

The Posi⊕ive Deviant

Forget what others are saying. Decide for yourself.



The Positive Deviant is a series of occasional Webless Blogs (WLBs) that seek to cut through knotty problems with rapier wit as honed as a Macedonian sword. In olden days, a WLB was known as *ex manus*, which is Latin for handout. OK, not really about the Latin, that was a joke. They didn't even have handouts back then, since it was too hard for Roman kindergartners to walk home from school with stone tablets pinned to their little togas.

Seriously, these WLBs come packed with info to help you decide for yourself about complicated issues. Like PST vaccinations, these should inoculate you, we hope generally against associating yourself with any lemmings rushing about, but with a more robust response, you might also acquire deeper immunity against becoming a mindless zombie after the apocalypse. (Please let us know if that works out for you.)

Malaria Meds



Summary: We at Peace Corps medical are asking you to decide with your PCMO which malarial prophylactic medication you think is best for you, and then commit to taking it for 100% of your time in Peace Corps, not just on the days you remember, or when you feel like it. Notice the effective use of bold formatting. The bold helps you recognize that this is important.

Malaria is a maddening disease. It can be prevented, and most of the time it can be fully treated. Yet the World Health Organization estimates that it kills 1.24 million people each year, half of which are anonymous and unreported, and most of those are children ☹. Ninety percent of malarial deaths occur in Africa. Severe malaria can kill you in just hours; alternatively, it can just leave you with permanent neurological deficits, if we can treat you fast enough.

Among travelers, there are 30,000 cases of malaria each year, and between 300 and 1200 of them will die from the disease. It appears you must get an active malaria infection 5 times before you develop any natural resistance, which is why PCVs and other travelers generally do not develop resistance. It is also why so many children die from the disease, since they get it repeatedly before they have any resistance. So, if you were not born and raised in a malarial country, or if you were and you had screens or air conditioning, then you do not have

resistance, period. This is true regardless of your race or ethnic heritage. (There might be an exception for people who are born with sickle cell anemia, but that's a WLB for another day.)

BFFs vs. the mini Terminators



Malaria is transmitted by a specific family of mosquitoes which evolution has kindly honed to find you. They track you down at night, and are attracted by your heat, your sweat, and the CO₂ that you exhale. Things you love to do and places you love to go, they love to do and go as well. They especially love the traces of alcohol in your sweat when you've been drinking and your skin is flushed. They're like your best friends forever, or worse, like a million mini Terminators, all searching for you. Unless you are holding your breath and living inside a refrigerator, they will find you. Once they find you, carrier mosquitoes will inject malaria parasites of one kind or another (there are 5 types to choose from) when they bite you.

There is nothing sexy about flirting with malaria, and nothing heroic about getting it. At Peace Corps, we would prefer that you not even try, thank you. We recommend a multi-pronged approach to avoid the mosquitoes, using nets and screens and repellent, etc, but since this WLB is called "Malaria Meds," I think I'll focus on how medications can be used to control the parasite once it gets inside you.

Venn beer caps



There are four FDA approved medications that can prevent the little buggers from thriving in your bloodstream. It takes a slightly different set of medications to treat an active infection, although there is overlap, like a Venn diagram. It takes yet another medication to kill the parasite where it hides in your liver. This last medication, primaquine, can also kill malaria in your blood stream, but it's not FDA approved for that, so Peace Corps doesn't use it that way. On the other hand, primaquine adds a nice third circle to our Venn diagram, which makes it look like Borromean rings, the very-nearly-almost famous topology puzzle from mathematics, or more likely, the actually famous Balentine beer cap.

Of the three rings, we're only going to be talking about the meds for keeping your bloodstream cleared in this WLB. When you finally leave a malarial country is when we give you the medication that kills the liver parasites. And we are hoping that we *never* find occasion to give you the medications that we use to treat the active disease.

As mentioned above, there are four medications that clear your bloodstream. These are the medications that we usually refer to as malaria prophylactics, but that's really a misnomer, since **the prophylactic medications only suppress active disease rather than prevent you from carrying malaria inside your liver.** And yes, you've detected a pattern. I made that sentence bold in case you might want to remember it. What I'm saying is that the prophylactic medications clear any parasites in your blood stream, but they don't prevent a mosquito from injecting you with live parasite in the first place.

You have to take one of the four medications continuously while you are in malarious areas. They are divided into two types: medications that you can take once a week, chloroquine and mefloquine, and those that you have to take every day, doxycycline and Malarone. I'll discuss the pros and cons of each in turn, but first I want to review a little science, maybe with some philosophy sprinkles on top.

Ice cream, exploding hamburgers, and conflicted philosophers



So, I hear this guy Einstein might have been pretty smart. He sits around the patent office and thinks for a bit, captures one of the simple beauties of the universe in $E = mc^2$, then kicks back and, rumor has it, visits a stylist named Van de Graff. But I can tell you Einstein knew squadoosh about how chronic stress can induce an inflammatory response in the vascular endothelium that makes lipid-laden foam cells adhere in layers to form atheromas, which eventually create the number one killer in the United States. And that's just one simple version of how heart disease happens. In biology, you just can't think this stuff up.

No single person can discern the truth in medicine, even if he or she is a genius with bad hair. It takes thousands of researchers and millions of patients to create the science of medicine. The reason I bring this up is because you will hear and read many complaints about malaria medications, particularly mefloquine. But even when you hear something from individuals who appear sincere and knowledgeable, compelling arguments and passionate pleas only rarely align with solid medical science.

Mistakes occur surprisingly often in the reasoning that interprets and applies medical research, occasionally among the scientists who do it for a living, but moreso among proselytizers with agendas. And now, in a subtle yet sophisticated attempt at literary foreshadowing, I would like to consider three common mistakes before moving on to the medication review.

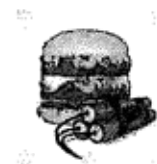


The first mistake is a statistical error, confusing association with causation. This happens all the time. For example, back in 1940, a tight association was found between polio and ice cream sales. It was so convincing that many municipalities recommended banning the nefarious treat from their neighborhoods.

After a decade of shriveling waistlines, researchers finally proved that the polio virus was getting transmitted in public swimming pools, which incidentally, just happened to generate a lot of ice cream sales. Flush toilets were also implicated, because indoor plumbing had interrupted the usual childhood exposures and had reduced the natural immunity in the herd of swimming kids. There are never simple answers in medicine, trust me. It took still more years to finally dislodge the notion that ice cream was dangerous. Ben and Jerry are just so grateful that association was dissociated from causation.

The second mistake is using a substitute for the thing that you're actually trying to understand. Biology and chemistry are very particular about how they conduct themselves, like they went to cotillion or something. For example, elemental sodium is a volatile metal that explodes when

it contacts water. There are 1040 mg of sodium in every Big Mac, and yet somehow I don't see a lot of exploding hamburgers at McDonald's. Don't stop me if you know this one.



The sodium in hamburgers is in an ionic compound with chloride, making salt, and that makes your happy meal tasty instead of incendiary. You simply can't extrapolate the interactions of one form of a molecule to another, however similar they might appear. So, if you want some dynamite hamburgers, 4 out of 5 chefs recommend cooking with elemental sodium. The 5th chef is still missing. But if you want to study salt, then you have to use salt in your study. I know, I know. Profound. (sigh) It's a gift.

The third mistake is using a specific instance to make generalized conclusions. There is a quote in medical science that goes, "the plural of anecdote is not evidence." In medicine, anecdotes are known as case reports or case studies, and the problem with them, even in plural, is that no confounding variables can be controlled, and with so many confounded variables out there, the outcome in a case can be due to anything, even ice cream behaving badly. Dramatic case reports are seductive, they often tug at our emotional strings and can convince juries of a verdict, but they actually can never prove causation, and their outcomes might well have occurred by chance alone.



This third mistake is more nuanced than it may appear at first, however. We do, in fact, use individual case studies to inform and motivate medical science. It's one of the first places we look to inspire new areas of research, and that means cases are familiar territory in science. And while the particulars of a case report don't generalize, the principles often do, so they do indeed teach us something. The schizoid nature of case studies was made famous (here comes the philosophy sprinkle) by my favorite philosopher, Wittgenstein. He spent the first half of his career arguing that unique case studies were irrelevant, then he notoriously changed his mind and spent the second half of his career disagreeing with himself. Maybe he was a bit schizo to begin with (a common philosopher malady, I believe), or maybe case studies made him so, but publicly changing your mind is about the bravest thing a philosopher can do. I'd play him at Nerd Heroes any day, if he wasn't so dead.

OK, enough of my literary devices. Moving on, we're ready for our little family of meds.

Chloroquine



Chloroquine is the granddaddy in the family of malaria prophylactics. For the most part he is a genial old fellow, but frankly he has become rather useless around the house. Chloroquine has been used to prevent malaria since 1947, and it is one of the two choices available for weekly dosing. Unfortunately, it has become basically ineffective in the tropics world-wide, and in Africa altogether, because *Plasmodium falciparum*, the type of malaria that causes the most aggressive disease, is resistant to chloroquine in all those regions. Peace Corps only uses chloroquine in temperate areas of IAP, if at all.

Chloroquine has a number of side effects that can happen, but it's rare that anyone actually stops the medication because of one. It can cause a mild thiamine (vitamin B1) deficiency by interfering with uptake. Paradoxically, it can also be a mild immunosuppressant, but that's OK if it still kills the malaria. We often put that feature to good use, using it to reduce the inflammation associated with rheumatoid arthritis and lupus. Chloroquine has another beneficial side effect in its ability to sensitize a tumor before chemo or radiation therapy, making cancer treatments more effective. It has two context-sensitive side effects: first, it can inflame the retina if you've been using it long term (over 5 years), and second, it can create or aggravate a rhythm disturbance in the heart when used in combination with other medications that have the same effect, or if you were born with a heart rhythm problem in the first place.

Individuals metabolize chloroquine at markedly different rates, so if you are taking it and develop any concerning features, please let your PCMO know as soon as you can. The variable metabolism is also the reason why we tend to avoid using it in children. On the other hand, it does appear safe during pregnancy, although the FDA has not approved it for such use. Chloroquine is usually very well-tolerated for the 27 months of Peace Corps service, and hands down it is the best choice if you are serving in an area where the malaria is still sensitive to it.

Mefloquine



Mefloquine, the other once-weekly medication, is the weird uncle in the family. Not everyone gets his jokes, and some people find it difficult to tolerate his very presence. He has a bad-boy reputation, and he generates considerable family gossip and innuendo as to what he's been up to. As many as 5% of people taking mefloquine have to stop it because of side effects. On the other hand, some advanced mathematical figuring will show that 95% of people can take mefloquine uninterrupted, and it has successfully kept hundreds of thousands of people safe from malaria over its 40 year history.

Mefloquine's most common side effects are upset stomach and dizziness (each can occur about 3% of the time), but the most impressive side effects tend toward the neuropsychiatric. These can occasionally be quite dramatic, so although they are uncommon, they tend to be emphasized on the web and in the news. With mefloquine, you've got to see past the hoopla -- more on that below. The neuropsych side effects we're talking about range from feeling unsettled to vivid dreaming to outright hallucinating. Yes, mefloquine gets into your brain, but then again, so does malaria. If you're going to get any side effects, most will have occurred by the third dose, so once you get past your 3rd week, you're likely to be fine for your entire tour.

There are things about mefloquine that I like. First, it is the only med in the prophylactic family that is FDA approved for use during pregnancy, and malaria in pregnancy is especially dangerous, so it's nice to have the option. Second, mefloquine lasts in your system for a few weeks after your last dose. That may sound scary at first, but what it really means is that the med is very forgiving if you're late with a dose. The level drops steadily down to zero over those weeks, so you can't rely on it forever, but if you were accidentally a few days late, you're covered for sure.



The long half-life leads to a practice in Peace Corps, as well as among other long term travelers, of taking half a dose of mefloquine twice a week. A lower dose taken more frequently does seem to curb the side effects, if you're right on the edge with tolerating them, and the lingering half-life allows one dose to slur right into the next. But the practice also leads to lower peak blood levels, which normally would occur an hour or two after whatever dose you're taking. A higher dose gives you a higher peak, and that may be critical in killing any stubborn parasites. There are small pockets of resistance to mefloquine forming along the Thai and Cambodian borders, but when those parasites take their show on a world tour, as microbes are wont to do, I would want a full peak dose as my wingman.

So far so good, but what's all this I hear about the evils of mefloquine? Just for fun, try searching the internet for that exact phrase. You will get an assortment of angry bloggers and lawyers with dollar signs for eyeballs. (I just made that up, the lawyers really have compassion welling up, it's just easily mistaken for dollar signs.) Recall from our last section how I cleverly foreshadowed our need to understand three common mistakes in interpreting scientific data. I will now rely on your refined scientific mind to evaluate two of the rumors going around about Uncle Mef. (The third common mistake we're going to save for la grande finale.)

This is the FDA's boxed warning: Mefloquine may cause neuropsychiatric adverse reactions that can persist after mefloquine has been discontinued. Mefloquine should not be prescribed for prophylaxis in patients with major psychiatric disorders. During prophylactic use, if psychiatric or neurologic symptoms occur, the drug should be discontinued and an alternative medication should be substituted.

The first of mefloquine's evilness rumors is that it causes psychosis or homicidal rage or suicidal depression. The recent famous example is the tragic rampage by Sgt. Robert Bales, when he massacred 16 Afghan civilians for no apparent reason (is there ever a reason?). The press has speculated that he was taking mefloquine, although his medical records were not released to confirm it. Even the FDA has been influenced by the possibility that an association will extrapolate to a causation, and it recently added a warning to mefloquine's label about possible neuropsychiatric side effects.

This is a bad ice cream mistake, AKA guilt by association. There has been no new scientific data that suggests something is occurring that is different or has previously failed to be detected.



On the contrary, we have several recent studies that show that when those confounded variables are well controlled, we cannot detect *any* differences in new psychiatric events between mefloquine and the other prophylactics. Psychiatric events can begin while on mefloquine, of course, but they happen with the others as well.

This is not to say that mefloquine is entirely innocent, either. Categorize mefloquine as an "active bystander." If a person's neurochemistry is already vulnerable, even if nothing in the past has ever hinted at that vulnerability, then mefloquine may give it an unwelcome nudge, and tax the system beyond its ability to re-center itself. Dysphoria or vivid dreams may combine with life stressors to create a positive feedback loop, so that such a person cannot

compensate. Mefloquine doesn't create the vulnerability, but it sure doesn't help it, either. For this reason, mefloquine is contraindicated for anyone who has had a significant past psychiatric history, head trauma, or seizures, and it should be promptly stopped for anyone who develops such symptoms while taking it. None of these limitations and recommendations are new whatsoever, but the recently refreshed association highlights the importance of following them.

If you experience any symptoms that you believe might be related to taking mefloquine, please do not stop your medication until you have consulted with your PCMO. Likewise, if you remember that you have a history of something neuropsychiatric, continue your medication but bring it up. You and your PCMO together will decide on your backup plan, and you will be started on a different prophylactic medication.



The second of mefloquine's evilness rumors is that it can cause long term brain damage, even after a single dose. This is an exploding hamburger mistake. The study that was originally cited for this involved giving 8-aminoquinolines to rats; subsequently, trace amounts of the chemicals were found retained in the rats' limbic system after death. The limbic system is a deep part of the brain associated with emotions in humans. It is also the site where PCP and other hallucinogens appear to be active, so it didn't take long before someone extrapolated from this study to infer damage from mefloquine. All the rest of the rumor mill were people referencing each other and then themselves again about that one study, in a big circular fashion, so the boisterous chatter made it appear that there was a lot more data out there than there really is.

It is possible that they're right, you know. It will shock you to know that medical professionals don't know everything, and never could. But let me say this: In the 40 years of using mefloquine, there has been absolutely no evidence to support the claim of brain damage of any kind, so the extrapolations and speculations are really just irresponsible fear-mongering, and nothing more, until new data suggests otherwise. The exploding hamburger mistake arises here because mefloquine is a 4-methylquinoline, everyone knows that, and although it is related to the 8-aminoquinolines, the chemistry is simply different. And rats, by the way, are not good proxies for people, except for maybe that one guy in Harry Potter.

Doxycycline



Doxycycline is the momma in the family. She is way underpaid for all that she does, she feels the need to be in your business every single day without fail, she demands that you use sunblock, and she can bug you until your stomach gets a bit queasy. Like most moms, you learn to love her even as you learn to live with her. What I especially love about doxycycline is how many tricky little infections it is able to treat, beyond malaria. It covers tick-borne illnesses, cleans up your acne, and seems to help a variety of undiagnosable intestinal ailments that Africa tends to dish up. And even though you need more pills because you have to take it every day, doxy is the cheapest of all the prophylactics.

Doxy has side effects, but they are manageable. First, it can sensitize your skin to the sun, kinda like sunblock with a negative SPF. Even people who don't usually burn can get burned

while on doxy, so real sunblock is a must. Apply it thick and apply it often, just like your momma taught you. Also, doxy can irritate your esophagus and stomach if it gets stuck, so you should never dry swallow it or take it right before lying down. Always wash it well down the hatch and then let it move a little farther down the chute before you head off to bed. There's another side effect that's important, but it won't affect you. Doxy can cause discoloration (white streaks) on developing teeth. For this reason we never give it to children under 8 (preferably under 12) or to moms during pregnancy. By the way, if you are seeking to avoid pregnancy in the first place, doxy does not interfere with the effectiveness of birth control pills. That's one side effect it does not have.

But there is a feature about doxycycline that I really don't like at all. It's not really a side effect, but doxy has a pretty short half-life and it gets cleared quickly from your system. That means that if you miss a single dose, you can get malaria. For this medication to successfully protect you from malaria, you really have got to get in the habit of taking it at exactly the same time every day.

Malarone



Malarone is the little princess in the family. Everyone coos over the rich pretty girl, but then she's genuinely nice, too, and that just gets you all conflicted when you find that you need her. Malarone is the name brand for generic atovaquone and proguanil hydrochloride in a fixed combination pill. Since that's such a mouthful to say, we all just refer to the brand name. Malarone has some of the exact same side effects as mefloquine, like dreams or feeling off your game, but overall those side effects are better tolerated, and less than 1% of people stop taking the medications because of them. Malarone can give some people diarrhea, so it's best taken with a bit of food at the same time.

Wait for it... Do you hear the other shoe that's about to drop? Here it comes: Princess Malarone slurps down cash like it was fruit punch at a tea party. It costs about \$10 to buy doxy for you for a 6 month supply, but that same 6 months will cost us between \$700 and \$1200 to get Malarone. They tell us that it takes a complicated manufacturing process to make Malarone, so even the generic is expensive. At least, that's what I heard.

I wish I could say that money was no object, but you all live in the same world as me, and we know different. The Department of Defense would run through Peace Corps' entire annual budget for 2014 in 6 hours and 18 minutes. We couldn't even make it to sunrise on New Year's Day running the nation's defense, so we have to be as smart as we can with what we have. This is not to say that if Malarone is the best choice for you that you'll have to whine and beg to get it. There was some of that in the past, but no more. At Peace Corps we are clear that you should get the medication that's right for you, period. My only point is that your vision of Peace Corps service may diverge somewhat from spending the budget feeding the already deep pockets of the pharmaceutical industry. Sorry, the pharm industry also has compassion in their eyes. I just keep mistaking it for dollar signs. Must be a side effect of something I'm taking.

Philosophy redux and the turkey forecast



Finally, I want to return to the conflicted philosopher error, where the plural of anecdote does not add up to evidence, but somehow convinces us anyway. Stories will typically arise from travel bloggers and ex-pats at a bar who say they've been all over the world and never took meds, and they're living proof that malaria meds are bogus. They imply that we at Peace Corps medical are all alarmists, and that we are prescribing unnecessary medications. Their stories might well be true, but I suspect they are more likely a form of bravado that seeks to impress you. Be strong, don't fall for that siren song of the Pied Piper leading lemmings to the precipice of mixed metaphors.



If medical professionals were somehow able to divine the future and see, in a particular case, whether by genetics or by air conditioning or by simple dumb luck, that a person was not going to get exposed to malaria while on their travels, then obviously we would not prescribe the medication for something they don't need. That's an easy one – why would we? We have no incentive for that prescription; we would only achieve side effects without any benefits. This may sound all kumbaya and hand-holding, but I was hired to help take care of you, and that is my only motive. Only the pharmaceutical companies have a true vested interest in getting pills in your mouth.

What is difficult for me to understand is how a few testimonials from strangers can hold sway over the tens of thousands of malaria cases that occur in travelers each year. Neither you nor Peace Corps can see your future, and neither of us knows what your personal risks are. That's why we are asking you to make a thoughtful decision here.

So, maybe your newly refined scientific sophistication, reinforced by some brilliant foreshadowing, I might add, has left you immune to the temptations of anecdotes? Well, let me tell you a parable.

A turkey is fed daily all year long. It believes that life is good and the farmer is its friend. As this continues throughout the year, the turkey's confidence grows and grows. Its sense of safety, happiness, and confidence is at an all time high on the Wednesday before Thanksgiving. All historical evidence available to the turkey indicates that it can reliably predict the future, namely, that more regular meals and more happy days are coming. The turkey's problem, however, is insufficient knowledge of its larger context and, catastrophically, the projection of a linear forecast in a nonlinear situation.

PCVs can too easily slip into the trap of feeling overconfident without understanding the larger context within which they are operating. Moreover, more experienced PCVs are actually at higher risk than new PCVs for contracting malaria. There are two reasons that the risk grows with time.

First, experienced PCVs have a longer exposure to the mosquitoes that carry malaria and have had more opportunities to contract latent infection (the kind that hides in your liver). Again, to be clear, **the prophylactic medications only suppress active disease rather than prevent you from carrying malaria inside your liver.** Aha, the pattern is repeating. Hence, it is a pattern. I'm using bold here, just in case you didn't notice.

Second, experienced PCVs may develop more familiarity and a diminishing concern with malaria over time. They may have lost that fear-of-God feeling left over from PST so long ago. They may have met many more ex-pats or USAID workers or even other PCVs who poo-poo our concerns for your health, and may have heard so many stories that it begins to seem like the stories are the only voices out there. And when the narratives ring true to your own experience, you start calculating that in some times and some places it's illogical to continue taking the meds, since the mosquitoes are gone in the dry season or you're traveling to places where malaria doesn't exist or whatever the reason. See how alluring the case reports become? See how hard it is to sift out hard science from convincing arguments?

The problem, of course, is that the mosquitoes didn't study logic, and they can live in a puddle under a faucet in the middle of a desert, and they certainly don't respect border patrols. And more importantly, there is a chance that you are already carrying malaria on the day that you decide to stop your meds, the parasites quietly biding their time in your liver, just waiting for your vigilance to lapse before exploding out into your blood stream. Don't ever give them that chance.



The most experienced turkeys are the ones who have the highest confidence. But their confidence is misplaced, because just by virtue of making it all the way to November

confers to them the greatest risk for becoming the featured guest at Thanksgiving dinner.

Final exam

So now, put away all your things and take out a number 2 pencil. We're going to have a little test. Think carefully about the following scenario and select the single best answer.

You're up late watching a scary movie. The leading man is stupidly ignoring the creepy music and close-up cinematography just because he has confidence that nothing bad could happen next. You decide to intervene from the safety of your living room. Which of the following do you shout at the TV?

A) "Dude, you're projecting a linear forecast in a nonlinear situation! Only a turkey would make that mistake!"

B) "Go ahead and check out the strange scraping noises because they couldn't possibly imply that something evil is afoot."

If you selected A), then you have chosen wisely, and my work here is done. If you selected B), however, then you did not choose wisely. I will have to ask that you re-read this entire WLB and suffer all the wise cracks again.



We at Peace Corps medical are asking you to decide with your PCMO which malarial prophylactic medication you think is best for you, and then commit to taking it for 100% of your time in Peace Corps, not just on the days you remember, or when you feel like it. Did you notice? It's déjà vu all over again. I'm repeating the pattern of repeating things. And using bold, too, in case you were sleeping. It's just a little mind control experiment that I've going on the side. How's it working?

OK, thank you for reading all the way to the end. Your prize is a million dollars and a medevac for two to Cancun. Sorry, I made that up too. The only thing you get is smarter. *Your* job is the heart and soul of Peace Corps. *My* job is to help keep you healthy and safe so you can do your job. Thank you for giving me the opportunity to do my job, and thank you for your service.

- Dr. Tom



Meet the author: Before becoming a doctor, Dr. Tom Wilkinson, M.D., was a classical archaeologist, which sounds kinda like a classical pianist, only there's more dirt and less tuxedo. He tells corny jokes to his wife and kids at their home in historic southern Maryland. He is still waiting for them to laugh, but he has confidence that they are secretly cracking up deep inside. Tom loves working as a medical officer at Peace Corps headquarters, where they don't laugh at his jokes either.