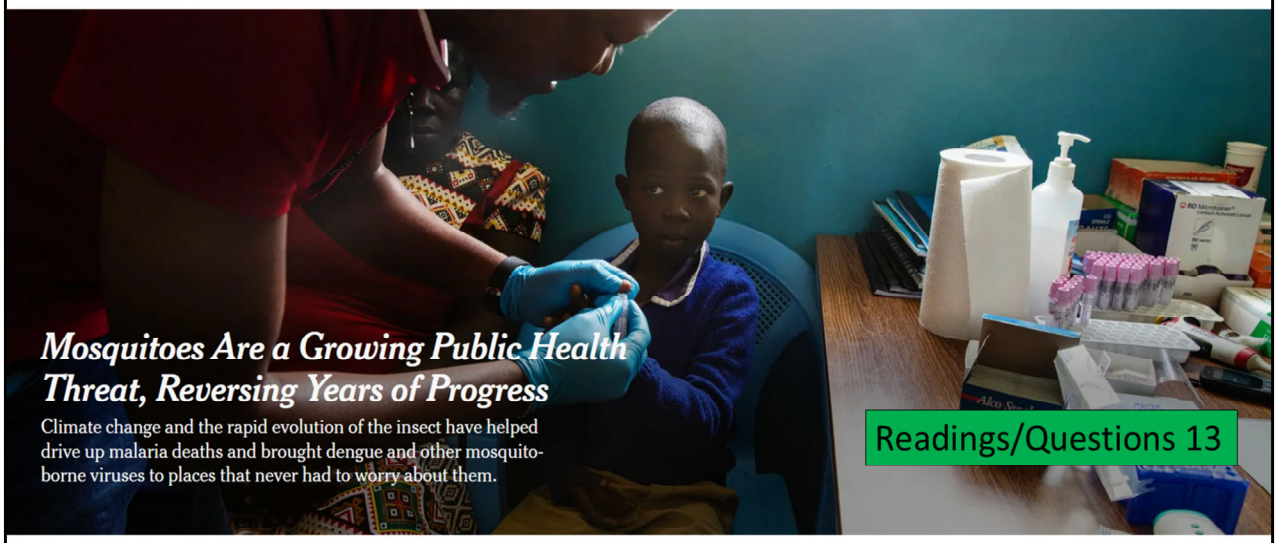
Malaria is a mosquito-borne disease caused by parasites of the genus *Plasmodium* (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*) and acquired through the bites of infected Anopheles mosquitos. With an incubation period of 10 to 15 days after the infective mosquito bite, the disease manifests with fever, chills, headaches, vomiting and tiredness. Although the disease is preventable and treatable, untreated malaria is typically associated with anemia and splenomegaly (enlarged spleen). In particular, *P. falciparum* cases commonly progress to life-threatening conditions including “cerebral malaria”, organ dysfunction and death.

https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021

- Most deaths are among young children in sub-Saharan Africa.
- Expansion of interventions and development of new malaria prevention technologies have saved millions of lives globally and cut malaria mortality by 36% from 2010 to 2020
- However, the last few years have seen a plateau in progress



https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021



https://www.nytimes.com/2023/09/29/health/mosquitoes-malaria-disease-climate-change.html

ANOPHELES		AEDES MOSQUITO
Malaria	Diseases spread	Dengue, Yellow Fever, Chikungunya, Lymphatic filariasis
Pregnant females	Which mosquitoes bite?	Pregnant females
Night	When do they bite?	Day
With abdomen sticking upwards	Resting position	Lies parallel to resting surface
Predominantly rural	Location	Predominantly urban
Bodies of water	Breeding ground	Shallow water surfaces

SOURCE: Centers for Disease Control and Prevention

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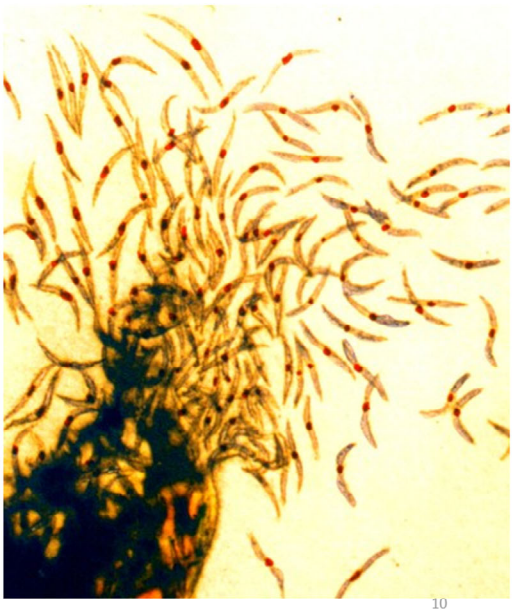
The genus *Plasmodium*

- Includes more than 200 different species that parasitize various hosts such as reptiles, birds, amphibians, and mammals
- 53 species parasitize mammals, of which 30 species parasitize primates.
- To date, six *Plasmodium* species have been identified as human pathogens
- A human can be infected with one or more different species of *Plasmodium* at the same time, or in sequence.



10

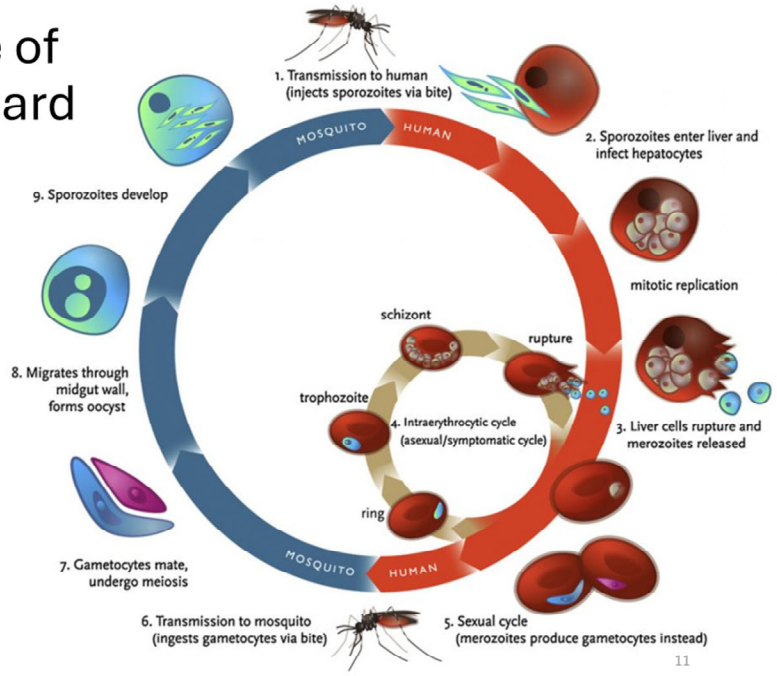
https://doi.org/10.1002/bies.201900138

Gitta, B., & Kilian, N. (2020). Diagnosis of Malaria Parasites Plasmodium spp. in Endemic Areas: Current Strategies for an Ancient Disease. *BioEssays*, *42*(1), 1900138.

Sporozoites, one of several different forms of the parasite, from a mosquito (right)

Complex life cycle of malaria makes it hard to eradicate

- Two stages of the life cycle, one inside the mosquito and one inside the human
- Some *Plasmodium* species can even regulate its abundance in the human body so that it remains low until the rainy season comes



11

The malaria parasite's complex life cycle and shifting surface proteins have challenged vaccine developers. But an alternative question is, why do some people live in conditions of poverty in which malaria is so rampant, while others do not and live in relative wealth and absence of malaria.

Malaria: the epidemic of the poor

- Malaria is constrained by climate, but it also has political, social and economic factors that dictate its prevalence
- The impact of malaria takes its toll on the poorest, those least able to afford preventative measures and medical treatment.
- Malaria contributes to poverty through lost productivity or income associated with illness or death.
- The countries affected by malaria are often unable to assume the economic burden it imposes, which may in some parts of the world be a legacy of colonialism

.

12

Mobility of people challenges malaria control

- Endemic malaria: malaria is established and being transmitted person-to-person
- Imported or non-local malaria: travelers bring it back but the parasite does not get transmitted by mosquito
- Local malaria: malaria is transmitted via mosquito from a traveler to someone living in the country that did not travel

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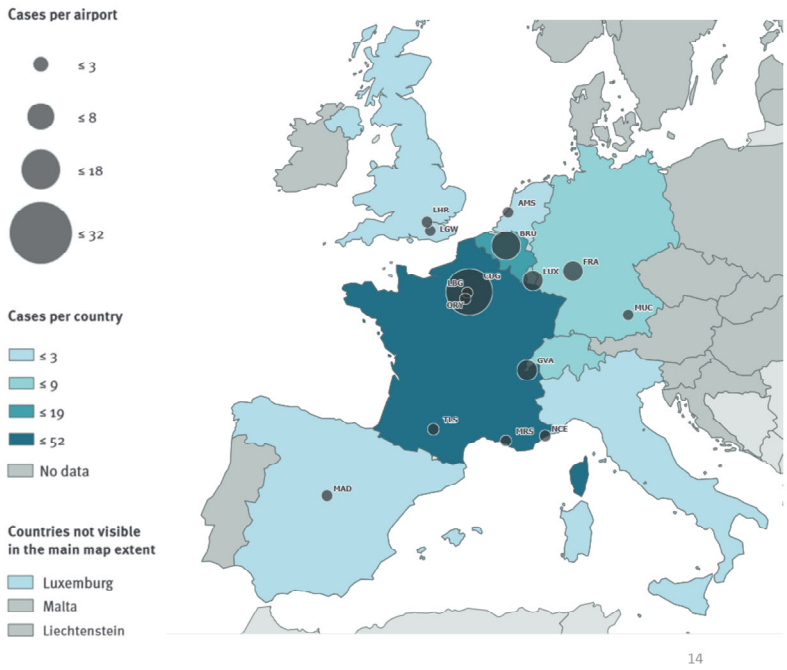
https://www.nytimes.com/2017/04/24/health/fatal-malaria-united-states.html

How malaria deaths occur in the US, as based on the above NY Times article:

Although the study was based on hospital data rather than interviews with patients, the authors suspect that many of the victims grew up in malarial areas, developed immunity in childhood from repeated infections, and then did not realize that their childhood immunity had disappeared after years in the United States. "They just think they're going home, so they don't have to prepare for anything," Dr. Khuu said. The fact that malaria immunity wanes after a few years away from repeated exposure is well-known to malaria experts, but not common knowledge, so immigrants may not get prescriptions for anti-malaria drugs before traveling or sleep under mosquito nets in a malarial area.

Airport and luggage malaria

- Infrequent, but does occur
- Mosquitoes transported in airplane cabins or in luggage
- Location of local malaria cases tend to cluster around international airports in Europe



14

Amsterdam airport Schiphol (AMS, n = 3), Brussels airport (BRU, n = 18), Charles de Gaulle airport (CDG, n = 32), Frankfurt airport (FRA, n = 8), Geneva airport (GVA, n = 5), Paris–Le Bourget airport (LBG, n = 3), London Gatwick airport (LGW, n = 2), London Heathrow airport (LHR, n= 2), Luxembourg airport (LUX, n = 5), Madrid–Barajas airport (MAD, n = 1), Marseille Provence airport (MRS, n = 2), Munich airport (MUC, n = 1), Nice Côte d'Azur airport (NCE, n = 1), Paris-Orly airport (ORY, n = 3), Toulouse Blagnac airport (TLS, n = 2).

Hallmaier-Wacker, Luisa K., Merel D. van Eick, Olivier Briët, Hugues Delamare, Gerhard Falkenhorst, Sandrine Houzé, Harold Noël, Javiera Rebolledo, Wim Van Bortel, and Céline M. Gossner. "Airport and luggage (Odyssean) malaria in Europe: a systematic review." *Eurosurveillance* 29, no. 41 (2024): 2400237.

Sri Lanka eliminated **endemic** malaria in 2012 and certified as malaria free in 2016

- **Imported** malaria cases are regularly reported, but no **local** transmission until 2018
- In 2018, laborer from India traveled to Sri Lanka to work at a construction site. A month after arrival he became ill with malaria. The stage of his malarial infection indicated he was already infected when he arrived in Sri Lanka (**non-local malaria**).
- A Sri Lankan salesman visited the same construction site few weeks after the laborer. Twelve days after his return to the capital city Colombo, he developed malaria, which was initially misdiagnosed.
- 100% genetic identity in the parasite in both patients, strongly suggesting that both patients were infected with the same *Plasmodium* strain carried by a mosquito at the construction site
- Transmission stopped with the salesman because of timely public health response. There is still no endemic malaria in Sri Lanka, but imported, non-local cases still occur.

15

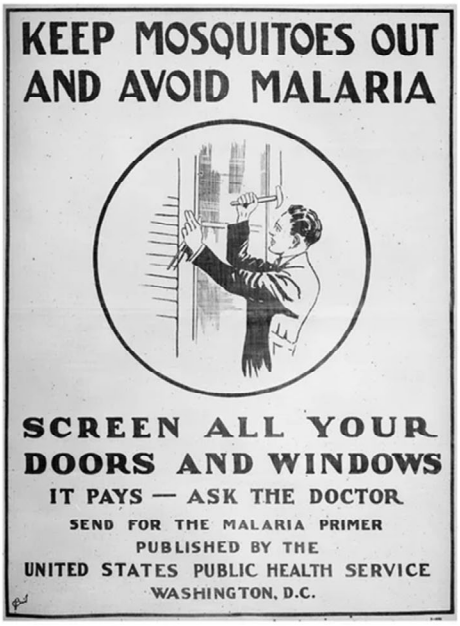
This slide illustrates the constant threat of malarial reintroduction either through endemic transmission or in this case through imported malaria.

Karunasena, V. M., Marasinghe, M., Koo, C., Amarasinghe, S., Senaratne, A. S., Hasantha, R., ... & Mendis, K. N. (2019). The first introduced malaria case reported from Sri Lanka after elimination: implications for preventing the re-introduction of malaria in recently eliminated countries. *Malaria Journal*, *18*(1), 210.

https://doi.org/10.1186/s12936-019-2843-6

Imported malaria in the US

- Malaria officially eradicated from US in 1951
- Non-local malaria arrives in US regularly via travelers infected abroad in malaria-endemic area
- A few cases since 1951 saw malaria become locally-acquired, when a mosquito in the US bit a traveler with malaria and then bit someone who had not left the US and gave them malaria



Locally acquired malaria in the USA in 2023

- *Florida*: Seven cases of *Plasmodium vivax* malaria
- *Texas*: One case of *Plasmodium vivax* malaria
- *Maryland*: One case of *Plasmodium falciparum*
- *Arkansas*: One case of *Plasmodium vivax* malaria
- The last case of locally acquired malaria in the United States before the 2023 cases occurred in 2003
- Despite these occurrences, the overall risk of locally acquired malaria in the United States remains very low.

17

Mobility of mosquitoes also challenges control and eradication

- These dispersals can be natural or they can be through movement of mosquitoes through shipping and transportation
- As many as 17 nonnative mosquito species are established in the state. 11 of 17 nonnative species first reported in the past two decades, and six of these 17 detected in only the past five years
- Many have the potential to transmit arboviruses – but no introduced mosquito can transmit malaria, only three native Anopheles mosquitos can

18

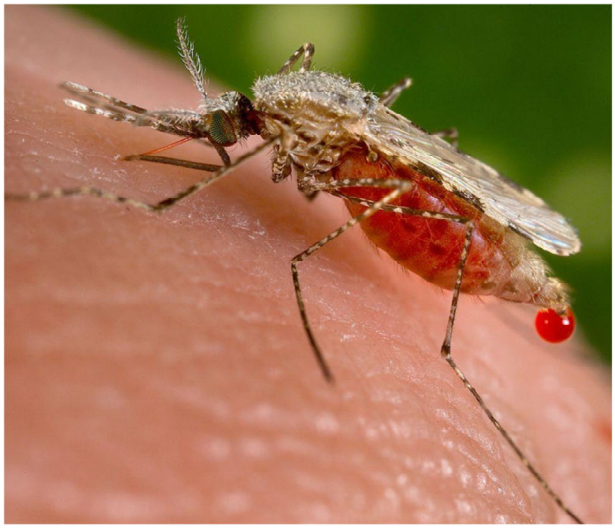
https://pulitzercenter.org/stories/new-mosquito-bringing-disease-north-America

https://blogs.ifas.ufl.edu/news/2023/03/22/uf-ifas-study-new-mosquito-species-reported-in-florida/

https://www.nytimes.com/2023/09/29/health/mosquitoes-stephensi-malaria-africa.html

Anopheles stephensi

- *Anopheles stephensi* prefers to feed on non-human animals (zoophilic) but also is flexible in its feeding behaviors and will bite humans if no other prey available
- Also prefers to nest in poorly constructed buildings or animal sheds, structures characteristic of unplanned urban sites found around and within many rapidly expanding cities in Africa.
- It has also evolved to bite during the day
- *Anopheles stephensi* is likely to colonize rapidly urbanizing cities across Africa
- 126 million people living in African cities could be at risk of malaria if *A. stephensi* continues to spread across the continent.



20

Range expansion of mosquitos and plastic behavior also make malarial control difficult, as exemplified by A. stephensi, shown in photo.

Surendran, S. N., Sivabalakrishnan, K., Sivasingham, A., Jayadas, T. T., Karvannan, K., Santhirasegaram, S., ... & Ramasamy, R. (2019). Anthropogenic factors driving recent range expansion of the malaria vector Anopheles stephensi. *Frontiers in Public Health*, *7*, 53.

Sinka, M. E., Pironon, S., Massey, N. C., Longbottom, J., Hemingway, J., Moyes, C. L., & Willis, K. J. (2020). A new malaria vector in Africa: Predicting the expansion range of Anopheles stephensi and identifying the urban populations at risk. *Proceedings of the National Academy of Sciences*, *117*(40), 24900-24908.

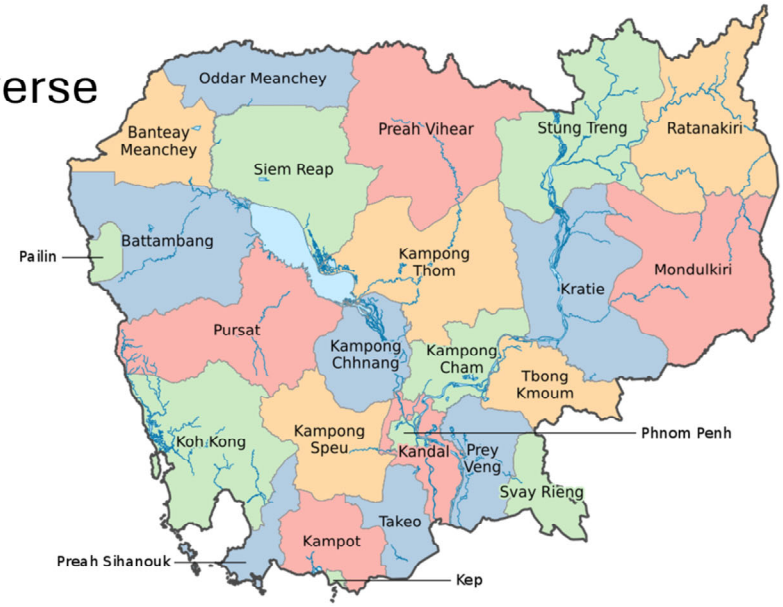
Malaria is surging in Ethiopia and reversing a decade of progress

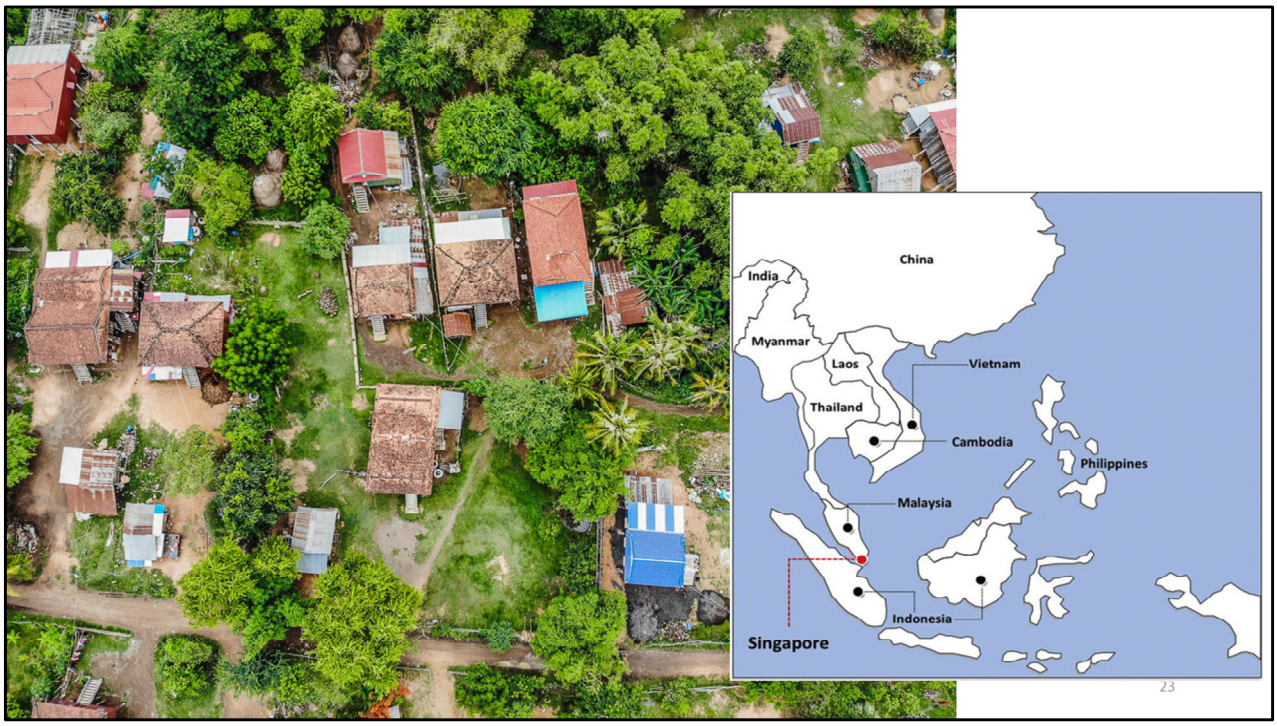
- Armed conflict:
  - Humanitarian agencies have been unable to distribute bed nets, medications or diagnostic tests.
  - People are displaced, homeless and exposed to mosquitoes
  - Malaria travels out of these regions with refugees
- Climate change: highland areas that were too cool for mosquito or the parasite they carry are becoming warmer and wetter
- Increasing resistance to current drugs and insecticides
- The invasive Asian mosquito species Anopheles stephensi is becoming established

21

Mosquitoes are abundant and diverse

- Adult mosquitoes were collected at 24 primary schools during the rainy and dry seasons of 2017 and 2018 in Kampong Cham and Tboung Khmum provinces in Cambodia




China
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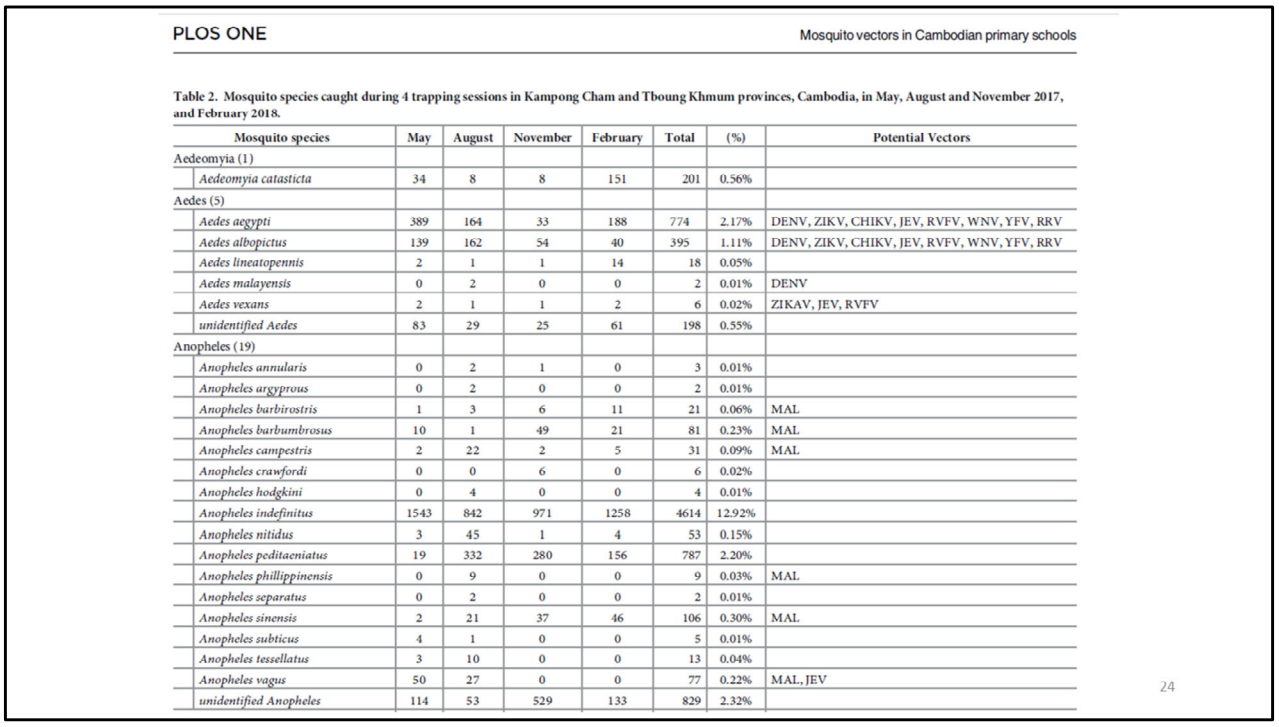
Vietnam
Thailand
Cambodia
Philippines
Malaysia
Indonesia
Singapore



PLOS ONE

Mosquito vectors in Cambodian primary schools

Table 2. Mosquito species caught during 4 trapping sessions in Kampong Cham and Tboung Khmum provinces, Cambodia, in May, August and November 2017, and February 2018.

Mosquito species	May	August	November	February	Total	(%)	Potential Vectors
Aedeomyia (1)							
Aedeomyia catasticta	34	8	8	151	201	0.56%	
Aedes (5)							
Aedes aegypti	389	164	33	188	774	2.17%	DENV, ZIKV, CHIKV, JEV, RVFV, WNV, YFV, RRV
Aedes albopictus	139	162	54	40	395	1.11%	DENV, ZIKV, CHIKV, JEV, RVFV, WNV, YFV, RRV
Aedes lineatopennis	2	1	1	14	18	0.05%	
Aedes malayensis	0	2	0	0	2	0.01%	DENV
Aedes vexans	2	1	1	2	6	0.02%	ZIKAV, JEV, RVFV
unidentified Aedes	83	29	25	61	198	0.55%	
Anopheles (19)							
Anopheles annularis	0	2	1	0	3	0.01%	
Anopheles argyprous	0	2	0	0	2	0.01%	
Anopheles barbirostris	1	3	6	11	21	0.06%	MAL
Anopheles barbumbrosus	10	1	49	21	81	0.23%	MAL
Anopheles campestris	2	22	2	5	31	0.09%	MAL
Anopheles crawfordi	0	0	6	0	6	0.02%	
Anopheles hodgkini	0	4	0	0	4	0.01%	
Anopheles indefinitus	1543	842	971	1258	4614	12.92%	
Anopheles nitidus	3	45	1	4	53	0.15%	
Anopheles peditaeniatus	19	332	280	156	787	2.20%	
Anopheles phillippinensis	0	9	0	0	9	0.03%	MAL
Anopheles separatus	0	2	0	0	2	0.01%	
Anopheles sinensis	2	21	37	46	106	0.30%	MAL
Anopheles subticus	4	1	0	0	5	0.01%	
Anopheles tessellatus	3	10	0	0	13	0.04%	
Anopheles vagus	50	27	0	0	77	0.22%	MAL, JEV
unidentified Anopheles	114	53	529	133	829	2.32%	

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Boyer, S., Marcombe, S., Yean, S., & Fontenille, D. (2020). High diversity of mosquito vectors in Cambodian primary schools and consequences for arbovirus transmission. *PLoS One*, *15*(6), e0233669.

Armigeres (1)								
	Armigeres subalbatus	185	108	53	43	389	1.09%	DENV, JEV
	Armigeres sp	1	1	2	22	26	0.07%	
Coquilletidia (2)								
	Coquillettidia crassipes	56	27	3	8	94	0.26%	
	Coquillettidia ochracea	4	23	3	5	35	0.10%	
	Coquillettidia sp1	1	7	2	1	11	0.03%	
Culex (15)								
	Culex bitaeniorhynchus	33	324	25	48	430	1.20%	JEV, RVFV
	Culex brevipalpis	678	360	146	73	1257	3.52%	
	Culex fuscocephala	35	106	90	354	585	1.64%	JEV
	Culex gelidus	27	228	110	546	911	2.55%	JEV, RRV
	Culex hutchinsoni	0	0	0	8	8	0.02%	
	Culex malayi	8	9	0	1	18	0.05%	
	Culex nigropunctatus	4	59	29	12	104	0.29%	
	Culex quinquefasciatus	1215	745	314	702	2976	8.33%	ZIKAV, JEV, RVFV, WNV, RRV
	Culex sinensis	0	28	0	0	28	0.08%	
	Culex sitiens	0	5	0	0	5	0.01%	
	Culex tritaeniorhynchus	150	320	49	33	552	1.55%	JEV, RVFV, WNV

25

Boyer, S., Marcombe, S., Yean, S., & Fontenille, D. (2020). High diversity of mosquito vectors in Cambodian primary schools and consequences for arbovirus transmission. *PLoS One*, *15*(6), e0233669.

Mosquito species	May	August	November	February	Total	(%)	Potential Vectors
Culex vishnui.g	1708	5670	5243	5801	18422	51.57%	JEV
Culex whitmorei	0	12	0	0	12	0.03%	
Culex sp1	24	5	4	2	35	0.10%	
Culex sp2	2	32	21	4	59	0.17%	
Culex sp3	0	0	0	4	4	0.01%	
unidentified Culex	46	96	24	37	203	0.57%	
Lutzia (2)							
Lutzia fuscana	3	5	0	60	68	0.19%	
Lutzia halifaxii	0	1	0	0	1	0.00%	
Lutzia vorax	0	1	0	0	1	0.00%	
Lutzia sp	0	1	0	0	1	0.00%	
Mansonia (2)							
Mansonia annulifera	5	45	5	0	55	0.15%	
Mansonia uniformis	325	360	180	65	930	2.60%	RVFV, WNV, RRV
Mansonia sp	1	0	2	1	4	0.01%	
Mimomyia (3)							
Mimoyia aurea	0	0	1	0	1	0.00%	
Mimomyia elegans	6	5	1	5	17	0.05%	
Mimomyia hybrida	5	9	0	0	14	0.04%	
Mimomyia luzonensis	4	26	13	61	104	0.29%	
Mimomyia sp	9	15	2	4	30	0.08%	
Uranotaenia (8)							
Uranotaenia micans	0	0	1	0	1	0.00%	
Uranotaenia nivipleura	0	0	4	2	6	0.02%	
Uranotaenia rampae	29	11	3	1	44	0.12%	
Uranotaenia subnormalis/latelaris	3	0	1	2	6	0.02%	
unidentified Uranotaenia	3	3	25	8	39	0.11%	
Unidentified specimen	0	0	2	0	2	0.01%	
Total	6970	10390	8362	10003	35725		

26

Boyer, S., Marcombe, S., Yean, S., & Fontenille, D. (2020). High diversity of mosquito vectors in Cambodian primary schools and consequences for arbovirus transmission. *PLoS One*, *15*(6), e0233669.

Human influence on mosquito evolution

- *Aedes aegypti* was long ago a species of mosquito that did not feed on humans
- Began feeding on humans approximately 5000 years ago, at the end of the African Humid Period, when the Sahara dried and water stored by humans became a uniquely stable, aquatic niche for them
- The Atlantic slave trade took human-specialist mosquitoes to North America
- Rapid urbanization in Africa has also selected for huma specialization, as wel as urban habitat preferences and daytime biting

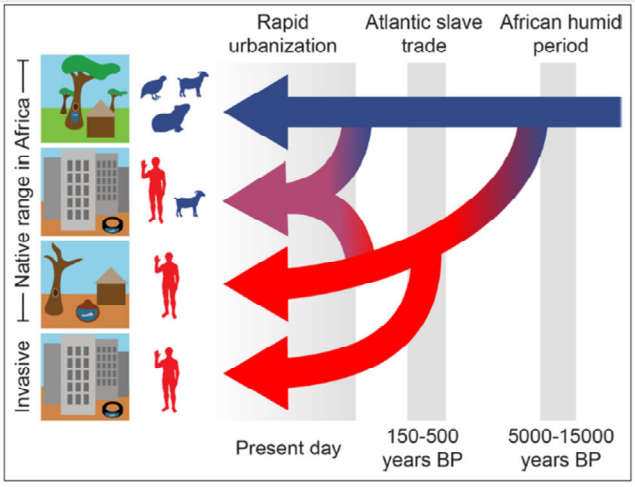


Figure 4. Three epochs define the origin and spread of the human-specialist form of *Ae. aegypti*. Our analyses suggest that human-specialized *Ae. aegypti* rapidly diverged from their generalist counterparts after the end of the African Humid Period, with the emergence of settled human societies in intensely seasonal habitats with long, hot dry seasons. Human specialists then migrated from West Africa to the Americas during the Atlantic Slave Trade. Finally, we find evidence of a recent influx of human-specialist ancestry into the rapidly growing cities consistent with an ongoing shift in the ecology of *Ae. aegypti* in present-day Africa.

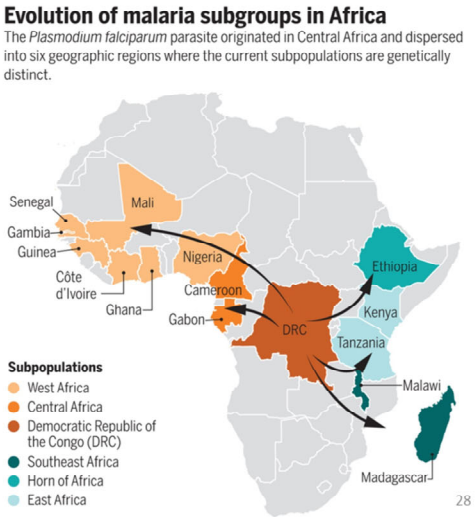
27

Rose, N. H., Badolo, A., Sylla, M., Akorli, J., Otoo, S., Gloria-Soria, A., ... & McBride, C. S. (2023). Dating the origin and spread of specialization on human hosts in Aedes aegypti mosquitoes. *Elife*, *12*, e83524.

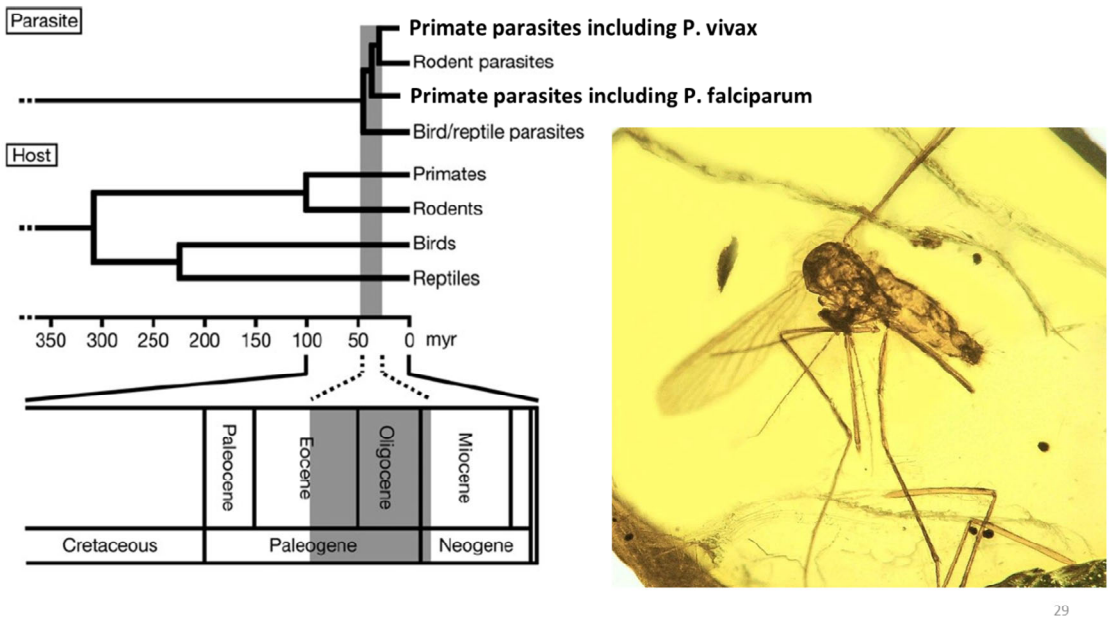
This mosquito can bite people without being noticed because it approaches from behind and bites on the ankles and elbows.

Plasmodium is highly successful evolutionarily and ecologically

- Different *Plasmodium* species have jumped from animal reservoirs into humans in the past
- New spillovers can be expected
- Even with a single species of *Plasmodium*, there are different subgroups reflecting different evolutionary histories and subsequent differences in how malaria may respond to treatments



https://www.science.org/doi/10.1126/science.aay0988



Plasmodium appeared in mammals millions of years ago. A chance genetic mutation arose in *Plasmodium falciparum* around 50,000 years ago that enabled the parasite to switch from gorillas to humans as hosts. Plasmodium evolution and diversification make tracking and understanding the parasite all the more challenging.

https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000490

Hayakawa, T., Culleton, R., Otani, H., Horii, T., & Tanabe, K. (2008). Big bang in the evolution of extant malaria parasites. *Molecular Biology and Evolution*, *25*(10), 2233-2239.

Oldest mosquito fossil with Plasmodium malariae, 15-20 million year old, in amber https://www.flickr.com/photos/oregonstateuniversity/25762256070/

Malaria Parasites That Infect Humans

Species	Global distribution*	Distinguishing characteristics	Dormant liver stage?
Plasmodium falciparum	80–90% of cases in Africa; 40–50% of cases in Western Pacific and Southeast Asia; 4–30% in South Asia, South America, and rest of tropics	Causes a majority of deaths globally; most prevalent species in sub-Saharan Africa	No
Plasmodium vivax	70–90% of cases in most of Asia and South America, 50–60% of cases in Southeast Asia and Western Pacific, 1–10% in Africa	Duffy antigen, common in African populations, provides immunity to *P. vivax*; can cause severe malaria in roughly 1/5 of cases	Yes, up to 2 years dormancy
Plasmodium malariae	2–3% in Africa, sporadic in Asia and South America	Produces fever at 3-day intervals instead of typical 2-day; clinically milder symptoms; little-studied, disease burden probably underestimated	No
Plasmodium ovale	8% of cases in parts of Africa, stray cases in Asia	Clinically similar to *P. vivax*, though with milder symptoms; disease burden probably underestimated. May be two distinct species	Yes, up to 4 years dormancy
Plasmodium knowlesi	Reported from Southeast Asia; 70% of cases in some of those areas	Primarily infects macaques; becoming more prevalent in humans	No

*Percentages are rough estimates because specific species are rarely diagnosed in patients

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There are five types of *Plasmodium* which cause human malaria, each causing a different severity of symptoms and responding to different treatments. Six types if you consider the two types of Plasmodium ovale.

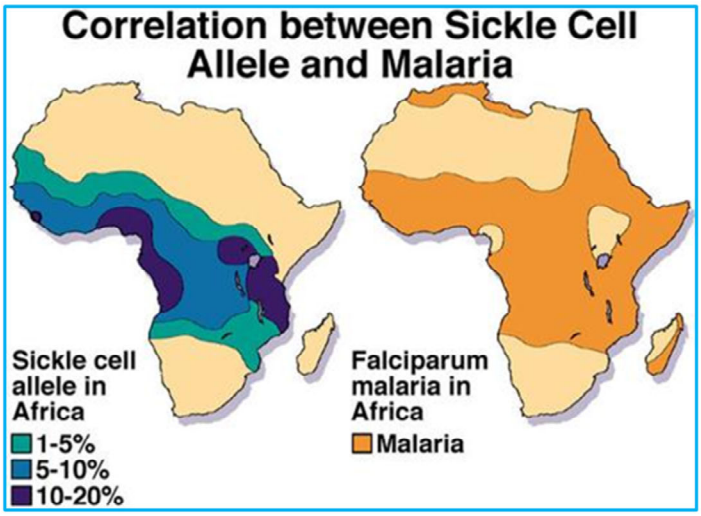
P. knowlesi is known as zoonotic malaria since the parasite still resides in macaques.

P. vivax and *P. falciparum are* responsible for the majority of clinical cases and deaths worldwide.

Plasmodium parasites emerging in humans

- *Plasmodium knowlesi* primarily infect macaques but has recently made jump to humans and can now spread from human to humans
- *Plasmodium gaboni* identified in chimpanzees and bonobos but has not yet jumped to humans
- New species of *Plasmodium* are likely to evolve and emerge

- Evolutionary interactions between humans and malaria evidenced through adaptations to:
  - *Plasmodium falciparum*
    - Sickle cell
    - Dantu blood group
  - *Plasmodium vivax*
    - Duffy antigen

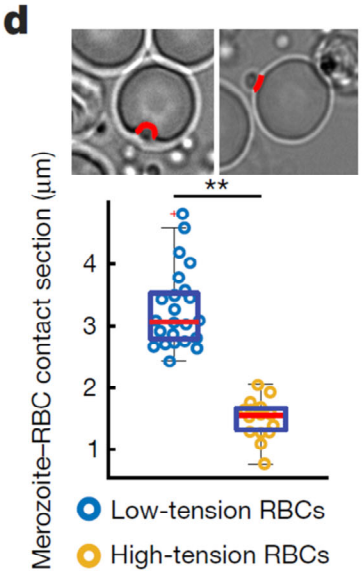


People who are heterozygous for the sickle cell allele (HbAS) have one normal hemoglobin gene (HbA) and one sickle hemoglobin gene (HbS). These individuals usually do not develop severe sickle cell disease but carry red blood cells that are less hospitable to P. falciparum infection. This provides a survival advantage in malaria-endemic regions.

Homozygous Individuals: Those who inherit two sickle cell alleles (HbSS) develop sickle cell disease, which can be life-threatening without proper medical care. In areas without malaria, this genetic mutation does not confer an advantage and is generally detrimental.

Dantu blood group

- The Dantu human blood group found in coastal east Africa has a novel protein is expressed on the surface of red blood cells
- This increases the surface tension of the RBCs, making it difficult for *Plasmodium* to enter it
- In Kilifi, a town on the Kenyan coast, 10% of the population have one copy of the Dantu gene, which confers up to 40% protection against malaria.
- One per cent of the population have two copies, conferring up to 70% protection



33

The RBC surface is ‘pulled tighter’ in the Dantu blood group.

Plasmodium falciparum – the malaria of sub-Saharan Africa

- Most malarial death is caused by *P. falciparum* in Africa, mostly in Nigeria, Democratic Republic of Congo, Mozambique, and Uganda.
- In most other malarial regions, *P. vivax* predominates.
- The clinical symptoms of *P. falciparum* and other malarial parasites (fever, chills, headaches) are caused by the destruction of red blood cells.
- Alteration of the surface properties of red blood cells by *P. falciparum* causes them to adhere to blood vessel walls, potentially leading to obstructed circulation, organ failure, and cerebral malaria.

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Plasmodium falciparum is also associated with the development of blood cancer (Burkitt's lymphoma) and is classified as a carcinogen.

Plasmodium falciparum is lethal – the malaria that most often causes death.

Plasmodium vivax – the once global malaria

- A century ago, *Plasmodium vivax* endemic in every country of the world, including regions north of the Arctic Circle
- The parasite is carried by at least 71 mosquito species, many which live in temperate climates—as far north as Finland
- More than 100 countries have eliminated malaria in the past century, all of them overcame Plasmodium vivax.
- Eradications closely linked to economic development and mosquito control (insecticide spraying, eliminating mosquito habitat)

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Plasmodium vivax

- Unlike *falciparum,* vivax parasites form hypnozoites ("sleeping parasites") that hide inside liver cells
- Remain there for weeks, months, or even years
- Allow parasite to survive in more temperate zones and wait out the winter for warm-season mosquitoes to begin biting
- Hypnozoites not detected by blood tests
- A single infectious bite can trigger six or more relapses a year, as the dormant parasites in the liver activate and cause a new bout of disease.
- Recurrent vivax episodes leave people chronically anemic
- Fighting off those episodes can leave people more vulnerable to other diseases—and to poverty and malnutrition, because they can't work while ill.

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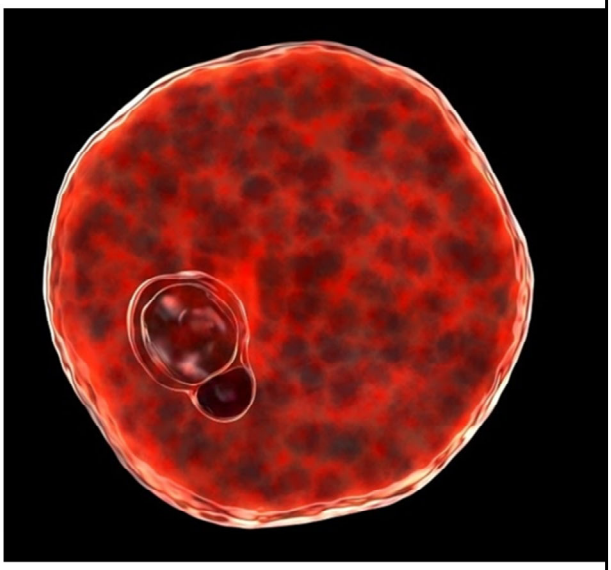
Plasmodium ovale, can also form hypnozoites, but it is much rarer than *P. vivax*

https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-7-S1-S9

Plasmodium falciparum kills you quickly, Plasmodium vivax more slowly.

Duffy negative

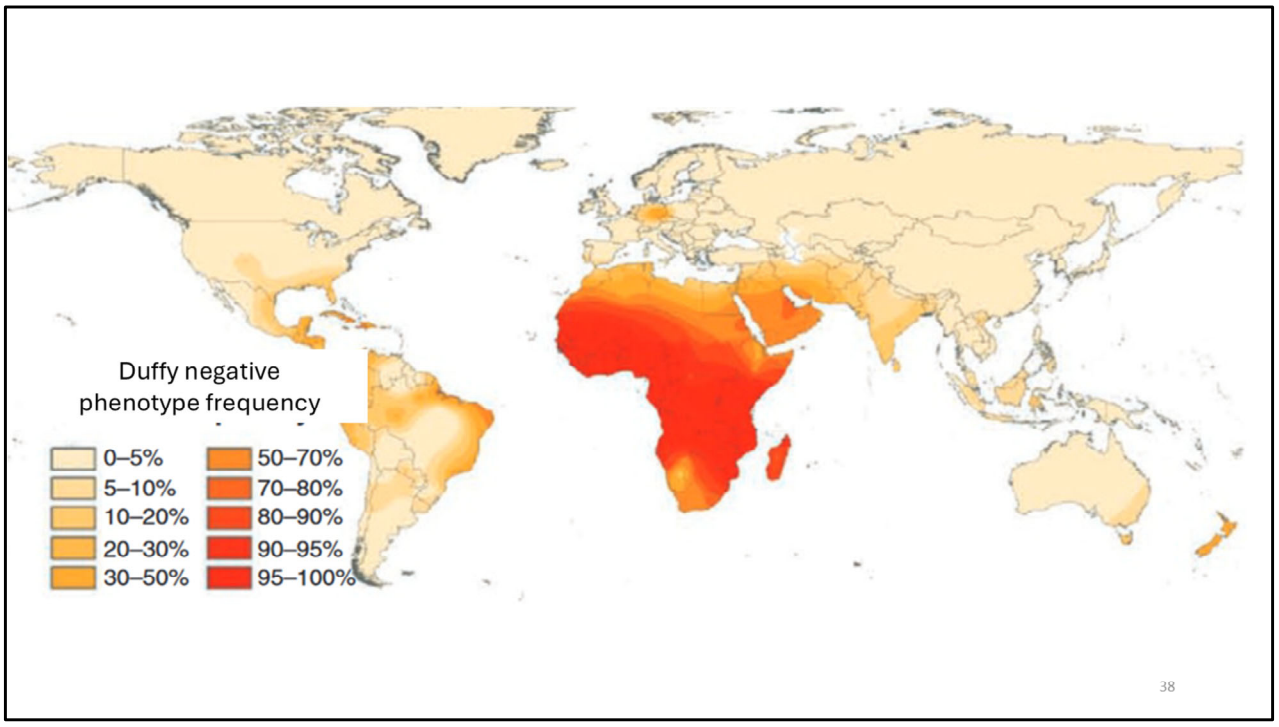
- *P. vivax* is much of less of a problem than *P. falciparum* in sub-Saharan Africa
- In sub-Saharan Africa, most of the population lacks the Duffy antigen, a protein on the surface of red blood cells
- *P. vivax* uses this protein to invade RBCs: no Duffy antigen, greatly reduced susceptibility to *P. vivax*.
- The parasite can't spread effectively in populations in which most people are Duffy-negative.



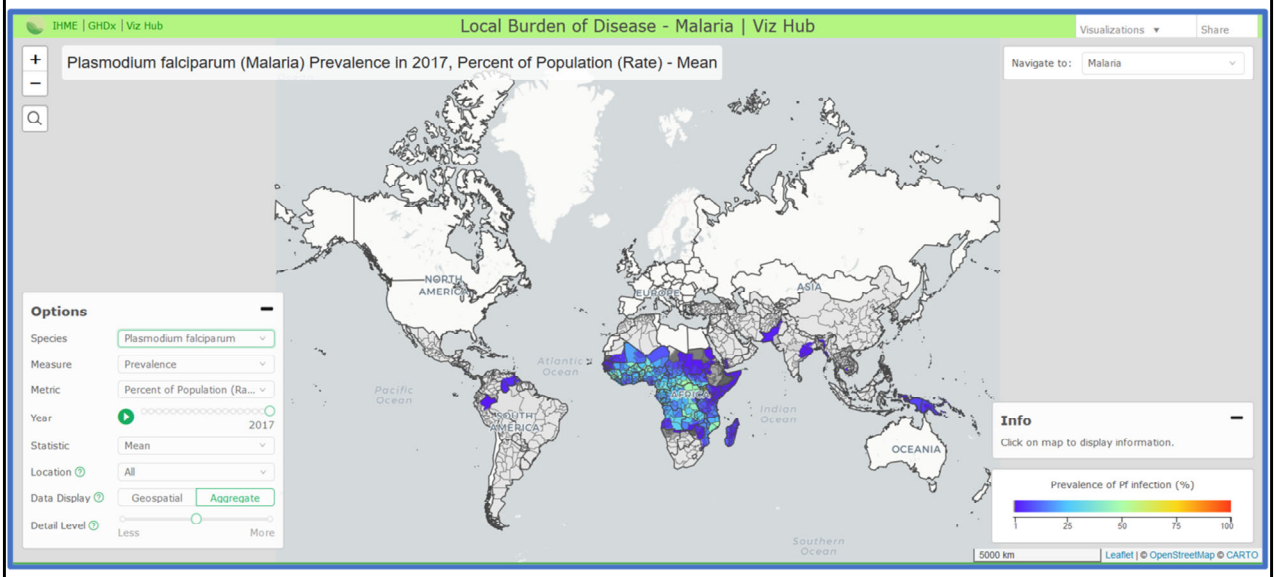
37

Howes, R. E., Patil, A. P., Piel, F. B., Nyangiri, O. A., Kabaria, C. W., Gething, P. W., ... & Ménard, D. (2011). The global distribution of the Duffy blood group. *Nature Communications*, *2*, 266.

Plasmodium vivax inside red blood cell.



Howes, R. E., Patil, A. P., Piel, F. B., Nyangiri, O. A., Kabaria, C. W., Gething, P. W., ... & Ménard, D. (2011). The global distribution of the Duffy blood group. *Nature communications*, *2*, 266.



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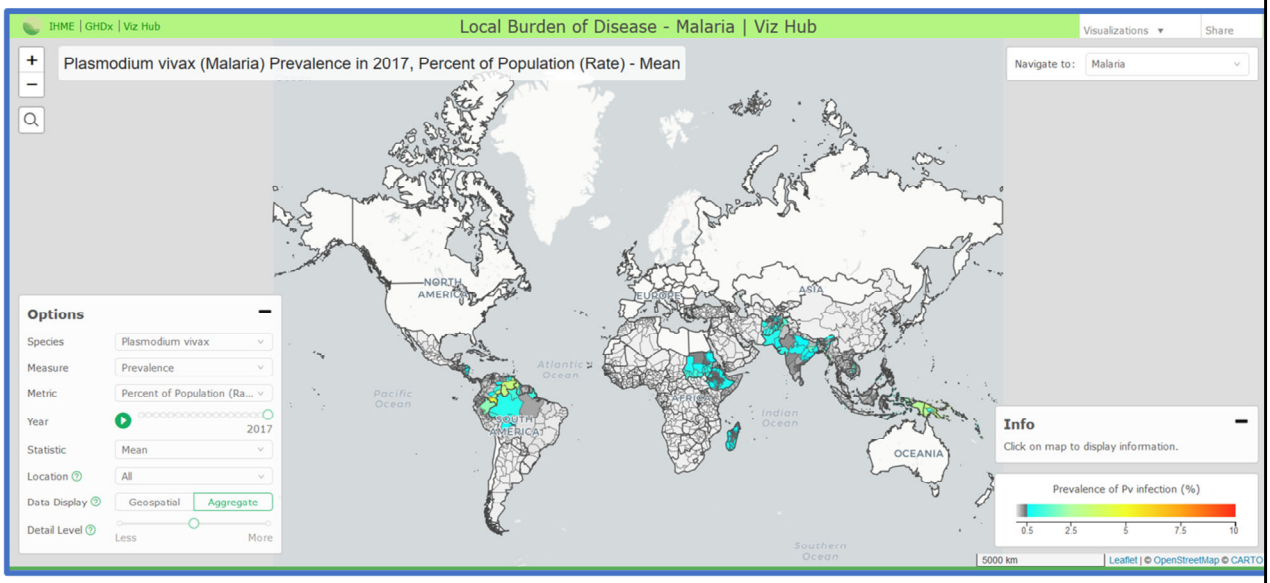
https://vizhub.healthdata.org/lbd/malaria#



40

https://vizhub.healthdata.org/lbd/malaria#

Controlling malaria: the colonial-global history of quinine

- In 17th century, Spanish discovered that indigenous peoples in Peru used a bark to remedy fevers
- Bark from cinchona tree quickly became favored treatment for fevers in Europe.
- Eventually discovered that it could also prevent malaria. The bark—and its active ingredient, quinine, became an important commodity in Europe and eventually became critical to the health of the British empire in India

Quinine remained the antimalarial drug of choice until after World War II, when other drugs, such as chloroquine, that have fewer side effects largely replaced it.

- By the 1840s British citizens and soldiers in India were using 140,000 pounds of cinchona bark annually.
- By the 1930s Dutch plantations in Java were producing 22 million pounds of cinchona bark, or 97% of the world's quinine production
- Quinine was bitter, so British in India and other tropical posts mixed the powder with soda and sugar to make tonic water
- Daily dose of protective this quinine tonic was mixed with gin to become gin and tonic

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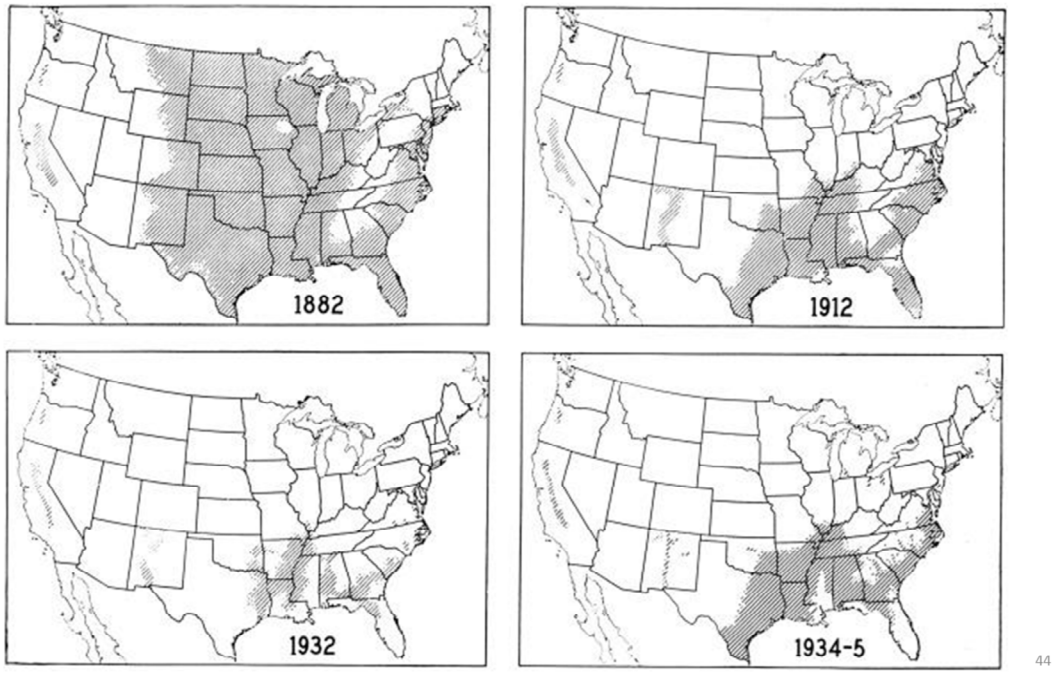
Quinine was first isolated in 1820 from the bark of a cinchona tree. Bark extracts have been used to treat malaria since at least 1632.

Can be used as a prophylactic, a preventative, or as a way to treat malaria once contracted



https://www.cdc.gov/malaria/about/history/elimination_us.html

1947 - The National Malaria Eradication Program began in the United States. The disease caused widespread illness among soldiers training in the southern U.S. during World War Two. Homes were sprayed with DDT insecticide and mosquito breeding sites were drained.

1951 - Malaria was eliminated in the United States.

While malaria was reduced by draining wetlands, this also marked the loss of large tracts of biodiverse habitats and ecosystems that provided other ecosystem benefits

https://archive.curbed.com/2019/1/16/18185454/real-estate-south-florida-everglades-the-swamp

Cartoon Everglades Drainage, 1916 Swamp Land Act of 1850 transferred swamp federal lands to the states.

Four Pests Campaign

- Took place in China from 1958 to 1962 as part of the Great Leap Forward of communist China
- Hygiene campaign aimed to eradicate the pests responsible for the transmission of pestilence and disease as part of the Great Leap Forward
- Targeted the mosquitoes responsible for malaria with spraying
- Reduced malaria burden in some regions

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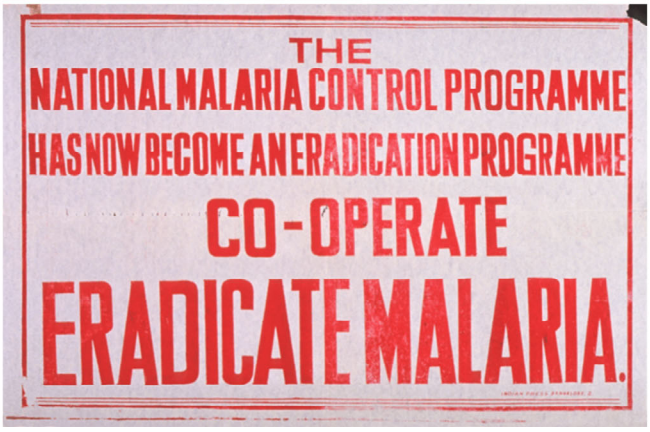
1955 – 1969: the first global malaria eradication campaign (World Health Organization)

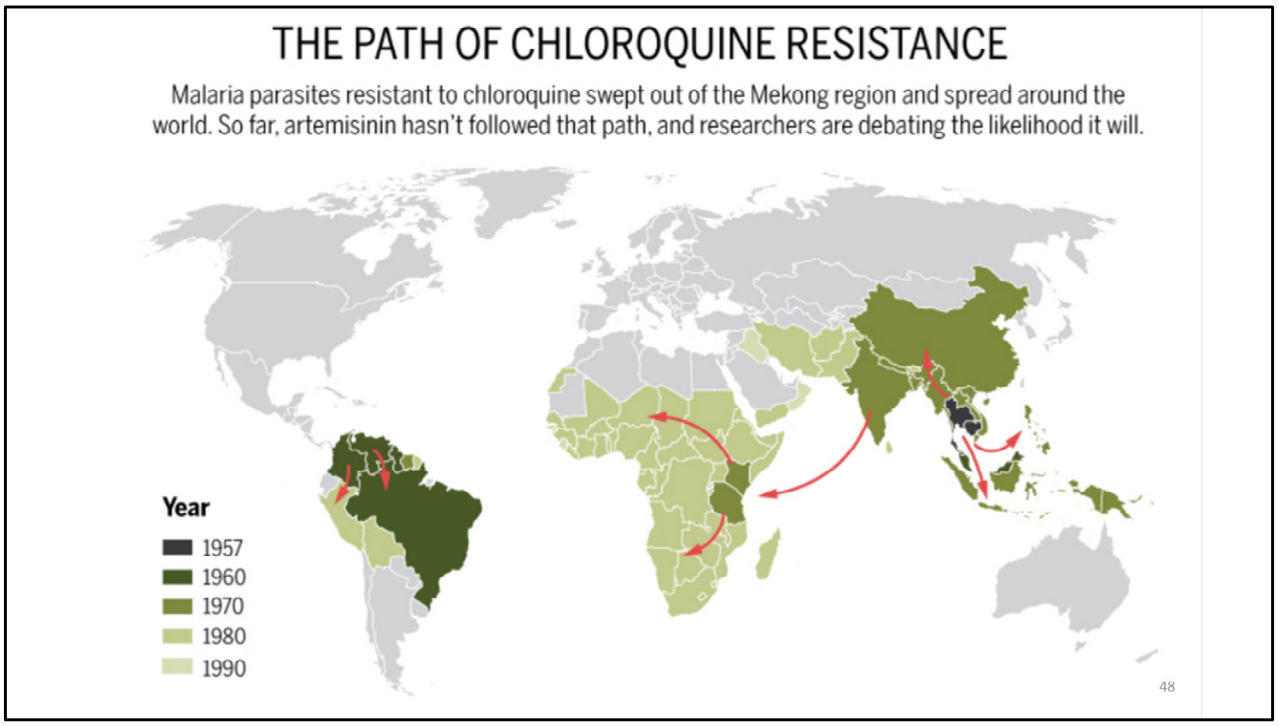
- Malaria (mostly *P. vivax)* was eliminated from much of Europe, North America, Caribbean and parts of Asia, South-Central America
- Malaria persisted in sub-Saharan Africa
- Mosquitoes increasingly resistant to DDT and *Plasmodium* became resistant to quinine-based drugs
- Financial support of this international effort collapsed and campaign failed



47

https://www.reuters.com/article/us-africa-malaria-events-timeline/timeline-the-long-road-to-malaria-eradication-idUSKCN0YU0ER

https://circulatingnow.nlm.nih.gov/2016/04/25/setting-our-sights-on-a-world-without-malaria/



Southeast Asia has served as a launch pad for drug-resistant malaria multiple times, with disastrous consequences. In the 1950s, Cambodian authorities reported that chloroquine, the main cure for malaria at the time, had stopped clearing some infections. Within three decades, chloroquine-resistant strains had spread to Africa, where 90% of the world's malaria cases occur, and the death toll started to climb. By 2000, malaria was killing about one million people a year globally.

Quinine has been used an anti-malarial drug for centuries. Chloroquine became a major anti-malarial drug treatment after its invention in the 1930s.

- Resistance first observed in malaria-causing *Plasmodium falciparum* parasites in Southeast Asia
- Chloroquine resistance arrived in East Africa in late 1970s, spread through Central Africa and reached the west African seaboard in late 1980s
- Consequences were devastating. Malaria mortality in children between 1980 and 2004 more than tripled from 493,000 to 1,613,000
- The continued use of chloroquine killed millions who could have been saved if a more effective treatment available.
- By 2004, chloroquine treatment was ineffective in up to 80% of patients who received it

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2000: Second global campaign to eliminate malaria begins

- World Health Organization, Global Fund to Fight AIDS, Tuberculosis and Malaria, Bill Gates Foundation
- Targeted sub-Saharan Africa and *P. falciparum*
- Large reductions in the prevalence of malaria achieved in the last two decades
- Areas exist where endemic transmission of malaria has been stopped

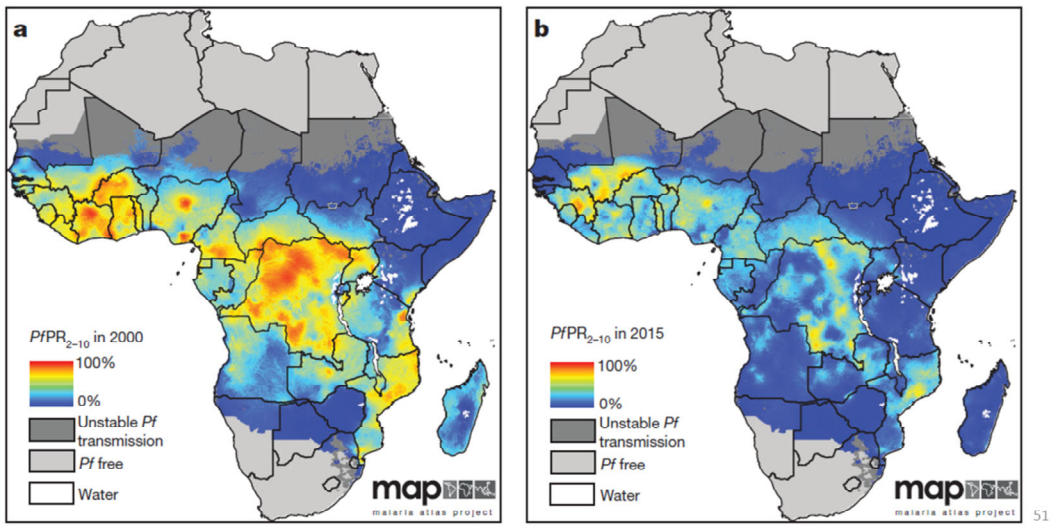
Investing in our future

The Global Fund

To Fight AIDS, Tuberculosis and Malaria

50

Plasmodium falciparum rates of transmission 2000-20015

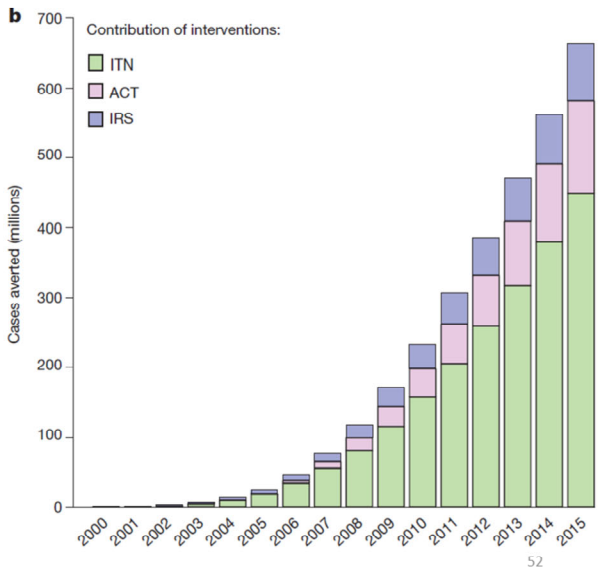


51

Colors simply indicate abundance of malaria

Interventions in second eradication campaign

- Indoor residual spraying (IRS) followed by efforts to improve water drainage, sanitation, and house design
- Treatment of clinical malaria with artemisinin-based combination drug therapy (ACT)
- Insecticide-treated bed nets (ITNs)
- However, overreliance on one intervention exclusively will lead to greater resistance of mosquitoes and the *Plasmodium* parasite



Last 15 years have seen international financing for malaria control increase approximately twentyfold – the distribution of free bed nets has been a large part of this reduction

Nets have been responsible for approximately 68% of the estimated reduction in malarial transmission since 2000.

Insecticide treated nets

- In 2005, George W Bush's Malaria Initiative provided free bed nets to protect sleeping children
- Bed nets impregnated with long-lasting insecticides called pyrethroids
- Pyrethroids are inexpensive and considered safe around people (but are toxic to aquatic insects and fish)

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The distribution of mosquito nets or bednets impregnated with insecticides such as permethrin or deltamethrin has been shown to be an extremely effective method of malaria prevention. ITNs protect people sleeping under them and simultaneously kill mosquitoes that contact the nets.

Video

- Malarial mosquitoes are often "endophilic"; that is, the mosquito rest inside houses after taking a blood meal.
- This make them particularly susceptible to control through indoor residual spraying.
- First generation insecticides to kill mosquitoes like DDT replaced with new ones, the pyrethroids

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https://www.usaid.gov/news-information/videos/protecting-ghanaians-malaria-through-indoor-residual-spraying

DDT is still used to control malaria in some countries, although it is banned in the US. There are some people who argue that the ban on DDT resulted in malarial deaths that could have been avoided. Pyrethroid are also used for spraying. These are a later generation insecticide than DDT, which was first put into widespread commercial use in the 1940s. Pyrethroids were discovered in the 1960s. However, pyrethroids are beginning to loose their effectiveness as the mosquitoes acquire resistance.

The second eradication campaign had artemisinin to treat and prevent malaria

Artemisinin is derived from a Chinese herb that has been used in the treatment of fevers for over 1,000 years, thus predating the use of quinine in the western world. Artemisinin began to be used since quinine-based drugs were increasingly ineffective.

55

Artemisinin is derived a Chinese herb (qinghaosu) that has been used in the treatment of fevers for over 1,000 years, thus predating the use of quinine in the western world

http://www.who.int/malaria/media/artemisinin_resistance_qa/en/

2015 Nobel Prize awarded to Youyou Tu of the China Academy of Traditional Chinese Medicine in Beijing for isolating the compound in sweet wormwood

Artemisinin began to be used since quinine-based drugs were increasingly ineffective

- North Vietnamese troops were suffering due to *Plasmodium's* resistance to quinine and chloroquine
- Chairman Mao of China had secret program to find new medicine and recruited scientists to examine herbs used in traditional Chinese medicine (TCM)
- Sweet wormwood, (*Artemisia annua*) identified and used in TCM to treat fevers.
- Youyou Tu isolated the active ingredient and introduced the world's next anti-malarial drug

Viet Cong soldiers of North Vietnam. China was backing North Vietnamese in their war with US and South Vietnam 56

Viet Cong soldiers of North Vietnam. China was backing North Vietnamese in their war with US and South Vietnam

- In late 1980s and 1990s, China shared knowledge with Western countries as their country opened up economically
- Photo at right shows early meeting between Chinese and French officials about bringing artemisinin to the world in early 2000s

57

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3671478/

Artemisinin combination therapy (ACT)

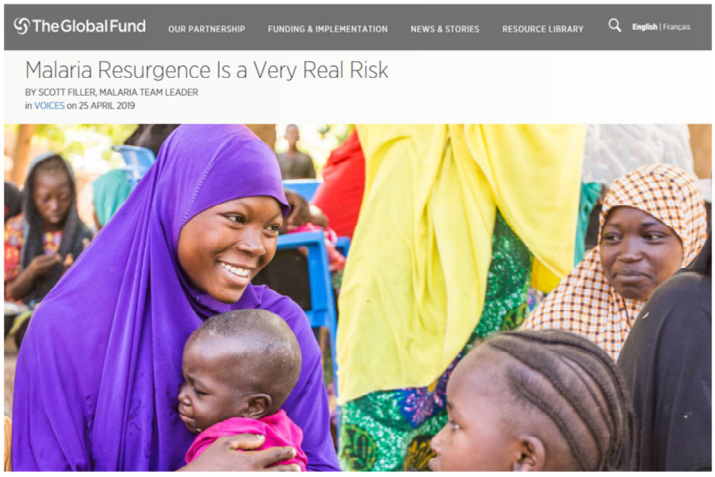
- Quinine-based antimalarials lost their effectiveness because *Plasmodium* became resistant - artemisinin has filled the gap
- ACTs pair the drug artemisinin or a derivative with one of five partner drugs.
- Different combinations are used in different parts of the world.
- Artemisinin hits hard and fast, wiping out malaria parasites in hours, while partner anti-parasite drug works over a longer period

Companion drugs include lumefantrine, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, piperaquine and chlorproguanil/dapsone.

And as you would suspect, available without a prescription in some countries, like this one from Pakistan. But in countries where going to a doctor is prohibitively expensive for many, is it wrong to consider this an entirely negative circumstance?

Leveling off of the successes of second global campaign

- Resurgence of malaria due to:
  - Difficulty of preventing introduced transmission
  - Resistance of mosquitoes to insecticides
  - *Plasmodium* is now becoming resistant to artemisinin in southeast Asia
  - Weakening of malaria control programs due to political instability
  - Complacency after initial successes



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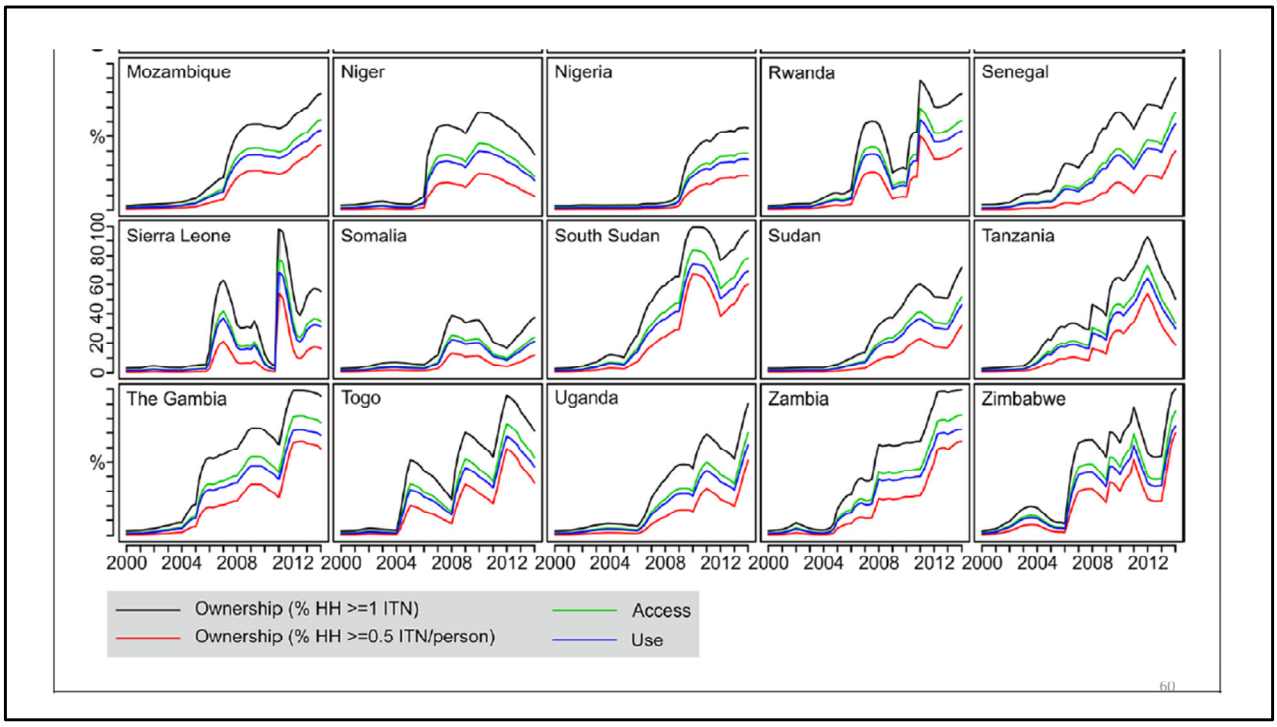
https://www.theglobalfund.org/en/blog/2019-04-25-malaria-resurgence-is-a-very-real-risk/



Overall use of nets has increased but rates of availability and adoption variable from country to country. Period is for 2000-2013. Black line indicates percent of households with at least one ITN. Red line indicates percent of households with at least one ITN for every two people.

https://www.newvision.co.ug/new_vision/news/1492183/imported-mosquito-nets-derailing-war-malaria

Also counterfeit nets that have no insecticide or are poorly made

Video

AFRICA

Meant to Keep Malaria Out, Mosquito Nets Are Used to Haul Fish In

By JEFFREY GETTLEMAN JAN. 24, 2015

Millions of mosquito nets are given out fight to malaria in Africa, yet many faced with hunger use them as fish nets, creating potential environmental problems. By Ben C. Solomon on January 24, 2015. Photo by Uriel Sinai for The New York Times. Watch in Times Video »

Embed

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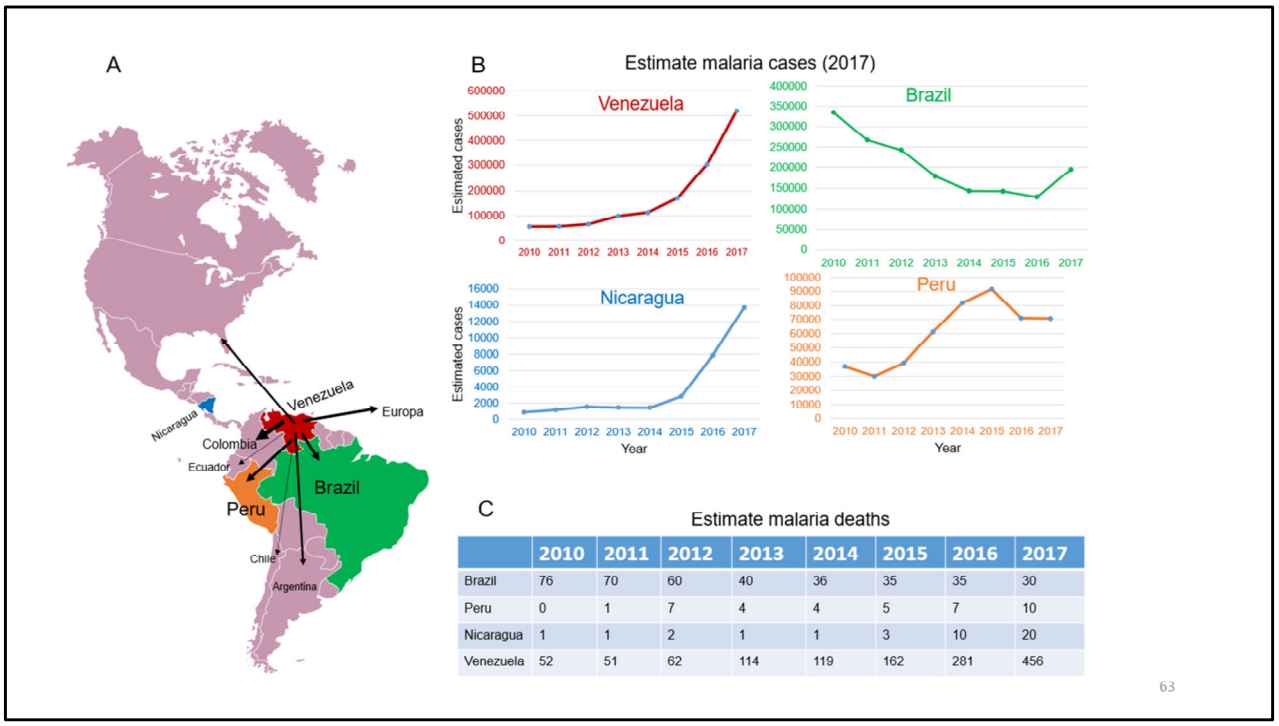


	2010	2011	2012	2013	2014	2015	2016	2017
Brazil	76	70	60	40	36	35	35	30
Peru	0	1	7	4	4	5	7	10
Nicaragua	1	1	2	1	1	3	10	20
Venezuela	52	51	62	114	119	162	281	456

Malaria cases have been increasing in some parts of the Americas, South-East Asia, Western Pacific and Africa,

A severe shortage of first-line antimalarial drugs, scarce investment in vector control measures, loss of equipment and infrastructure, and a collapsed health system as a result of the ongoing political and economic crisis (annual inflation rate of 1,000,000%), are major determinants of the malaria resurgence in Venezuela. Malaria cases in Venezuela have spilled over to other neighboring countries in the region, overloading local health care services in Brazil and Colombia. The large-scale migration of Venezuelan nationals, aggravated in the last six months, is a reasonable concern that the growing malaria epidemic in Venezuela could spread to the entire region.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6471461/

Mosquitoes continue to evolve resistance to insecticides

- First generation insecticide: DDT
- Second generation insecticide: pyrethroids
- Third generation pesticides: neonicotinoids

A solution of clothianidin and another insecticide is sprayed on the walls of a home in Rwanda.

64

Makoni, Munyaradzi. "Malaria fighters' latest chemical weapon may not last long." (2020) Science: 1153-1153.
DOI: 10.1126/science.369.6508.1153

https://www.nature.com/immersive/d41586-018-05772-z/index.html

Emergence of artemisinin resistance (ART-R) in southeast Asia during second global campaign

- First detected in 2005 in the same region where resistance to chloroquine drugs emerged during first global malaria eradication campaign.

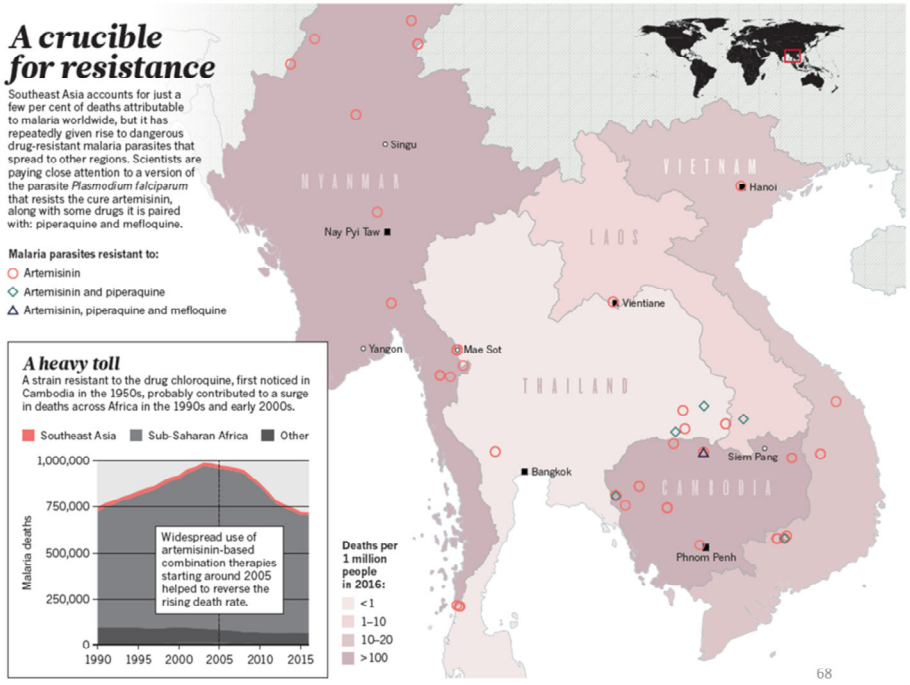
Artemisinin rapidly wipes out the majority of parasites, and a longer-acting partner drug in the combo mops up the rest. When ACTs are working as they should, the number of parasites detectable in a finger-prick of blood drops by half within three hours of taking the medicine. But in 2008, researchers in western Cambodia reported that parasite numbers in some patients were not falling as quickly as they ought to.

Roberts, L. (2016). Drug resistance triggers war to wipe out malaria in the Mekong region. *Science*, *10*.

Reasons ART-R developed in southeast Asia

- Health systems here have been historically underdeveloped and inconsistent in health delivery because of war and political turmoil, particularly in rural areas.
- High use rates of anti-malarial drugs in larger cities of southeast Asia contributes to resistance
- Anti-malarial drug quality has been sporadic and unpredictable, which can lead to resistance
- Many species and subspecies of the *Anopheles* mosquito in southeast Asia. Small isolated mosquito populations can rapidly pass on genes for resistance

- Role of political instability in a consistent control and treatment plan
  - Japanese occupation in 1940-1945
  - Region designated French Indochina until 1954
  - Vietnam War (1955-1975)
  - Cambodian Civil War (1967-1975)
  - Hostilities among communist factions in Cambodia, Laos, and Vietnam through early 1990s



Artemisinin resistance has emerged in southeast Asia - the very same region as where chloroquine resistance emerged. Why?

https://www.nature.com/immersive/d41586-018-05772-z/pdf/d41586-018-05772-z.pdf?origin=ppub

Counterfeit anti-malarial drugs remain a problem in south Asia as well as sub-Saharan Africa

- Globally, some 200,000 preventable deaths occur each year due to anti-malarial drugs that do not work.
- One-third of anti-malarial medicines distributed in southeast Asia and sub-Saharan Africa are of poor quality.
- This illegal activity is most common in places with little government oversight and limited access to safe, affordable and high-quality medicines.

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https://theconversation.com/fake-drugs-are-one-reason-malaria-still-kills-so-many-92712

The double burden of counterfeit drugs: Patients who unwittingly purchase ineffective anti-malarial drugs are out of pocket for medicines that do nothing. Then, they pay for additional treatments when the first course of medicine fails. Patients pay twice – for the ineffective drugs and for the additional drugs when the first treatment fails

Drug quality and use has been sporadic and unpredictable, which can lead to resistance to malarial drugs and the persistence of malaria

- Drugs may be deliberately and fraudulently mislabeled with respect to identity, source or pharmaceutical content. Some contain no active ingredients at all or contain them in incorrect amounts.
- They may be short on artemisinin, and some anti-malarial drugs found in poor countries have either expired by the time they reach consumers or been damaged by exposure to extreme heat.
- These practices can lead the malarial parasite to develop drug resistance

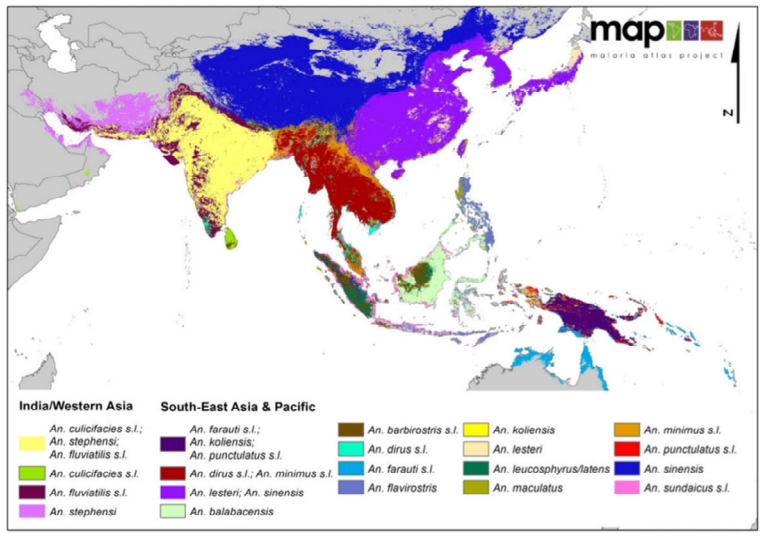
National November 6, 2020

Cambodia destroys over 540 tons of counterfeit medicines, products

The counterfeit medicines and medical products going up in flames. National Police

70

https://theconversation.com/fake-drugs-are-one-reason-malaria-still-kills-so-many-92712



regional map showing the distribution of 16 dominant malaria vectors in the Asian-Pacific region.

High diversity of *Anopheles* in SE Asia

- Small isolated *Anopheles* mosquito populations in southeast Asia
- In small populations, *Plasmodium* is able to pass on mutations that confer resistance easier and these can then spread to other populations

71

https://www.intechopen.com/books/anopheles-mosquitoes-new-insights-into-malaria-vectors/understanding-anopheles-diversity-in-southeast-asia-and-its-applications-for-malaria-control

Sinka, M. E., Bangs, M. J., Manguin, S., Rubio-Palis, Y., Chareonviriyaphap, T., Coetzee, M., ... & Hay, S. I. (2012). A global map of dominant malaria vectors. *Parasites and Vectors*, *5*, 1-11.

Slowing of ART-R in southeast Asia achieved through the Regional Artemisinin-resistance Initiative (RAI)

- The Global Fund to Fight AIDS, Tuberculosis and Malaria and governments of Cambodia, Lao PDR, Myanmar, Thailand, and Vietnam formed RAI
- Transmission of malaria interrupted so that resistance genes would not spread
- Key to success was support given to networks of village malaria workers to improve access to malaria diagnosis and treatment in hard-to-reach areas.
- *Falciparum* malaria declined markedly in Cambodia, Lao PDR, Thailand, and Vietnam

72

Dhorda, M., Kaneko, A., Komatsu, R., Kc, A., Mshamu, S., Gesase, S., ... & von Seidlein, L. (2024). Artemisinin-resistant malaria in Africa demands urgent action. *Science*, *385*(6706), 252-254.

NEWS | 14 November 2024

Resistance to crucial malaria drug detected in severely ill kids in Africa

The development worries researchers because children are particularly vulnerable to the disease.

By Mariana Lenharo

NEWS | AFRICA

Drug-resistant malaria is gaining a foothold in Africa

Analyses of patient blood samples suggest artemisinin effectiveness is slipping

22 SEP 2021 • 5:00 PM • BY DENNIS NORMILE

ceives a malaria test result from a community health worker in Rwanda, where researchers recently identified artemisinin resistance. NICHOLE SOBECKI/VU/REDUX

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Of great concern is that the mutations that cause resistance to artemisinin begin to occur in Africa

The same mutations in Plasmodium that have contribute to artemisinin resistance in southeast Asia are now popping up in parts of Africa. They were not imported from Asia through transport of people or mosquitoes with the resistance parasite.

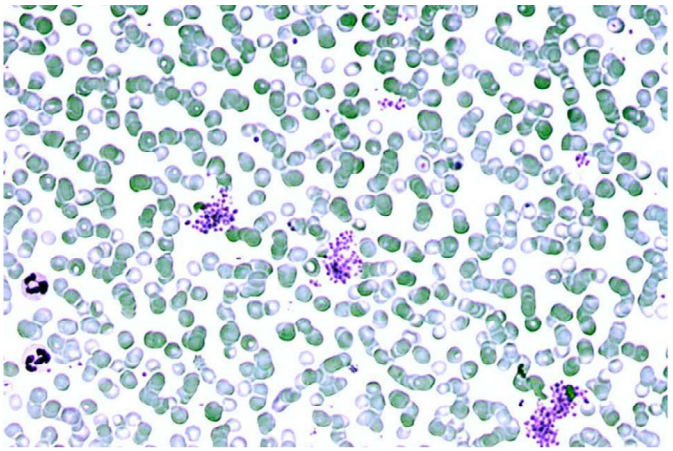
https://www.science.org/content/article/drug-resistant-malaria-gaining-foothold-africa

Public health authorities have long worried that the emergence in Africa of malaria resistant to artemisinin was only a matter of time. Parasites that can thwart this key component of front-line treatments appeared in Southeast Asia in the early 2000s and eventually led to clinical failures. The stakes are higher for Africa, which in 2019 saw 94% of both malaria cases and deaths worldwide—estimated at 229 million and 409,000, respectively. Two recent papers provide evidence that the dreaded resistance now has a foothold on the continent. The findings are “a game changer,” says malaria researcher Philip Rosenthal of the University of California, San Francisco. For now, there’s no evidence that current treatments are failing outright; patients

with the resistant parasites simply take longer to clear them. “I don’t think this is a reason to panic,” Rosenthal says, “but we should be very concerned that things may be changing, and we definitely need new drugs.”

2020: start of the third eradication campaign

- New insecticides and antimalarial drugs under development
- Better tests to detect the *Plasmodium* parasite in human blood samples
- Vaccines will likely play a greater role

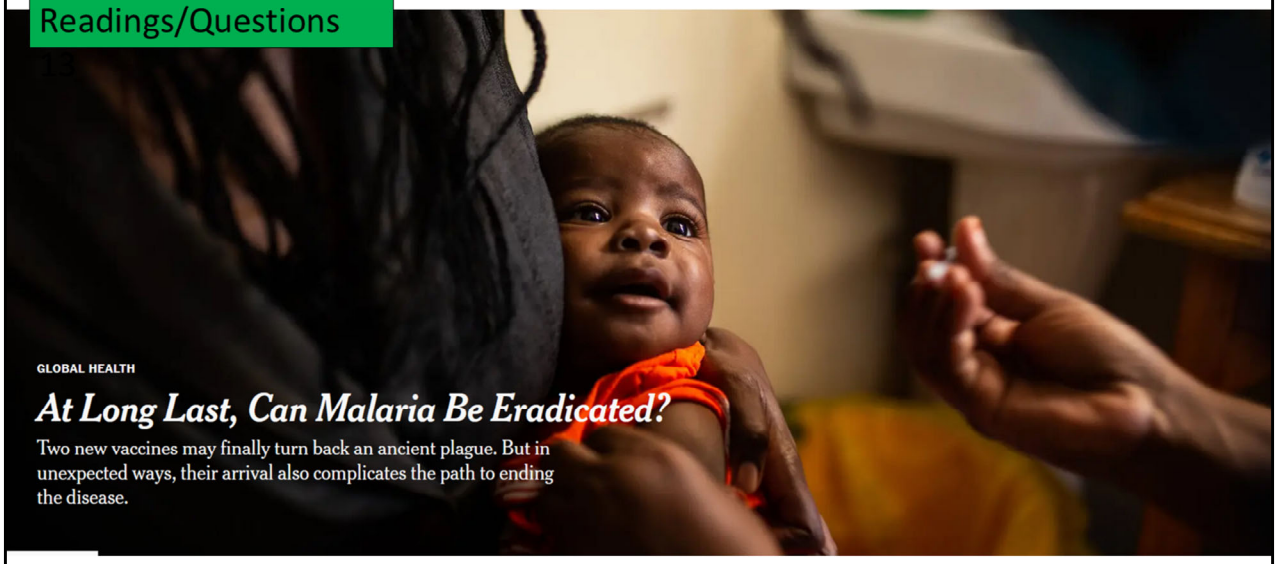


Improvements in tests to detect malaria

- Malaria is a curable disease if you know you are infected.
- If eradication is the goal, people with low levels of the parasite and who are asymptomatic, will have to be identified
- The microscopic examination of stained blood films still remains the gold-standard in Plasmodium detection today, but it is hard to detect low levels of infection
- Need is for alternative diagnostic methods that are simple, fast, highly sensitive, and ideally do not rely on blood-drawing and can potentially be conducted by the patients themselves

https://www.nytimes.com/interactive/2023/09/29/health/mosquitoes-new-solutions.html

Readings/Questions



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https://www.nytimes.com/2022/10/04/health/malaria-vaccines.html

Malaria vaccines: RTS,S/AS01(Mosquirix) and R21/Matrix-M

Two safe and protective malaria vaccines, RTS,S/AS01 and R21/Matrix-M, have been registered and licensed in several African countries over the past 2 years.

These vaccines target children under 5 years who bear the main burden of malaria.

Both vaccines target *Plasmodium falciparum*, the most common and most lethal of four malaria parasite species

RTS,S/AS01: Efficacy of approximately 56%, approved for use in 2021

R21/Matrix-M: Efficacy of about 78% and lower costs to produce, approved for use in 2023. The WHO has said that R21 will be available across Africa as early as mid-2024

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RTS,S/AS01 (Mosquirix) versus Ozempic

- 37 years to bring to market
  - 1987: The project to develop RTS,S is initiated by GlaxoSmithKline
  - 1998: The first Phase 1 clinical trials begin in adults in the United States.
  - 2021 RTS,S recommended for use by WHO
  - 2024: RTS,S is now being integrated into routine childhood immunization programs in several African countries,
- 16 years to bring to market
  - 2002: Research and development of semaglutide begins at Novo Nordisk
  - 2012: Phase 1 clinical trials start
    2018: Ozempic is launched

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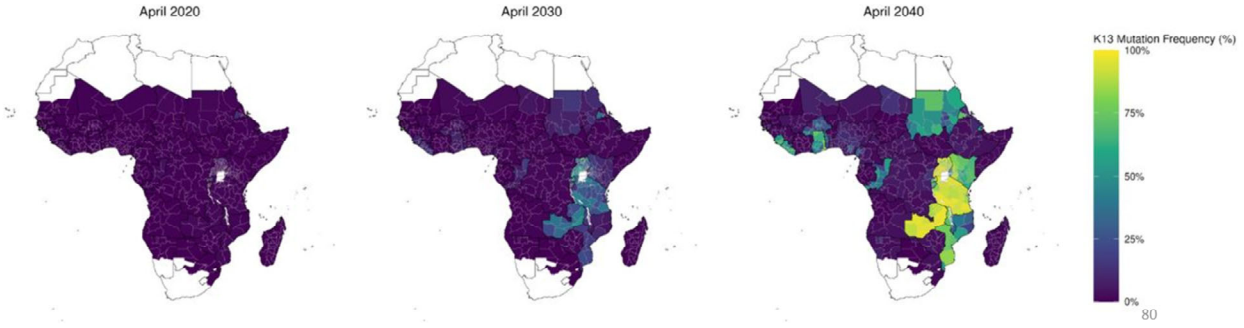
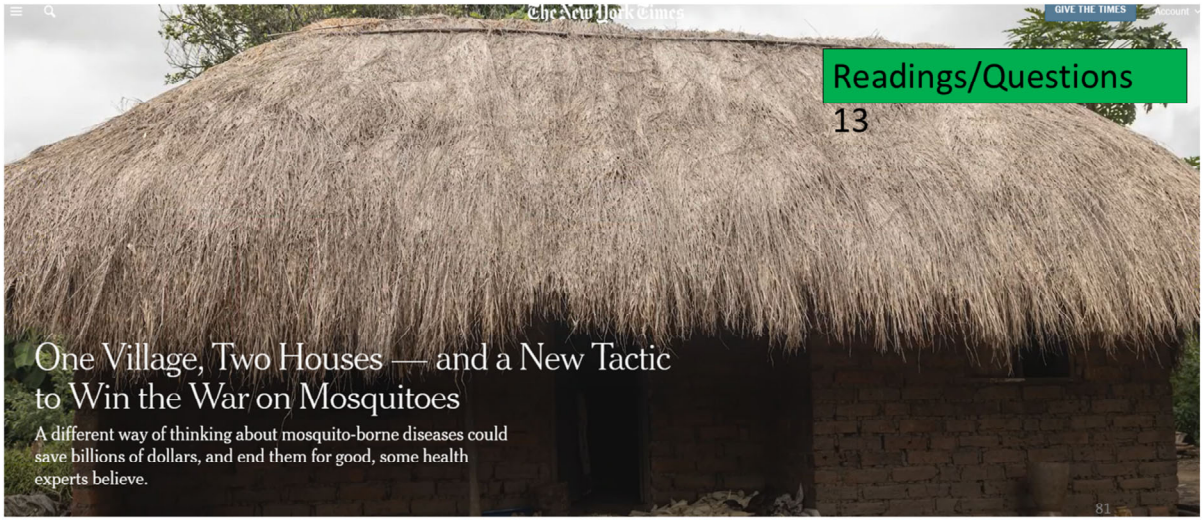
More than 18 million people, most of them young children, have died of malaria in the quarter-century since the vaccine's 1998 trials.

- This benefits vaccinated children, but the unvaccinated population will continue to transmit malaria.
- New vaccination strategies will need to include all age groups are be deployed in or around areas reporting parasites with artemisinin resistance genes like the K13 mutation
- Dual benefits of reducing malaria transmission while also reducing propensity for artemisinin resistance to spread



DOI:10.1101/2024.08.28.24312699

Do vaccines take a lot of money away from simpler solutions?



https://www.nytimes.com/2023/09/29/health/mosquitoes-malaria-strategies-house.html

How will climate change impact the distribution of malaria?

- Warmer = more mosquitoes = more malaria is reasonable assumption, but there are more factors to consider.
- Climate change is not just a change in temperature patterns, but also changes in rainfall and how patterns in each coincide spatially and temporally
- Warmer temps without adequate rainfall may not promote more malaria
- This complexity intersects with life cycle of the mosquito **and** the thermal ecology of the *Plasmodium* parasite

An ephemeral pool in Niger provides a perfect breeding site for Anopheles mosquitoes. This and other northern parts of West Afric could become too hot to sustain malaria.

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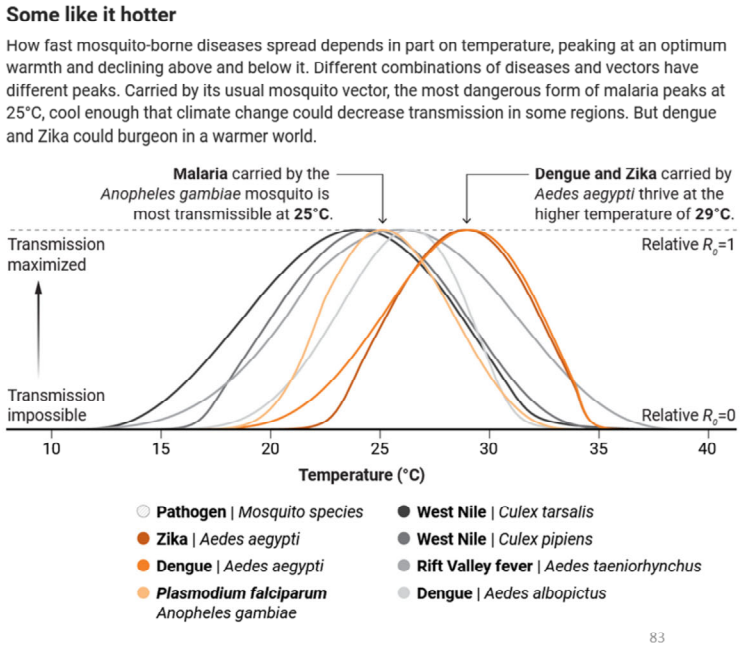
Remember, mosquitoes require water to lay their eggs and for the larval stage of the mosquito to develop.

At temperatures below 68°F, the parasite *Plasmodium falciparum* can not complete its growth cycle in the mosquitoes so it can not be transmitted. However, *Plasmodium vivax,* which can complete its life cycle in lower temperatures.

- Temps may be too warm in some locations for malaria – malaria may decrease in some parts of Africa
- Dengue may increase more in response to warmer temps than malaria



https://doi.org/10.1126/science.adl0412

The baseline assumption is that warmer climate will make vector-borne disease worse because people observe that most [such] diseases occur in the tropics, and in more temperate places they occur in the summer. However, the effect of rising temperatures can go either way. For many years the temperature optimum for malaria was pegged at about 31°C. Recent studies indicate that the temperature optimum is likely dramatically lower: just 25°C. Above 28°C, transmission decreases rapidly. Parts of sub-Saharan Africa may undergo reductions in malaria. However, in the highlands of South America and southern Africa, warming temperatures increasingly favor malaria transmission. And in once-malarial regions of Europe and North America that have controlled the disease, keeping it in check may become more challenging.

Deforestation and urbanization trends will also shape mosquito disease potential

Economic change and instability can push people into remaining forests to make a living, bring them in contact with mosquitoes and the *Plasmodium* parasite

https://e360.yale.edu/features/turning-the-tide-on-the-relentless-destruction-of-cambodias-forests

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https://e360.yale.edu/features/turning-the-tide-on-the-relentless-destruction-of-cambodias-forests

Kibera, Kenya

Some of the fastest growing cities in the world are in Africa. Urban habitats can also support mosquitoes and spread of malaria depending upon vegetation cover and availability of water, type of buildings, and human population density. However, malaria is far less of a problem in cities than another mosquito-borne disease, dengue

Overflow from dengue ward in Telangana state, southern India

Dengue

- Endemic to more than 100 countries
- Fast growing infectious global disease – by 2080, two-thirds of the planet's population will be susceptible to exposure to dengue
- Dengue, like malaria, is an arboviruses, a term used to refer to a group of viruses that are transmitted by arthropod vectors (**ar**thropod-**bo**rne virus).
- While malaria is a disease of rural poverty, dengue transcends class more readily and is often an urban problem
- While many get dengue and few die, it creates economic disruption for individuals, families and societies

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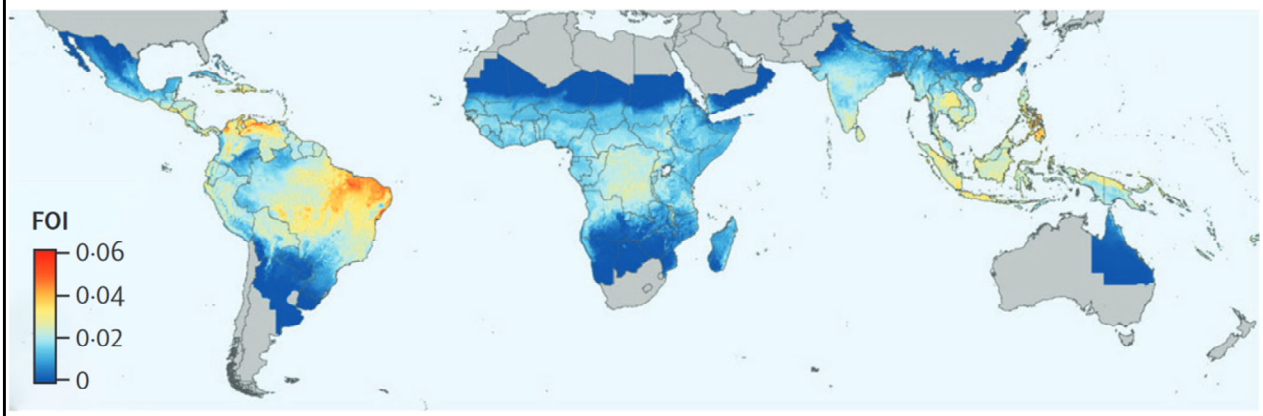
Dengue ward in hospital in the Philippines

At present, half the world is susceptible to exposure to dengue



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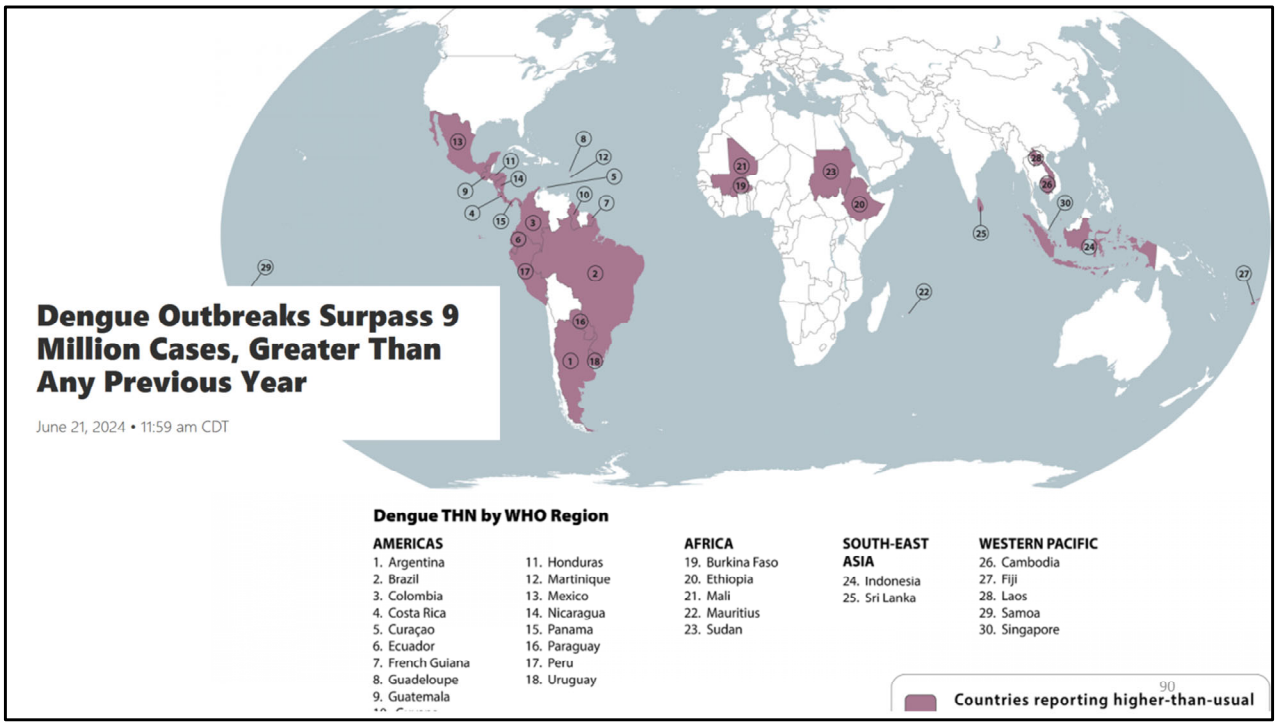
The estimated force of infection (FOI) for dengue, which is the per capita rate at which susceptible individuals become infected


Dengue Outbreaks Surpass 9 Million Cases, Greater Than Any Previous Year
June 21, 2024 • 11:59 am CDT
Dengue THN by WHO Region
AMERICAS
1. Argentina
2. Brazil
3. Colombia
4. Costa Rica
5. Curaçao
6. Ecuador
7. French Guiana
8. Guadeloupe
9. Guatemala
11. Honduras
12. Martinique
13. Mexico
14. Nicaragua
15. Panama
16. Paraguay
17. Peru
18. Uruguay
AFRICA
19. Burkina Faso
20. Ethiopia
21. Mali
22. Mauritius
23. Sudan
SOUTH-EAST ASIA
24. Indonesia
25. Sri Lanka
WESTERN PACIFIC
26. Cambodia
27. Fiji
28. Laos
29. Samoa
30. Singapore
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Countries reporting higher-than-usual

More places are seeing local transmission of dengue for the first time

- Cases are appearing outside of tropics, including the US because of
  - Increased international travel
  - Importation of virus into areas where it doesn't occur
  - Spread of mosquitoes that carry dengue
  - Climate change
  - Since 50-90% of people are asymptomatic, dengue can travel undetected or goes undiagnosed

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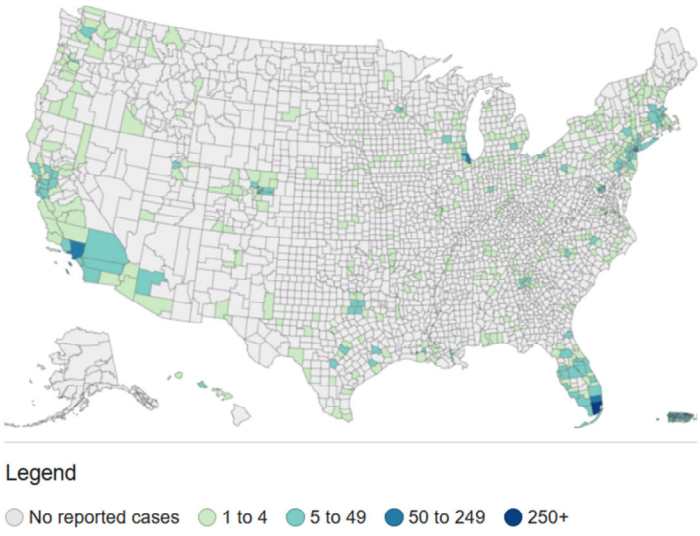
https://www.washingtonpost.com/world/2024/03/10/dengue-fever-brazil-outbreak-epidemic/
https://www.nytimes.com/2023/10/24/health/what-is-dengue-fever.html

Local transmission of dengue in the US

- Limited local transmission of dengue has been reported in Florida, California, Hawaii, Texas, and Arizona in 2023-2024.
- Most cases are from travelers returning from dengue-endemic areas



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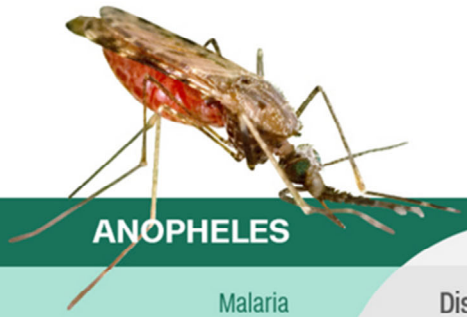
https://www.cdc.gov/dengue/data-research/facts-stats/current-data.html



ANOPHELES		AEDES MOSQUITO
Malaria	Diseases spread	Dengue, Yellow Fever, Chikungunya, Lymphatic filariasis
Pregnant females	Which mosquitoes bite?	Pregnant females
Night	When do they bite?	Day
With abdomen sticking upwards	Resting position	Lies parallel to resting surface
Predominantly rural	Location	Predominantly urban
Bodies of water	Breeding ground	Shallow water surfaces

SOURCE: Centers for Disease Control and Prevention

- Spread by *Aedes aegypti and Aedes albopictus*. They also transmit yellow fever, chikungunya and Zika viruses
- Dengue causes fever, severe joint pain, muscle aches. Also known as breakbone fever. Less common is a hemorrhagic fever that can potentially lead to death.

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Aedes aegypti (left) is also known as the yellow fever mosquito. *Aedes albopictus* (right) is known as the Asian tiger mosquito.

Dengue ward in hospital in the Philippines

- *Aedes aegypti* is from tropical Africa and most likely spread throughout the world via slave and trading ships during 17th to 19th centuries
- Feeds mostly at dusk and dawn and in shady places
- Two subspecies of *Aedes aegypti*: *Aedes aegypti formosus* in sub-Saharan Africa and *Aedes aegypti Formosus*
- *Aedes aegypti aegypti* is the mosquito that has spread around the tropical and subtropical world outside Africa.

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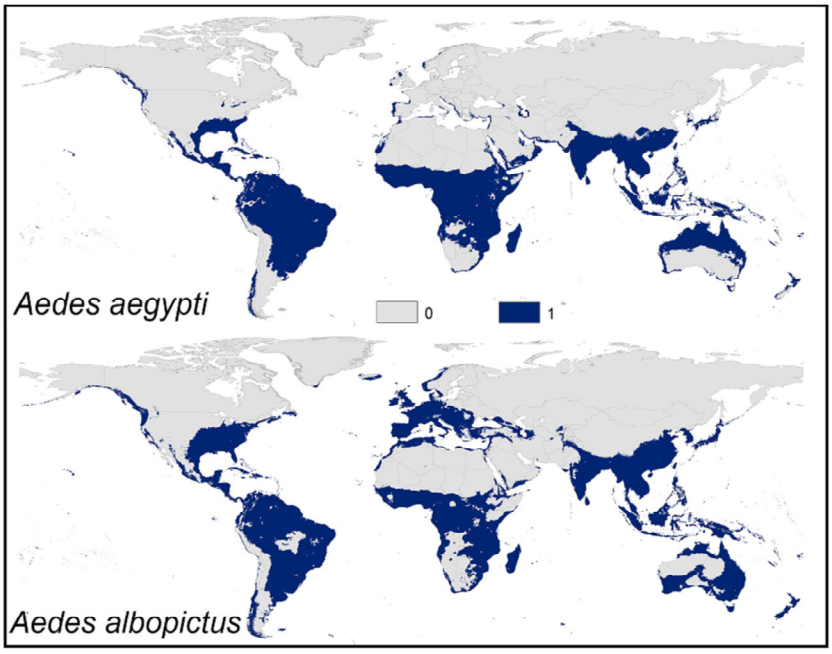
Known as the Yellow fever mosquito, but it also transmits dengue, Zika, and chikungunya



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Note the more northern distribution of *Aedes albopictus*

Aedes albopictus

- Native to Southeast Asia
- Also known as the Asian tiger mosquito
- Prior to 1979, found only in Asia and Western Pacific
- Spotted in Houston in 1985
- Hypothesized to have arrived via shipment of tires from Japan
- Remains active and bites all day
- Prefers human habitats over wetlands more than *Aedes aegypti* and will lay eggs in water-filled artificial containers

Figure 3. Photographs of tiger mosquitos in cars submitted by citizen scientists through *Mosquito Alert*.

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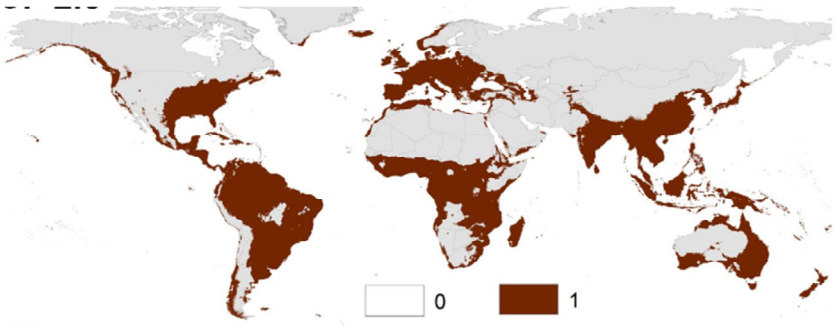
https://source.wustl.edu/2014/10/hot-on-the-trail-of-the-asian-tiger-mosquito/

Eritja, Roger, John RB Palmer, David Roiz, Isis Sanpera-Calbet, and Frederic Bartumeus. "Direct evidence of adult Aedes albopictus dispersal by car." *Scientific Reports* 7, no. 1 (2017): 14399.

This mosquito has become a significant pest in many communities because it closely associates with humans (rather than living in wetlands), and typically flies and feeds in the daytime in addition to at dusk and dawn

- Range of *A. albopictus* stretches farther north than that of *A. aegypti*, and its eggs are somewhat resistant to subfreezing temperatures, raising the possibility that *A. albopictus* could mediate a re-emergence of dengue in the United States



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Range of Aedes albopictus in brown

Singapore

https://www.todayonline.com/big-read/big-read-warming-temperatures-and-increased-urbanisation-fight-against-dengue-will-only

https://www.dw.com/en/singapores-mosquito-police/av-41991007

Urbanization and dengue

- Expansion of dengue associated with rapid urbanization and population growth in tropical cities
- Rapid development can lead to unplanned infrastructure problems involving control of stormwater that can breed mosquitoes
- Seasonal dengue outbreaks endemic to many large tropical cities
- Dengue is hyper-endemic in some countries, like the Philippines, where by age 9, 90% of Filipinos have been exposed to the virus

https://www.hindustantimes.com/gurgaon/dengue-cases-at-27-likely-to-rise-further-say-gurgaon-doctors/story-HVBxrCOxlavg2ItkKcGxyI.html

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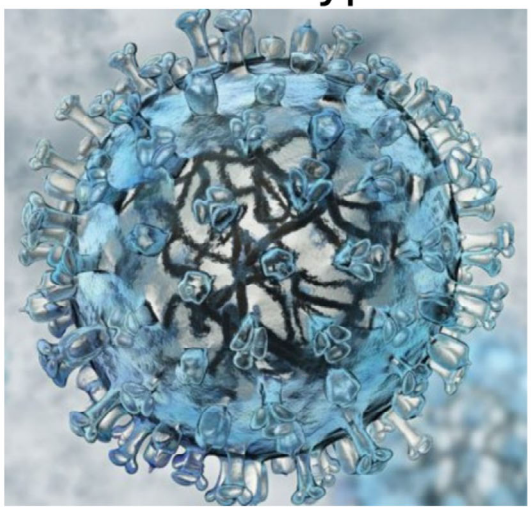
From Brazil

- Initial infection with any of the four confers lifelong immunity to that serotype.
- After dengue infection, the immune system protects against a second infection with any serotype for one to two years
- But after that period, people are protected only from the serotype to which they were first exposed,
- They are then at increased risk of antibody dependent enhancement (ADE) .
- When infected with other serotypes. ADE can lead to dengue hemorrhagic fever, which can cause massive fluid loss, organ failure, and death.
- ADE involves cytokine storms, a runaway immune system response

Four distinct dengue viral serotypes



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Protective antibodies can turn double agent, teaming up with the dengue virus to make an infection more severe, even life-threatening.

http://scim.ag/dengue_antibodies

The ADE hypothesis builds on the fact that an antibody to the first dengue serotype can bind to the virus, but not strongly enough to “neutralize” it. This binding antibody/virus complex more easily enters host cells, allowing the virus to copy itself at even higher levels. The intensified infection leads the immune system to storm the body with chemical messengers called cytokines, ultimately increasing the likelihood of blood vessels leaking, causing hemorrhage and shock.

Rothman, A. L. (2011). Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. *Nature Reviews Immunology*, *11*(8), 532.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7439999/

Origins of dengue and the *Aedes* mosquito

- The four dengue viruses originated in monkeys and independently jumped to humans in Africa or Southeast Asia 100 - 800 years ago and spread slowly around the world
- Remained a relatively minor, geographically restricted disease until the global slave trade brought dengue to the South America
- Isolated outbreaks of dengue occurred in cities of southeast U.S. from 1820 to 1945
- Dengue exploded after 1950, due to World War 2 and the coincidental transport of *Aedes* mosquitoes with the dengue virus around the world

http://link.springer.com.ezproxy.uky.edu/article/10.1007/s40475-013-0008-1

Troop ship bringing Americans home after WW 2, along with dengue virus and mosquitoes carrying it

Aedes aegypti females of the African subspecies *Aedes aegypti formosus* (left) and the globally distributed subspecies *Aedes aegypti aegypti* (right). *Ae. aegypti aegypti* (abbreviated Aaa) prefers human blood-meals and is adapted to breed in human habitats. The ancestral form of Aaa in sub-Saharan Africa, *Ae. aegypti formosus* (Aaf, left), breeds in nonhuman-disturbed habitats such as forests and vegetated ecotones and prefers non-human blood meals.

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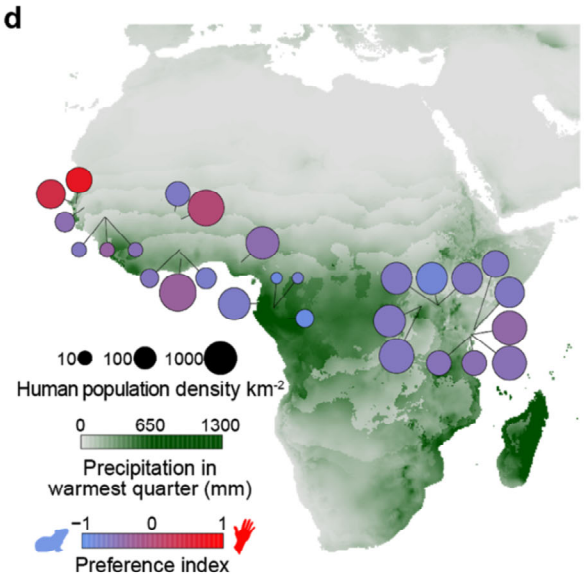
A. aegypti formosus (Aaf) is evolving and is now beginning to be found in urban areas in Africa, whereas before it was primarily a species that would lay eggs in natural water bodies.

- In east Africa, where the mosquito is native, *Aedes aegypti formosus* (Aaf), prefer to suck blood from other animals, such as monkeys and rodents.
- However, they are evolving to feed more on humans and thereby are increasing the likelihood of more dengue in Africa
- Drier climate, particularly in areas that experience a wet-dry season, along with proximity of dense human populations in urban areas are leading to the evolution of Aaf that feed on humans



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Rose, N. H., Sylla, M., Badolo, A., Lutomiah, J., Ayala, D., Aribodor, O. B., ... & Kriete, A. L. (2020). Climate and urbanization drive mosquito preference for humans. *bioRxiv*.

https://doi.org/10.1101/2020.02.12.939041

The image shows that in west Africa, Aaf is evolving to prefer more human blood meals. This highlights again one of the same points raised about malaria. Natural selection and adaptation are part of the global problem of mosquito-borne disease. Arboviruses that cause disease in humans are hard to control because the mosquitoes that carry them are dynamic in space and time.

Dengvaxia vaccine for dengue

- Dengvaxia consists of an attenuated yellow fever virus that expresses genes of each of the four types of dengue virus
- Dengvaxia requires three doses and is can only be given to people aged 9–16 who have had dengue
- Approved for public use in 2015; created by the French pharmaceutical company Sanofi Pastuer
- Prior to its use, warnings were expressed that Dengvaxia might still be given to children who never had dengue, thereby increasing the risk of ADE and hemorrhagic fever

Dengvaxia in the Philippines

- Philippines approved Dengvaxia for use but did not screen for prior exposure because they thought benefits outweighed risks of ADE
- A massive national vaccination campaign began, while other countries like Brazil proceeded cautiously
- Filipino children who had not been exposed to dengue were vaccinated, and when they developed complications, 800,000 children had been vaccinated
- Twenty children in Philippines died as a result

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https://www.sciencenews.org/article/measles-global-spread-vaccination

They also didn't screen because they thought that most children would have been exposed to dengue early in their life, as dengue is hyper-endemic in the Philippines

- Protests erupted across the country.
- Philippine government immediately ended all dengue vaccinations and suspended license for Dengvaxia to be used in the Philippines
- The deaths led to a upsurge in anti-vaxxer attitudes, and vaccinations for all diseases declined, including routine childhood vaccinations

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https://www.sciencenews.org/article/measles-global-spread-vaccination

- The Philippines subsequently had a severe dengue epidemic as well as a resurgence of measles
- Polio also re-emerged
- Dengvaxia is in limited use today
- Company that makes Dengvaxia is discontinuing it in the third quarter of 2026 due to low global demand

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https://www.dw.com/en/dengue-vaccine-controversy-sparks-panic-in-philippines/a-42711828
https://doi.org/10.1080/21645515.2018.1522468
https://www.nytimes.com/2019/08/06/world/asia/philippines-dengue.html
https://www.cdc.gov/vaccines/acip/recs/grade/CYD-TDV-dengue-vaccine.html
https://www.pharmaceutical-technology.com/features/dangvaxia-philippines/?cf-view

Odenga

- Much more widely used than Dengvaxia
- Developed by the Japanese pharmaceutical company Takeda
- Requires two doses and is for people aged 4-60 regardless of prior history of infection
- 80% efficacy

A girl receives a dose of the Qdenga dengue tetravalent vaccine in Brazil. Michael Dantas/Agence France-Presse — Getty Images

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https://www.nature.com/articles/d41586-023-03115-1

Butantan-DV

- Single-dose and 80-90% effective
- Made by Brazilian researchers
- Vaccine targets all four dengue virus serotypes.
- Safe for people with or without a prior dengue infection
- Not yet been approved for public use

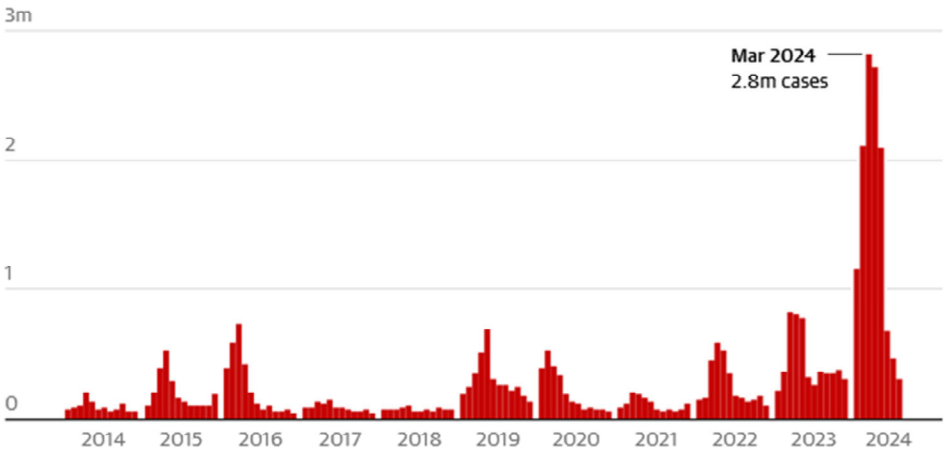
Dengue is raging in Brazil. A promising local vaccine is at least a year away

Record-breaking outbreak, fueled by an unusually hot rainy season, is disproportionally affecting poor people

5 MAR 2024 • 4:00 PM ET • BY MARCIA TRIUNFOL

Global cases of dengue fever rose steeply in 2024

Monthly global cases, millions



Guardian graphic. Source: WHO. Note: case reporting requirements vary by country

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Readings/Questions 13

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https://www.nytimes.com/2024/02/10/health/dengue-brazil-americas.html

Dengue is hyperendemic in Brazil, its high prevalence remains constant from one year to the next. The start of 2024 saw a large increase in dengue, so large that it became a public health emergency that overwhelmed hospitals.

- Millions of Brazilians live in densely populated, irregular communities called favelas
- Because of their rapid growth and spontaneous character, favelas are often beyond the reach of government services and basic utilities.
- Inadequate stormwater and sanitation infrastructure

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- With unreliable water service, people often resort to storing water outside, creating countless mosquito breeding sites.
- Uncollected rubbish becomes a breeding ground for the insects
- If water sits for one week, the mosquito life cycle can be completed

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One of the favelas or shantytowns of São Paulo, Brazil's largest city, where local residents have turned a stream into an open-air garbage dump and a source of frequent flooding due to lack of sewage and garbage collection. Nor do favelas in Brazil’s cities have piped water.

Other causes for Brazil's current dengue crisis:

- Warming climate particularly in areas of southern Brazil where climate has historically been cooler
- Limited availability of Qdenga
- Limited hospital capacity for large number of dengue cases
- After several years during which only two of the viral subtypes of dengue predominated in Brazil, the other two have recently returned. Many Brazilians are vulnerable to these subtypes, so they are more likely to become infected.

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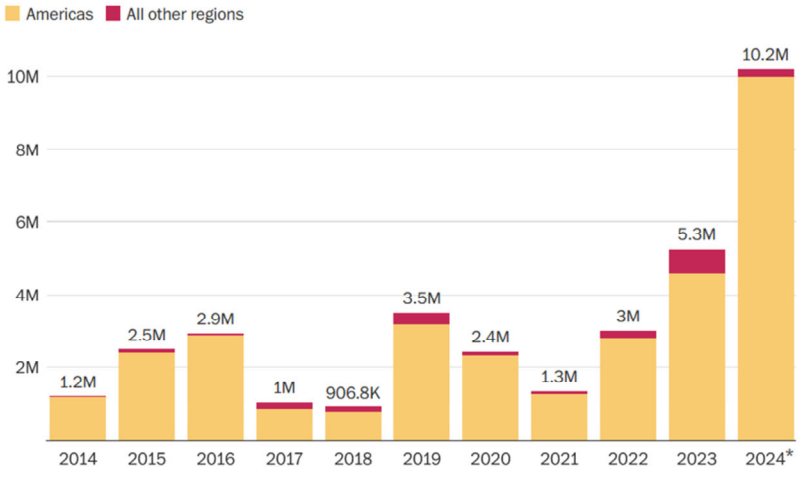
https://www.nature.com/articles/d41586-024-00626-3
https://www.washingtonpost.com/world/2024/03/10/dengue-fever-brazil-outbreak-epidemic/

Surging cases in the Americas fuel a record dengue epidemic



*2024 case numbers as of June 26 for the Americas, May 31 for all other regions

Source: World Health Organization

SARAH KAPLAN / THE WASHINGTON POST

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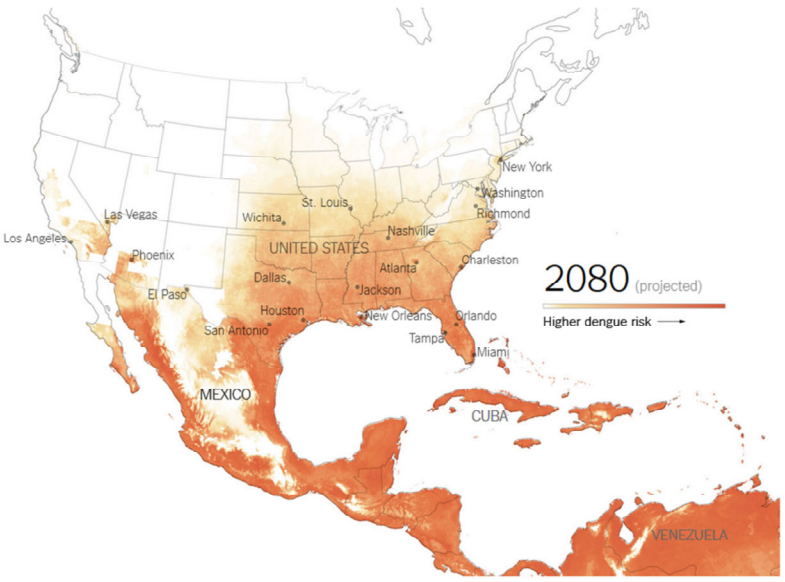
- Dengue is the most likely mosquito-transmitted disease to become established in the US because of climate change
- *Aedes aegypti* is here, just need the virus to expand out of where local transmission has taken place



Source: Messina, Brady et al. Nature Microbiology

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Model projections of dengue risk

https://www.nature.com/articles/d41586-024-00626-3

Targeted methods of mosquito control

- Older strategies of control worked but could be inefficient and have negative side effects
- More recent approaches
  - Precision public health
  - Biocontrol of mosquito populations
    - Sterile mosquito treatments
    - Wolbachia biocontrols
    - Gene drives

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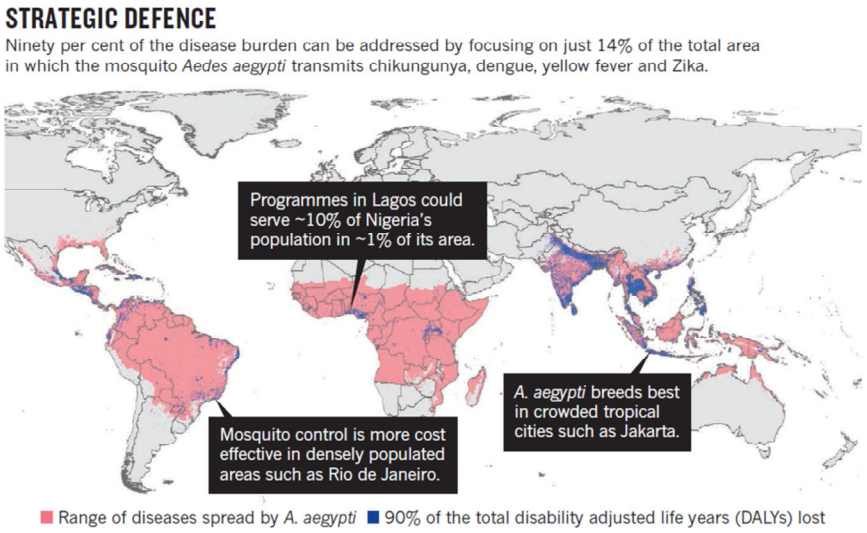
Precision public health



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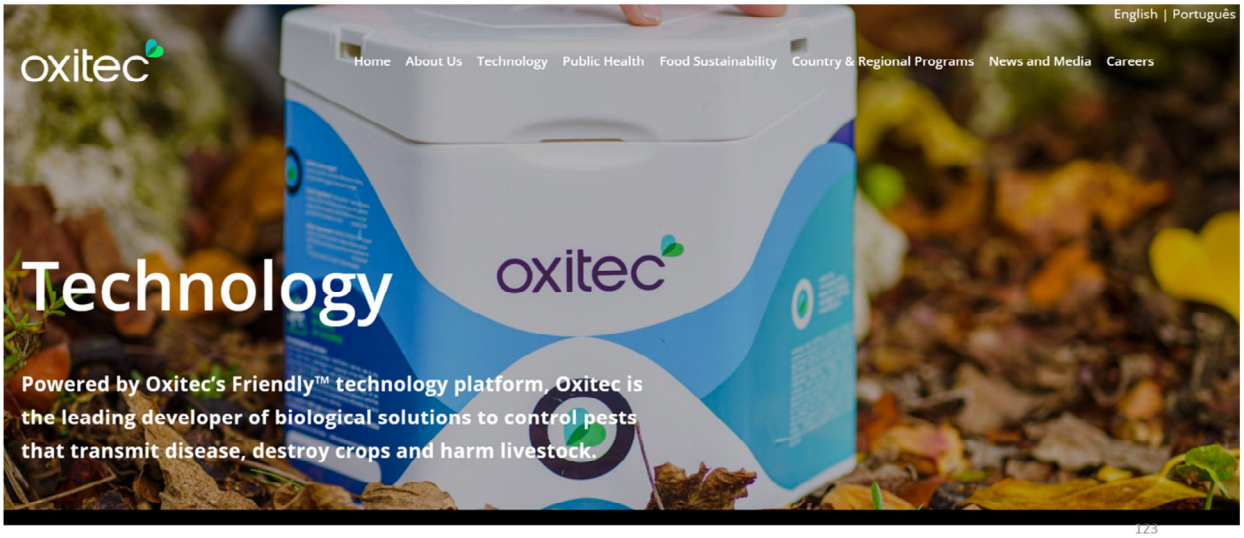
When domestic transmission of Zika virus was confirmed in the United States in July 2016, the entire country was not declared at risk — nor even the entire state of Florida. Instead, precise surveillance defined two at-risk areas of Miami-Dade County, neighborhoods measuring just 2.6 and 3.9 square kilometers. Travel advisories and mosquito control focused on those regions. Six weeks later, ongoing surveillance convinced officials to lift restrictions in one area and expand the other.

By contrast, a campaign against yellow fever launched this year in sub-Saharan Africa defines risk at the level of entire nations, often hundreds of thousands of square kilometers. More granular assessments have been deemed too complex. Precision public health focuses on specific areas where disease outbreaks are more likely or where their effects impact a large number of people. This is a more cost effective refinement to the idea of complete global surveillance.

Sterile insect treatments



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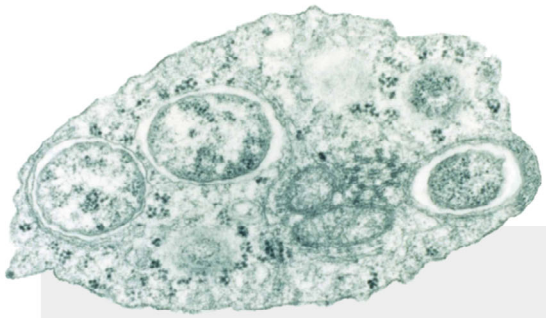
Beebe, N. W., Pagendam, D., Trewin, B. J., Boomer, A., Bradford, M., Ford, A., ... & Ritchie, S. A. (2021). Releasing incompatible males drives strong suppression across populations of wild and Wolbachia-carrying Aedes aegypti in Australia. *Proceedings of the National Academy of Sciences*, *118*(41).

- Male mosquitoes have been genetically modified to carry a gene that is lethal to female offspring.
- Male mosquitoes have to be raised and released to initiate the control
- When released into the environment, the engineered males will mate with wild females, and their female offspring will die before they can reproduce.
- Male offspring will carry the gene and pass it on to half of their progeny.
- As each generation mates, more females will die, and mosquito populations dwindle

https://www.oxitec.com/en/our-technology#how-it-works

Wolbachia biocontrol

- *Wolbachia* is a genus of bacteria that live inside many different insects.
- Although it is not typically found in disease-carrying mosquitoes, it can be artificially introduced Into them.
- Wolbachia have been shown to stop the malarial parasite's capacity to infect mosquitoes and is considered an effective biocontrol agent



Unleashing a New Weapon on the Mosquito: A Mosquito

Readings/Questions 13

https://www.nytimes.com/interactive/2023/09/29/health/mosquitoes-wolbachia-disease-viruses.html

Microscope image is of Wolbachia bacteria inside an insect cell

Beebe, N. W., Pagendam, D., Trewin, B. J., Boomer, A., Bradford, M., Ford, A., ... & Ritchie, S. A. (2021). Releasing incompatible males drives strong suppression across populations of wild and Wolbachia-carrying Aedes aegypti in Australia. *Proceedings of the National Academy of Sciences*, *118*(41).


OUR
WOLBACHIA
METHOD
World
Mosquito
Program
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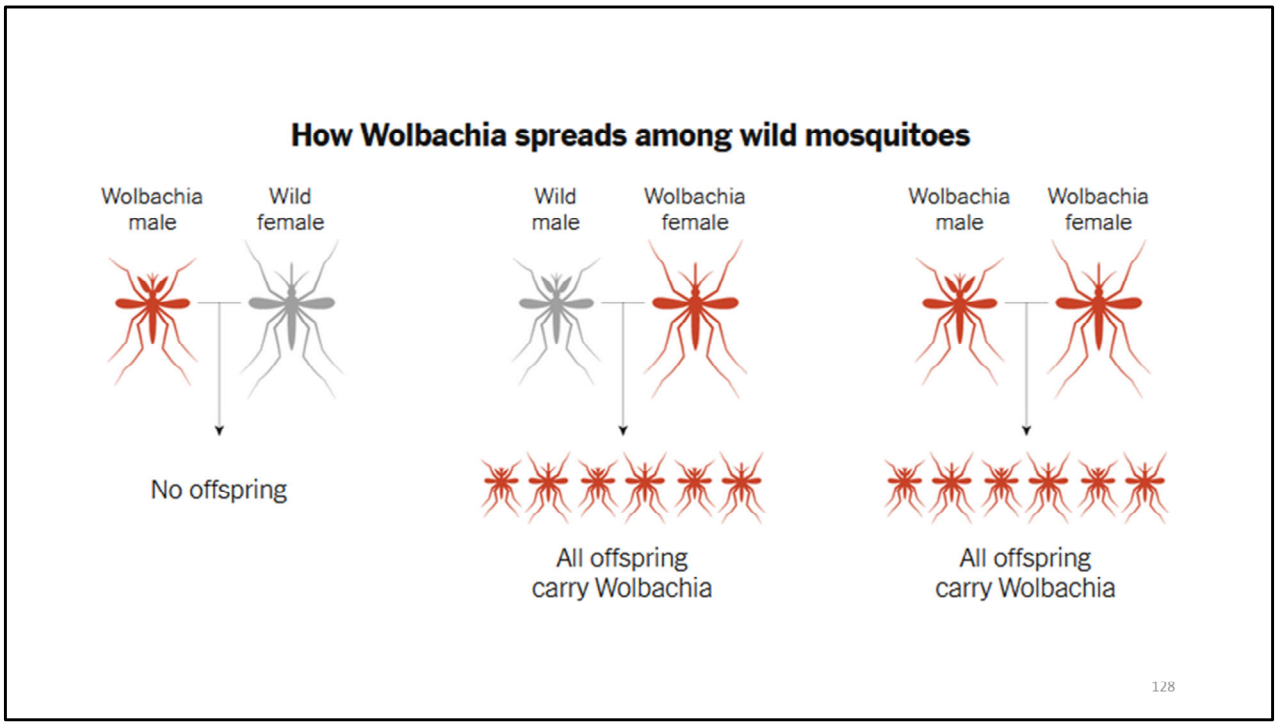
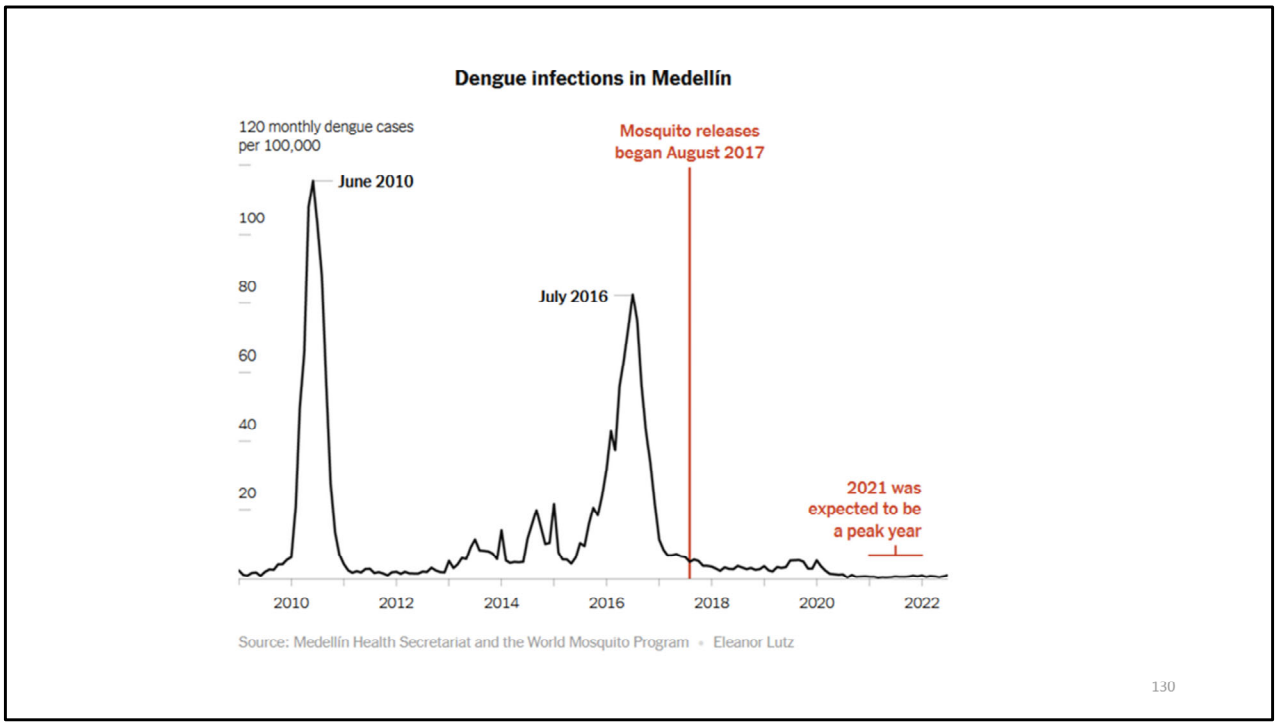


https://int.nyt.com/data/videotape/finished/2023/05/1684848644/900-900w.mp4
https://www.nytimes.com/interactive/2023/09/29/health/mosquitoes-wolbachia-disease-viruses.html

https://www.youtube.com/watch?v=gzT96OxPa9U&t=139s



This image shows the impact of the release of Wolbachia-infected mosquitos on the incidence of dengue fever in the city of Medellin, Columbia

Gene drives

https://www.nytimes.com/2023/09/29/health/mosquitoes-genetic-engineering.html

- The unique and useful attribute of gene drives is that the genetic change they induce in a population of organisms spreads on its own very efficiently.