

A conversation with Professor Sir Brian Greenwood, January 4, 2017

Participants

- Professor Sir Brian Greenwood – Professor of Clinical Tropical Medicine, London School of Hygiene & Tropical Medicine (LSHTM)
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Note: These notes were compiled by GiveWell and give an overview of the major points made by Professor Greenwood.

Summary

GiveWell spoke with Professor Greenwood of LSHTM as part of its investigation into seasonal malaria chemoprevention (SMC). Conversation topics included: possible timelines for the emergence of resistance to antimalarial drugs, particularly sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ); known genetic mechanisms for resistance to common antimalarials; and monitoring for new mutations in the malaria parasite.

Predicting timelines until resistance development

Predicting how long it will take for malaria parasites to develop resistance to a particular drug is very difficult. Professor Greenwood and other experts can only make educated guesses as to whether a given resistance will appear in 10, 20, or 50 years. ("Resistance" here denotes a gradual reduction in efficacy, rather than a sudden, complete loss of effectiveness.)

Recently, the median time for resistance to a given drug to develop has been roughly 10 to 15 years; for instance, resistance to sulfadoxine-pyrimethamine (SP) resistance took roughly 10 years to emerge in Southeast Asia (where SP was being used as a mainline treatment for malaria).

Potential resistance to SP/AQ

SP and amodiaquine (AQ) are used in combination (as SP/AQ) for SMC. It is very likely that if SP/AQ is used for SMC on a wide scale, resistance will eventually develop (as has been the case with nearly all antimalarial drugs used in the past).

Resistance to SP/AQ would require mutations granting resistance to both SP and AQ, since these operate via independent mechanisms. If a parasite is resistant to either SP or AQ but still fully sensitive to the other, this is unlikely to reduce SP/AQ's overall efficacy.

Professor Greenwood's best guess is that SP/AQ will still be working, at least partially, in 5-10 years' time, but this is quite uncertain (it is possible, though unlikely, that an unanticipated type of resistance mutation could appear at any time).

Resistance to SP

SP is a combination of two drugs, sulfadoxine and pyrimethamine, for which there are different known resistance mechanisms: mutations in the dihydrofolate reductase (DHFR) gene for resistance to pyrimethamine, and in the dihydropteroate synthase (DHPS) gene for sulfadoxine.

SP has been used alone for intermittent preventive treatment in pregnancy (IPTp) for roughly 20 years. This is likely to have contributed to resistance to SP developing in Tanzania and East Africa, and SP is no longer very effective in those places for IPTp. However, it is still effective in much of the rest of Africa. A mutation associated with a particularly high level of SP resistance that appeared in Southeast Asia (the DHFR 164 mutation) also appeared in Uganda but has not spread in Africa.

The “triple mutation” in the DHFR gene, which confers some resistance to pyrimethamine, has been present for some time in West Africa. However, additional mutations in the DHPS gene are required to impact the efficacy of the SP combination.

SP-resistant genes mainly emerged when SP was being used for treatment, rather than prevention, of malaria (which exposes larger numbers of malaria parasites to a drug than prevention therapy alone). Artemisinin-based combination therapies (ACTs) have now largely replaced SP as the primary malaria treatment (though it is possible that SP is still being used for treatment in some places if a private pharmacy has reserves of it and no other drug is available).

Because multiple mutations are necessary for full resistance to develop, it is unlikely that SP would shift suddenly from working effectively to not working at all; a gradual decline in effectiveness as various resistance-conferring mutations emerge is more likely. It’s also likely that resistance to SP would emerge more slowly when used in combination with AQ, rather than alone.

Resistance to AQ

AQ has relatively little history of resistance, compared to SP. Some resistance has been reported, but overall efficacy has remained high despite extensive use in West Africa for 40 years.

AQ is used for treatment mainly as part of the ACT artesunate/amodiaquine (ASAQ); it is not used much alone. While ASAQ is used as first-line therapy in some West African countries, the most commonly used ACT is artemether/lumefantrine (accounting for about 80% of ACTs), which works by a different mechanism and has no effect on AQ efficacy.

Professor Greenwood sees the use of ASAQ for treatment as the biggest potential harm associated with the potential emergence of AQ resistance. It has been recommended that areas receiving SMC switch to artemether/lumefantrine for treatment to avoid using AQ for both prevention (in SP/AQ) and treatment (in ASAQ).

Resistance to AQ or SP would probably not impact the effectiveness of ACTs generally (other than ASAQ).

Correlations between resistances to different drugs

If the mechanism by which two drugs work is the same (e.g., proguanil is similar in mechanism to SP), then resistance to one usually entails resistance to the other. Most common antimalarials, however, work through different mechanisms.

There is no evidence that development of one type of resistance correlates with a faster development of other types of resistance (via independent mechanisms) in a given population. There is an area of Cambodia where SP resistance and artemisinin resistance both emerged; it is possible that the parasites in that region are unusual in some way that makes them more prone to developing resistances. However, this does not seem to be typical.

Reversion to wild-type when drug pressure is removed

When widespread use of a drug is discontinued, sometimes the parasite population loses the mutations that confer resistance to it and reverts to the wild-type versions of those genes, because the resistance mutations reduce fitness in some other way. This has not happened with SP resistance mutations, despite SP no longer being used for treatment. The wild type of the primary gene for AQ resistance does seem to return when drug pressure is removed.

Acceptable efficacy in prevention vs. treatment drugs

The World Health Organization (WHO) formerly categorized a 20% treatment failure rate as “resistance” requiring a switch in drugs; it now recommends switching drugs if there is a 5% increase in treatment failure rate.

The majority of people who receive SMC either do not have parasites or have them in such low numbers that it may not matter much to their health whether they are eliminated. Therefore, the consequences of reduced efficacy for SMC drugs are less serious than for treatment drugs. In general, a higher rate of failure is viewed as acceptable for a drug that is only used for prevention. For example, when resistance to SP emerged in East Africa, WHO’s Malaria Policy Advisory Committee ultimately decided to recommend that SP continue being used for IPTp, despite its reduced effectiveness. That likely would not have been the case if SP were being used for treatment, rather than only for prevention.

Possibility of using DHAPQ

While Professor Greenwood thinks it is likely that SP/AQ will maintain its effectiveness for up to 10 years, if resistance to SP/AQ does develop, dihydroartemisinin-piperaquine (DHAPQ) could be used to replace its role in prevention. However, there is some risk that broad use of an artemisinin-based drug like DHAPQ for prevention could encourage artemisinin resistance, e.g., by encouraging an artemisinin-resistant parasite that already exists in Cambodia to emerge in Africa. While Professor Greenwood would be concerned about using

artemisinin in prevention, he would not rule it out as an option, and other experts might disagree about the level of risk.

Monitoring for resistance mutations

There are several known mutations contributing to SP resistance that can be monitored for. For example, many countries host *Plasmodium falciparum* parasites that have mutations at sites 51, 59, and 108 on the DHFR gene (which determines resistance to pyrimethamine) but not at other key sites on the DHPS gene (e.g., the A581G mutation on the DHPS gene, which is particularly bad for SP resistance). If a particular set of five or six mutations across these genes is present, SP will probably not be effective at all. Monitoring for these mutations can be done using molecular markers in blood spots.

Less is known about which mutations to monitor for AQ resistance.

Sources of monitoring

A new mutation to a drug would most likely be first noticed if the drug were being used for treatment and began to fail. Monitoring by ACCESS-SMC might also identify new mutations; for example, if SMC were reported to be losing effectiveness in a particular district, it might then investigate whether a new mutation has appeared.

There is also ongoing surveillance that might catch a new mutation. For example, Colin Sutherland (Reader in Parasitology, LSHTM) and his colleagues might observe a new mutation and attempt to determine whether it poses a risk of resistance.

Possibility of new mutations appearing in unexpected genome areas

If SP or AQ resistance were to appear in the next 15 years, Professor Greenwood thinks it would more likely be due to a known potential mutation than an unexpected new mutation, though either is possible.

Parasite mutations in general are common, but most reduce fitness and are selected out of the population. The emergence of viable, resistance-conferring mutations is quite rare (relative to the massive amount of parasite reproduction occurring).

Propeller gene

The "propeller" gene in the malaria parasite appears to mutate particularly easily. In Southeast Asia, it carries mutations associated with artemisinin resistance. Surveys in Africa have also found mutations in the gene (though not the same ones, and not resistance-conferring), which suggests that it might be easy for the same resistance-conferring mutations to appear at some point. Whether mutations in the propeller gene lead to artemisinin resistance may be determined in part by the structure of the rest of the parasite's genome.

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