PLOS Science Wednesday: We're Laura Pollitt and Andrew Read, and we found that mosquitoes can harbor multiple infections of the malaria parasite at once and transmit a double-dose of malaria infection,

PLOSScienceWednesday [1] and r/Science AMAs[1]

[1]Affiliation not available

April 17, 2023

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ABSTRACT

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CORRESPONDENCE:

DATE RECEIVED:
September 17, 2015

DOI:
10.15200/winn.144240.05823

ARCHIVED:
September 16, 2015

CITATION:
PLOSScienceWednesday , r/Science , PLOS Science Wednesday: We're Laura Pollitt and Andrew Read, and we found that mosquitoes can harbor multiple infections of the malaria parasite at once and transmit a double-dose of malaria infection,, *The Winnower* 2:e144240.05823 , 2015 , DOI: 10.15200/winn.144240.05823

What are practical arguments for and against total mosquito eradication? I get that other species rely on them for food...species we tolerate largely because they kill mosquitos! What happens when mosquitos are gone?

Air_Hellair

Laura: There are some environments where mosquitoes are likely to play an important role in ecosystems. For example, in the artic mosquito eggs hatch after the snow melt and there is a brief period where they are extremely abundant and therefore provide an important food source for migratory birds and change behaviour of other animals such as caribou. Other insects, spiders, fish, lizards and frogs will all feed on mosquitoes or their larvae but in general this only represents a small part of their diet so it is likely that something else could fill the gap. Mosquitoes also act as pollinators for many plant species but they are not generally the main pollinator so it is likely the impact of their loss wouldn't be huge in this regard. In general I would think that the largest ecological impact of mosquito eradication would be increasing human populations in areas where mosquitoes are currently abundant.

What are your opinions on the use of *Wolbachia* as a method of biocontrol for mosquitoes carrying diseases like malaria or dengue fever?

Would it be possible to pair *Wolbachia* with the driving Y chromosomes you find in natural populations of some mosquito species to increase *Wolbachias* probability of spreading?

tomhilll

Laura: Wolbachia is a common bacterium that infects insect cells which seems to block dengue virus. Trials were Wolbachia has been used to prevent the transmission of the virus that causes Dengue have been promising and the initial trails in Australia are not being followed in South-East Asia and Brazil. However malaria parasites are transmitted by a different species of mosquito and wolbachia protection does not seem to work so well. In fact some studies have actually suggested that wolbachia infection could enhance the ability of malaria parasites to infect mosquitoes.

What is the best repellent and do you two have to use it in your line of work?

Bkeeneme
Laura: luckily our mosquitoes are safely contained in cages so we don't need to worry too much about bites at work. Outside work though it is known that different people vary markedly in their attractiveness to mosquitoes so I would suggest the best strategy may be to carefully choose friends who they will pick over you! Failing that DEET based repellents and mosquito nets are probably still your best protection.

What is the best repellent and do you two have to use it in your line of work?

Bkeeneme
Andrew: Speaking as the lab boss, something is going very seriously wrong in the lab if any of the people in it get bitten.....

Good morning Laura and Andrew, thank you for doing this AMA. I was wondering how detrimental is Plasmodium to the mosquito health and how do the mosquito hosts fight off the infection? Is there a limit to how long Plasmodium can survive in the mosquito or the mosquito have Plasmodium survive in it? Also I was wondering if you think it is an issue that there is an overwhelming amount of research done on Falciparum and not other species like Knowlesi or Vivax.

Bmyers221
Laura: This is a good question and doesn't have a clear answer. There have been various studies looking at cost of infection with malaria parasites for the mosquito and it seems to depend on the conditions the mosquitoes are experiencing, the density of the infection and the specific combination of parasite and vector. In the lab high density infections result in higher mosquito mortality but low density infections do not have much cost. However, in the lab mosquitoes are generally kept in ideal conditions so may be better able to tolerate infection.

How much genetic variation is there is the malaria parasite species?

nallen
Andrew:

A lot.

It's a bit hard to compare genetic variation, but the way I think about it, the parasites have a genome about 20% the size of ours, so that's a bucket load of genes, and a bucket load of genetic variation. Think about it: a person really sick with bigh parasite densities has a billion or even ten billion parasites in their body...and there might be 10 million or more people in that condition every year. That's a lot of genomes to contain a lot of variation. No doubt that's part of the reason they evolve around drugs so fast, and why it's been so hard to develop a vaccine that stays working.

Is there any truth to the claims that Malaria has been the single most damaging sickness/affliction to plague mankind? Aside from hunger, old age, etc. How is that possible given most of our population moved out of its current 'hotzones' long ago?

Ferelar
Andrew: It sure has been one of the most serious sicknesses afflicting human kind. You can tell that by the number of genes in the human genome that confer resistance (or semi-resistance) - many of the

best known examples of natural selection on human genes are anti-malaria genes. So the implication is that malaria is imposing very serious selection on human genomes now and in the recent (on geological timescales) past. We didn't move out of the hot zones all that long ago - and the hot zones until recently included much of North America and Europe. Its housing and health care infrastructure, as well as environmental modifications - in short wealth - which stopped malaria in what we now call the rich world.

So mosquitoes that feed on multiple blood meals acquire multiple malaria infections which is ultimately beneficial for malaria with no ill effect on vector health.

What about interactions with other blood borne parasites picked up during those multiple feeds? Is much known about the effect of various parasite cocktails? i.e. How they might facilitate or hinder each other in mosquitoes? Or is this not very common?

Thanks :)

TheToiletDuck
Laura: Good question.

It is likely that mosquitoes will be picking up multiple blood borne parasites and very little is known about how these interact. There is some evidence that some bacteria may hinder malaria establishment through activation of the mosquitoes immune response but this has generally been looked at under pretty unnatural conditions.

A parasite interaction which could be very interesting would be between malaria parasites and filarial worms which cause lympathic filariasis. Both these parasites are transmitted by Anopheles in the same area. There is some data suggesting that previous infection with filarial worms may reduce the chance that mosquitoes will become infected with malaria parasites but more research is needed.

Do you guys receive any funding from Monsanto? There's been like a single case of west nile in St. Louis, and all of a sudden now you have suburban families dousing themselves with pesticides as if it were cologne before they start their day. I think it's absurd and actually a much larger risk to spray that crap all over yourself.

lonewolf227z
Andrew: Our work is funded by the National Institutes of Health.

I do think public reactions to infectious disease are very interesting. I was teaching a class of 200 students last year when that nurse got Ebola in Dallas. The students were really freaked out. I could not explain to them how there worries were so misplaced until I heard the obvious statistic: they were more likely to meet Kim Kardashian than to catch Ebola in the US.

The timing and duration of life cycles of ectothermic organisms are strongly influenced by temperature. How does temperature variation, at diel and/or seasonal scales influence mosquito phenolgy and how do these changes affect or mediate the dynamics of the malaria parasites living within the mosquitoes?

farsong
Andrew: temperature is hugely important. It affects the speed of development (time to infectiousness) of the parasite in the mosquito, as well as just about everything of the mosquito - immunity, life length, fecundity, speed of development, size of mosquito, propensity to get infected, lethality of insecticides.... Broadly speaking malaria does best in the 26-28deg range; away from that, the cold slows it down or the mosquito can control it; above that, it starts to die, either from the heat directly or

because the mosquito immunity is running hot.

Lots of questions about the effect of the eradication of mosquitos, is this a realistic goal? How would one go about totally eradicating mosquitos? and when can we start with the plan to eradicate?

Tyrant-i
Andrew: My view is that eradicating mosquitoes is a fantasy. There are hundreds of species. I think eradicating the main malaria vector species would be fantastically good, but its hard for me to imagine any implementable technology that could get them all. These days, we couldn't get enough insecticide out there to get them all. Maybe some selfish genetic elements could spread widely, but even then, with geographic and ecological barriers, its asking a lot of them to drive themselves everywhere. I hope I am wrong.

Do Mosquitoes provide anything, ANYTHING, of value to anyone or anything on or for this planet what-so-ever?

alexgorale
Laura: In some environments they can be very important. For example, in the artic mosquito eggs hatch after the snow melt and there is a brief period where they are extremely abundant and therefore provide an important food source for migratory birds and change behaviour of other animals such as caribou. Also in pitcher plants the larvae breaking down nutrients and help the growth of the plant. In general though most ecosystems could cope without them.

1. **What is it about Anopheline mosquitoes that make them the only vector of malaria to human hosts?**
2. **Dr. Read, in your paper "How to make evolution-proof insecticides for malaria control" you suggest the use of late-life acting (LLA) insecticides and support it with evidence of decreased insecticide resistance in senescent mosquitoes. However, the enzymes that metabolize or sequester an insecticide is low in the teneral stage of the adult mosquito and the senescent mosquitoes. Would using a lower dose of insecticide to kill senescent mosquitoes also kill the teneral mosquitoes, possibly negating the effect that an LLA would have (to allow insecticide susceptibility alleles to remain in the population)?**
3. **How common are multiple malaria infections in human hosts?**
4. **Does it matter if the malaria parasites share the same host (i.e., can a mouse malaria enhance a human malaria and vice versa)?**

Thanks for doing this AMA. Hope to catch you at AMCA this year.

bobbo9
Andrew: 1. Million dollar question. I can give you trite questions (human malarias don't develop in the others), but why they don't really isn't at all clear. 2. I don't see any evidence for that. In our work, the adults become increasingly sensitive to insecticides as they age. 3. Very. Most malaria parasites share their human host with genetically distinct malaria parasites 4. Malaria parasites, at least the mammalian ones, are super host specific. There can be spill over from one species to another, but the real risks seem to come with the ones that specialize on us.

Do you think Hadyn Perry and team's technique of genetically engineering mosquitoes to reduce populations will yield realistic, effective, and sustainable outcomes in the fight against mosquito-borne disease?

chadfromthefuture

Andrew: I think it has enormous potential for some mosquito-borne diseases, for instance when the mosquito population involved is relatively low density and self contained, and the mosquito can be easily bred in huge numbers and released without too much bother. This is true for some dengue situations, and might even be true for some malaria situations (e.g. islands). But it works by inundating the mosquito population with lab-bred mosquitoes. If new ones move into an area, or the numbers released can't be gotten high enough....

I envision AR (augmented reality) as making great strides in the next couple of years that could have so many applications - a few I can foresee happening in the realm of insect occlusion/identification.

Are there any impending technologies you are aware of or have dreamed up that have you excited about its applications to your work?

hipcheck23
Andrew: I'm excited about what's happening with gene driver technologies. The ability to drive novel genes through populations seems to be getting easier (at least the technology aspect). This opens up immense ethical issues, but it sure isn't boring.

In my other work, I'm excited about trying to develop evolution-proof drugs that would work forever - or at least a long time - rather than be undermined by the evolution of drug resistance. There are ways to do this, but it's a very fresh field.

I'm regularly attacked my mosquitoes when I go outside. Is time dream of a mosquito free world farfetched? Would it really be detrimental to the ecosystem if all mosquitoes died?

Fruhmann
Laura: A mosquito free world is a long way off sadly. In terms of impacts on ecosystems of eradicating mosquitoes there would be some specific examples where there could be dramatic knock-on effects but I would still do it if possible. Longer answer to a similar question further up.

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Laura: There are millions of parasites within a host and millions of people infected with malaria. This means that even a rare mutation that confers drug resistance is likely to occur within a relatively short amount of time. That drug resistant parasite is then going to have a huge advantage over the susceptible genotypes and therefore going to rapidly spread. We have seen this repeatedly with every new anti-malarial drug which has been introduced being followed by the emergence and spread of resistance. This with the evolution of resistance to insecticides in mosquitoes have been major hurdles in the eradication of malaria. I would suggest we need to think carefully about ways that we can try and use smarter interventions that are not as susceptible to rapid evolution.

Is there any current work into malaria control along similar lines to this; wolbachia bacteria being used to control dengue fever?

nesrekcajkcaj
Laura: Malaria parasites are transmitted by a different species of mosquito and wolbachia protection does not seem to work so well. In fact some studies have actually suggested that wolbachia infection could enhance the ability of malaria parasites to infect mosquitoes.

You say there doesn't appear to be adifference in survival for the mosquito, wether they get amultiple strain infection or just one strain. How sick do the mosquitoes tyically get?
Also are you talking about different strains of the same species, for example a Chloroquine resistant and a sensitive strain of P. falc, or are you talking about different species like vivax and malariae?

unclear_plowerpants
Laura: How sick mosquitoes get when they are infected with malaria is a good question without a clear answer. There have been various studies looking at cost of infection with malaria parasites for the mosquito and it seems to depend on the conditions the mosquitoes are experiencing, the density of the infection and the specific combination of parasite and vector. In the lab high density infections result in higher mosquito mortality but low density infections do not have much cost. However, in the lab mosquitoes are generally kept in ideal conditions so may be better able to tolerate infection.

If science could come up with a way to eradicate every mosquito would it be an ecological disaster to use it? Because I've often fantasized about pushing the button that would end all of the little bastards lives but wondered what negative impact it might have.

RollieMe
Laura: There are some environments where mosquitoes are likely to play an important role in ecosystems. For example, in the Arctic mosquito eggs hatch after the snow melt and there is a brief period where they are extremely abundant and therefore provide an important food source for migratory birds and change behaviour of other animals such as caribou. Other insects, spiders, fish, lizards and frogs will all feed on mosquitoes or their larvae but in general this only represents a small part of their diet so it is likely that something else could fill the gap. Mosquitoes also act as pollinators for many plant species but they are not generally the main pollinator so it is likely the impact of their loss wouldn't be huge in this regard. In general the largest ecological impact of mosquito eradication could be increasing human populations!

Andrew, how do you think the upcoming malaria vaccines (RTS,S and Sanaria's developing sporozoite vaccine) will potentially impact *Plasmodium* evolution? Much of your lab's competition work suggests selection for higher virulence occurs in the blood stage, but if vaccination imposes selection for parasites that can somehow evade CD8+ liver-stage immunity, could that carry a fitness cost that might temper blood-stage virulence?

SerJorahTheExplorah
Andrew: I think it all depends on whether the vaccines leak parasites into the blood stream, and if they do, what that means. One possibility is that they never will (=no evolution). Another is that if they do, the blood stream infection is the same as if the person was never vaccinated (=no new selection pressures). Another possibility could be serious from an evolutionary point of view: if they leak but the resulting blood stream infection is less virulent, that would mean reduced selection against virulence and hence the potential evolution of more virulent malaria.

It should be pretty easy to look at this. The data may already exist, but I have not seen it published. RTS,S clearly does leak. When infections happen in vaccinated people, are they less severe or are the parasite densities reduced compared to vaccinated controls?

Hi Laura, I've never met another Pollitt before--nice to meet you!

Is there any validity to the notion that some people are more susceptible to getting bit by mosquitos?

dtpollitt

Laura: Hello dtpollitt - nice to meet you too.

Yes there is evidence that some people are more attractive to mosquitoes - I would suggest these are good friends to make!

Andrew/Laura, could you comment on the role of immature red blood cells in transmission-stage investment by malaria parasites? Laura's own work has seen the majority of gametocytes being produced immediately following the most severe period of anemia in *P. chabaudi* infections, and Matthias Marti's group found an enrichment of gametocytes in the bone marrow of children who died from *P. falciparum* malaria. Is this an adaptation by parasites that causes them to invest more heavily in transmission when immature RBCs are prevalent, or do you think gametocytes are more likely to survive in these cells because they're hardier/more nutritious than older RBCs?

SerJorahTheExplorah
Laura: Some old research suggests that parasites that invade immature young red blood cells are more likely to develop as gametocytes than those that invade mature red blood cells. This has led to researchers who want to use gametocytes in culture treating mice with a drug that causes them to produce more new red blood cells. Gametocytes take much longer to develop than asexual parasites so it could be an adaptation where developing in a young red blood means it is more likely to still be around when the gametocyte reaches maturity.

Hello! First off, thank you so much for doing this! As a recent eve-bio grad and (hopeful) epidemiology masters student, AMA's on subjects such as this are truly appreciated!

I just finished reading "The Malaria Project" by Karen Masterson and was amazed at just how prolific malaria research was during World War 2, when the consequences of infection on troops had huge implications for campaign success. Not only did it spur the creation and development of many pharmaceuticals to cure/prevent (i.e chloroquinine, sulfa compounds, etc.), but it created a vast wealth of knowledge about malarial transmission/strains/etc. However, it seems that once world war 2 ended, with the main impetus for research and development gone, malaria research drastically slowed down. In addition, with many massive (and successful) eradication efforts in western countries, I could see how the drive for developing malaria "cures" and prophylactics could decrease. Many of the prophylactics and medicines we have today have their fair share of side effects.

My question is, do you think this is indeed the case? What would it take for an increased amount of R&D in malaria, specifically in pharmaceuticals and prevention efforts? Possibly increased ranges of hosts due to climate change?

edit: Just to clarify, I understand that prevention efforts tend to have much larger impacts on malaria prevention/decreasing malaria morbidity. Just curious about your thoughts.

GoodCookYea
Andrew: No question, when malaria affects rich people, or their soldiers, there is more money for R&D.

I don't think climate change will impact that much. Sure, conditions for malaria transmission might improve in some areas, but rich people have air-con, well built houses, screening and access to good primary health care. So sadly, I am not expecting any big R&D input soon. Malaria is a disease of poverty.

Do you think it was effective (or funny) when Bill Gates released Mosquitos on an audience and said that it shouldn't only be poor people who have to deal with malaria? I know I thought it was

hilarious but I'd be interested in hearing your opinion on that.

althormoon
Andrew: I thought hugely effective.

I really like that Bill Gates has not only put a lot of his own money into malaria control, he has shamed rich countries, governments and others into doing more too.

Do the strains not compete for resources in the host?

Do you know if the same is true, in theory, for infections of multiple strains of dengue?

davidmanheim
Laura: In mice (and we suspect in humans) malaria strains are likely to compete for red blood cell resources. In our mixed strain infections in mosquitoes we didn't see any evidence of this occurring (strains did the same or better in competition). This may have been as the overall parasite numbers were low enough that there wasn't any resource limitation. It would be interesting to try the experiments with strains that reach high densities to test this.

I'm afraid I don't know the answer to this for Dengue.

[deleted]

[deleted]
Andrew: Hi.

There are two others I know in science, one at Duke who works on marine mammals and one in Australia on infectious diseases.

Kudos for using correct oocyst loads. Much more credible real world meaning.

Curious to see what the rate of mixed infections is mosquitoes in malaria endemic areas. Nice paper!

RabidMortal
Laura: Thanks. We would love to look at this in natural populations. There have been very few studies reporting rates of mixed strain infections in mosquitoes from natural populations although one study on mosquitoes in Tanzania showed that more than 60% of A. gambiae mosquitoes carried more than one genotype of the human malaria parasite P. falciparum.

This is probably a stupid question but how much worse is effects of double malaria than just single malaria?

Hongxiquan
Andrew: actually that varies around the world. Sometimes genetically diverse infections are associated with more severe disease, sometime less diverse; it depends on where you are. My read on it is that mixtures are more likely where transmission rates are higher, but immunity is also higher, so there is a lot going on.

In our mice, diverse infections are more virulent.