Homework due August 19th 2013
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"Competitive facilitation of drug-resistant *Plasmodium falciparum* malaria parasites in pregnant women who receive preventive treatment" by Harrington et. al. (PMID 19451638)

This paper explores the implications of preventive malaria treatment during pregnancy on development of drug resistance and pregnancy outcomes. It is interesting because it shows that using outdated drugs is not just less effective, but can actually be dangerous. We have provided some important definitions for acronyms that the authors failed to define in the paper.

IPT = intermittent preventive treatment
- IPTp = in pregnancy
- IPTi = in infants

SP = sulfadoxine-pyrimethamine
SP-IPTp = sulfadoxine-pyrimethamine intermittent preventive treatment in pregnancy
PM = placental malaria
SNP= single-nucleotide polymorphism

1. What are the parasite proteins DHPS and DHFR and what do they do? Why are these drug targets? (Consult PMID 16023986 Abstract FIRST and then Wikipedia)

DHPS is dihydropteroate synthase and DHFR is dihydrofolate reductase. These are enzymes that are active in the synthesis and reduction of folic acid. Humans do not have DHPS, but DHFR is found in all organisms. These are drug targets because the malaria parasite must synthesize folic acid de novo (from scratch), but humans do not use the de novo pathway and obtain folic acid through the diet. Note: Humans DO use DHFR to make use of dietary folic acid, and DHFR is also a drug target for cancer treatment.

2. How do pyrimethamine and sulfadoxine treatments work? Hint- Wiki Fansidar.

Both drugs are antifolate, which means that they inhibit the action of enzymes involved in the synthesis of folic acid within the parasite. Either drug by itself is only moderately effective in treating malaria, because the parasite *Plasmodium falciparum* may be able to use exogenous folic acid, i.e. folic acid which is present in the parasite's environment. In combination, the two substances have a synergistic effect which effectively overwhelms the parasite's folic acid synthesis, which prevents DNA and RNA synthesis.

3. From Table 1, what is meant by Primigravid, Secundigravid and Multigravid? What is maternal parity?

Primigravid: pregnant for the first time, Secundigravid: pregnant for the second time,
Multigravid: pregnant many times, Maternal Parity: The number of live births.
Note: Gravidity refers to pregnancy regardless of outcome (fetal death, abortion, live birth).

4. The researchers measured sulfa concentration in maternal plasma to verify the self-reported use of IPTp. Why was this step important for the study?

This step was important because the researchers needed to make sure the self-report was correct. If it was incorrect for any reason (maybe the patient received a lot of drugs and didn't keep track), the whole study's results would be questionable.

5. Why is the association of IPTp with an increase in parasitemia particularly troubling? What is special about the parasites in pregnant women who recently used SP-IPTp? (Compare Figures 1, 2 and 3)

The association of IPTp with an increase in level of parasitemia is particularly troubling, since otherwise healthy women take IPTp to reduce future malaria risk. Figure 3 shows that any IPTp use increased the level of parasitemia, and the highest levels occurred in women with recent IPTp use. Figure 2 demonstrates that IPTp reduced parasite diversity and Figure 1 indicates that IPTp increased the fraction of resistant alleles. The parasites are special because they contain more resistant alleles and there is less diversity- hence less competition to keep them in check.

6. Why were only four resistance markers evaluated in the placental samples? Why did the researchers end up exploiting data about only one of those markers?

The researchers explored multiple variable sites of DHFR and DHPS, but only 4 showed variability within the study population. Therefore, the researchers focused on those 4. However, they found that only one of those resistance markers (DHPS 581) was not yet overwhelmingly present in the population, resulting in it being a good candidate for observing varying levels of resistance in different study groups.