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Global Health Paper

Background

Each year, an estimated 200 million individuals are infected worldwide with *Plasmodium falciparum* malaria. Among that total, over half a million people die each year from the illness. Increased attention to malaria prevention and control has fortunately led to a 25% decline of malaria deaths worldwide since 2000. However, 90% of all malaria deaths today occur in the WHO Africa region. (These figures come from the 2012 WHO Malaria report) To fight this global pandemic, the most common therapies for malaria are Aretemether-Lumefantrine (AL), Artesunate+Sulfadozine-Pyrimethamine (AS+SP), Dihydroartemisinin-Piperaquine (DHA+PPQ), Artesunate+Mefloquine (AS+MQ), Artesunate-Amodiaquine (AS+AQ), Quinine (QN), and Chorloquine (CQ).

**Information about Quinine and Chloroquine was not available in the cited study, may want to include a separate study to reference for these two drugs specifically. (Need some help finding these studies, haven't been able to find anything useful myself yet)

The first line treatments, using these drugs, varies from country to country. The same is true for Chloroquine, the comparator we are using. Our ultimate aim with our overall project is to be able to rank pharmaceutical companies according to the impact of the drugs they produce at a global level. This paper provides background data towards that larger project. In order to rank these companies, we started by analyzing each of the previously mentioned malarial therapies. We obtained country-level statistics regarding disability-adjusted life years (DALY), defined as the measurement of the overall disease burden. This is expressed as the number of years lost due to ill-health, disability or early death. Using this information, we have an indication of the extent of burden of malaria for each particular country. For each of the therapies analyzed, we then collected detailed country-by-country information on comparators, sample size, age, sex, the year the study was conducted, pregnancy, inclusion criteria, blindness, randomization, primary and secondary endpoints, efficacy/conclusion data, day 28 adjusted/unadjusted, day 42 adjusted/unadjusted (the particular days we used differed by the drug we were looking at), transmission/endemicity, number of early treatment failures, number of late treatment failures, number lost to follow up, and number of protocol violations. The data provided in the spreadsheets below will be used to come up

with good estimates for the efficacies of the first-line drugs that we looked at. We also collected data on the treatment percentages. Combined, these pieces of information together will give us an estimate of drug impact on the basis of which we can eventually rate companies.

Among these drugs, we expected to find that AL and AS-AQ would be the most effective. Much of this hypothesis has to do with the fact that these two therapies are generally the most commonly used in countries all around the world. (I thought this was based on the report, is that incorrect?) However, we found that AS-MQ and DHA-PPQ were the most efficacious based on our spreadsheet data. (I found some info that said AL and AS-SQ have less side effects than the alternative, but not in a published study. Should I still include?)

We are mostly focusing exclusively on the first-line therapies for each of these countries. However, we are also exploring Chloroquine as well because it will be used as a comparator. Quinine, which is not a first line therapy, will also be looked at because it is the standard therapy for treatment failure.

Each of these therapies has different characteristics, dosage requirements, and efficacy rates depending on which country they are being used in. The 2012 WHO report says that we should use combination therapies therapies that are _% effective. (I believe this is >80% according to the WHO report, but I can't find the exact language yet) According to **include reference here after talking with Prof. H**, which characterized these drugs in order to determine which treatments are preferable to others depending on the circumstances involved, AL is a fixed-dose formulation. AL is possibly advantageous because it is not available as a monotherapy. (According to the 2012 WHO malaria report) It is important to note that AL absorption is enhanced "by co-administration with fat after eating/drinking". AS+SP is characterized by "separated scored tablets, sufficiently efficacious only where 28-day cure rates with sulfadoxine-pyrimethamine alone exceeded 80%. And resistance is likely to worsen with continued widespread use of sulfadoxine-pyrimethamine." . DHA+PPQ is a fixed dose combination, just like Al. AS+MQ comes in blister packs and is a "fixed-dose formulation of artesunate and mefloquine" used for advanced stages of development of malaria. Mefloquine is, however, associated with several side effects like nausea, vomiting, and dizziness. AS+AQ is a very common therapy that is also a fixed-dose formulation that comes in blister packs. In the ***source*** analysis, "the (AS+AQ) combinations was sufficiently efficacious only where 28-day cure rates with amodiaquine monotherapy exceeded 80%.

(All of the previous quotes in this paragraph came from the malaria study Professor Hassoun sent me.)

Methods

For each of the categories of data we collected, we followed a strict search methodology. We used PubMed, Google, and GoogleScholar as our primary databases. For the former, we first went to pubmed.com and entered "drug name" (i.e. "Artesunate-Amodiaquine (AS+AQ), but depending on which particular drug was being analyzed)), "efficacy", "falciparum". After looking through the relevant articles that immediately showed up, we went through all the "suggested" articles that were listed in the side bar of the database to see if any of those might also be relevant (known as an exploding search). When no additional relevant articles could be found, we amended our search process to include the name of the specific "country name" (i.e. "Kenya"). We then repeated the methodology described above using this additional information. Once we had exhausted all relevant articles once more, we repeated the previous process in google.com and scholar.google.com using a broader selection of search terms, including any combination of the follow search criteria:

1. "drug name" "efficacy" "Country Name"
2. "drug name" "Country Name" "efficacy"
3. "drug name" "falciparum" "Country Name"
4. "drug name" "Country Name" "falciparum"
5. "drug name" "malaria" "Country Name"
6. "drug name" "Country Name""malaria"
7. "Country Name""drug name" "efficacy"
8. "Country Name" "efficacy" "drug name"
9. "Country Name" "drug name" falciparum"
10. "Country Name" "falciparum" "drug name"
11. "Country Name" "drug name" "malaria"
12. "Country Name" "malaria" "drug name"
13. "falciparum" "Country Name" "drug name"
14. "falciparum" "drug name" "Country Name"
15. "efficacy" "drug name" "Country Name"
16. "efficacy" "Country Name" "drug name"
17. "malaria" "Country Name" "drug name"
18. "malaria "drug name" "Country Name"

After going through all these combinations, we repeated the search terms above but omitted "country name". We then looked for any studies in which the drug of interest was a comparator on any other completed sheets. And finally, we searched the references of all meta-analyses found in the Cochrane Review for additional references.

Once we had compiled a complete list of the relevant articles, we recorded all the information (comparators, sample size, age, sex, the year the

study was conducted, pregnancy, inclusion criteria, blindness, randomization, primary and secondary endpoints, efficacy/conclusion, day 28 adjusted/unadjusted, day 42 adjusted/unadjusted, transmission/endemicity, number of early treatment failures, number of late treatment failures, number lost to follow up, and number of protocol violations) into excel spreadsheets for each drug.

Primary and secondary endpoints refer to symptoms or signs that indicate one of the target outcomes of the clinical trial. The day 28 adjusted and the day 42 adjusted refer to the number of patients that withdrew from the clinical trial or were otherwise disqualified. The unadjusted total for these days, on the other hand, does not account for these changes that occur after the start of the respective trials. The number of early treatment failures, number of late treatment failures, number lost to follow up, and number of protocol violations all tie directly into these measures. For each of these categories of information, we listed them individually in the columns under the first row. The country names were listed in the rows below the first column.

We first went through the abstracts to find and record some of the basic information usually given related to the desired categories listed above. After reading the abstract for each study, the full text was opened or obtained through an interlibrary loan service if not immediately available on the Internet and the information entered into the data sheet. We read through each study several times initially to get a strong understanding of all the information that we being conveyed. After this we went on to search the actual paper for information on each of the categories that were incomplete. “Control F” was used to search for the names of the categories quickly throughout the entire studies. For each of the sheets, we had two different people look at all possible combinations using the aforementioned search methodology. And generally, when there was still incomplete spaces on the spreadsheet, it was in the following categories: “day 28 adjusted/unadjusted”, “day 42 adjusted/unadjusted”, “number of early treatment failures”, “number of late treatment failures”, number lost to follow up”, and “number of protocol violations”. We found this to be the case, often because the information related to these categories was contained in attached charts and graphs. As such, we finally went through those charts and graphs and recorded the rest of the previously incomplete information in the respective rows and columns of the spreadsheets.

Results

The following is a drug-by-drug analysis of the results we obtained from our spreadsheets:

Artesunate+Sulfadoxine-Pyrimethamine (AS+SP)

For this drug, the most common comparators were AS+AQ, SP, and AQ. We found that 23.1% of the studies were multicentric with a large difference in the sample sizes among them. The study with the smallest samples size had 53 participants while the largest had 1552. Generally, users of this therapy tended to be younger than for the other therapies we looked at. The age range for this drug was between .5 and 59 years old. None of these studies included pregnant women or required participants to consume provided food along with the therapy. However, 83% of the studies for this particular therapy had more male participants than female participants. Although only 3 out of 30 studies were blinded, 23 were randomized. Adjusted/Unadjusted data was unfortunately only available for about 10 out of the 30 studies we looked at.

** None of these studies listed specific inclusion criteria numbers like DHA-PPQ does below. However, one of them simply stated that it follows standard WHO protocol for its inclusion criteria.

Aretemether-Lumefantrine (AL)

We found a total of 36 studies relating to AL. Out of that total, 27 were compared to another drug. Only 3 of these studies were multicentric with a sample size range between 51 and 449. Unlike with AS+SP, the age range tended to vary more. The studies found yielded an age range between .5 and 65 years old. Two of these studies included pregnant women and only 3 were blinded. However, following the trend observed in AS+SP, 27 out of the 36 studies relating to AL were randomized. Perhaps more strikingly, 25 of the 36 studies saw participants that were lost to follow up. Only two of the studies involved pregnant women while 17 of the studies featured a majority of male participants. Just one of the studies we looked at for AL was conducted with exclusively male participants.

Three of the studies' inclusion criteria called for patient body temperature of >37.5 degrees centigrade. Two studies also excluded women who were pregnant or breast-feeding during the clinical trials. Three studies required participants to be at least 5 Kg, one required participants to be at least 10 Kg, and one required participants to be at least 12 Kg in weight. One study involved exclusively children that weigh between 10 and 20 Kg. The rest of the studies specified that they followed the standard WHO protocol as of the year 2000.

Artesunate+Mefloquine (AS+MQ)

We found a total of 14 studies relating to AS+MQ. Every study we found for AS+MQ had comparators, however each separate study had different

comparators. None of the studies were multi-centric and the sample size range was relatively limited (98-225). Similar to AS+SP, this therapy seemed to be used more by younger people with an age range from 4.6 to 23.6 years. None of the six studies were blinded, but they were all randomized. All of them had participants that were lost to follow up while half of them included transmission/endemicity information. Among those studies that included this information, we found that most were in low endemicity areas. Unlike with AL, none of these studies involved pregnant women and 5 out of the 6 had a majority of male participants.

One of the studies excluded participants with severe malaria who experienced effects like convulsions, anemia, jaundice, respiratory distress, or malnutrition. Nine of the studies required participants to have body temperatures of greater than 37.5 degrees centigrade. Two of the studies required participants to weigh at least 10 Kg. Otherwise, they all followed standard WHO protocol as well. (Is it a good idea to include the standard WHO protocol as an appendice?)

Dihydroartesiminin-Piperaquine-Primaquine (DHA-PPQ+PQ)

This drug therapy seems to be very limited in use. In fact, we were only able to find one study with a sample size of 374 and DHA+PQ as a comparator. The study was conducted in Lampung, Sumatra, Indonesia – apparently the only place in the world that uses this consistently as a first line therapy. No information regarding day 28/42 adjusted/unadjusted was available.

*** Wait to include for more studies relating to this

Aretesunate-Amodoquine-Primaquine (AS+AQ+PQ)

*** Still no information on this drug, should I remove this from consideration?

Dihydroartemisinin-Piperaquine (DHA+PPQ)

Among the 12 studies, we found a wide range in the sample size observed (116-1553). Unlike AS+SP and AS+MQ, which generally had very young participants, the participants in these studies were both young and old (range of .5-65 years). Most of the studies gave detailed information on day 28 adjusted/unadjusted and 4 gave information on day 42 adjusted/unadjusted. Unfortunately, no information on transmission/endimicity was provided in any of the 12 studies. 5 out of the 12 studies had participants that were lost to follow up. Four of the studies involved were multicentric while none of them involved pregnant women. Just 2 of the 12 studies were blinded but neither of them specified exactly how they were blinded. That said, 11 out of the 12 studies were randomized.

The most common inclusion criteria were: Uncomplicated p. falc: 12 studies
--- Number of studies with respective inclusion criteria provided in parenthesis

- At least 2 years old: (2)
- Older than 6 months: (3)
- Body weight greater than 5 kg: (2)
- Fever temp: (10)
- Informed Consent: (10)
- No other treatment in the recent past: (4)
- No pregnancy or nursing: (10)
- No on-going anti-malaria treatment: (10)

Aretesunate-Mefloquine+Primaquine (AS-MQ+PQ)

Just like DHA+PPQ+PQ, this therapy is very rarely used. We were able to find just one study, taking place in Antioquia, Columbia that analyzed this study. Moreover, Columbia is the only country that uses AS-MQ+PQ as its first-line response to malaria.

** wait for more info or do not include at all

Quinine (QN)

There were a total of 22 studies that we found relating to Quinine. These also exhibited a wide range of sample sizes (21-1189) and also showed a wide range of ages (.5 years to 60 years). None of the 22 studies were blinded. However, 10 of them were randomized using computer-generated randomization (or based on arrival). Interestingly, 5 out of the 22 studies involved pregnant women – a higher percentage than for any of the other therapies we looked at. Similarly, unlike any of the other drugs, just 5 of the 22 studies had more male participants than female participants. Just like DHA+PPQ, many of the studies for Quinine provided detailed information on inclusion criteria:

--- Number of studies with respective inclusion criteria provided in parenthesis

- Uncomplicated P.Falc (10)
- >5: (4)
- Previous meds (5)
- Pregnancy (4)
- Not Pregnant (1)
- Fever (2)

Artesunate-Amodiaquine (AS+AQ)

We were able to find far more studies for AS+AQ than for any other therapy. This is reasonable because the drug is, as mentioned earlier, among the top two most commonly used first-line therapy throughout all the countries we examined. We found 82 total studies and almost all of them had detailed information day 28/42 adjusted/unadjusted. There was a wide range of sample sizes that we observed, mostly due to the sheer number of studies that came up through our search methodology.

Most of the studies followed the standard WHO protocol which called for exclusion if any of the following criteria was met:

(1) absence of general danger signs or signs of severe malaria according to WHO [16],
2) no intake of antibiotics and no adequate antimalarial treatment within the previous 7 days,
3) absence of a history of hypersensitivity to any of the study drugs,
4) ability to tolerate oral therapy, and
5) informed consent provided by a parent/guardian)

For each of these drugs, we took account of the reported efficacy rating on a country-by-country basis. We averaged these reports and will use those results to compare to the expected results achieved by **the malaria study sent to me by Professor Hassoun**. For AS-SP, the average efficacy was 89.8%, 89.90% for AL, 98.00% for AS+MQ, ***DHA-PPQ+PQ efficacy information not available yet***, **Same for AS-AQ-PQ***, 94.20% for DHA-PPQ, **same for AS-MQ-PQ***, 90.8% for QN, and 86.60% for AS-AQ. The average efficacy for Quinine was 90.80* while the average efficacy for Chorloquine was very low – 63.70%.

Given these results, we can now compare them to the expected results from **cite paper**. The authors write, “In many countries, artemether plus lumefantrine, artesunate plus mefloquine or dihydroartemisinin plus piperaquine may give the highest cure rates. The main reason for restricting the use of AS+MQ in African children so far has been excessive vomiting associated with mefloquine.” In our analysis, we actually found very similar results. AS-MQ had the highest efficacy rate in the studies we collected (98%). The cited paper achieved similar results but noted that in children, AS+MQ is sometimes limited in use because of its tendency to make young children experience undesirable side effects. Interestingly, almost all of the studies that we found relating to AS+MQ were for young children, teenagers, and young adults. The ages in the studies ranged from 4.6 years old to 23.6 years old. (We don’t have information on the precise number that had those side effects)

The cited paper received similarly high efficacy results for DHA-PPQ. (Need some help looking into these some more). I looked into the references but was

not able to find anything pertinent) Our results were again very similar to those that they achieved. The average efficacy rates for DHA-PPQ according to our studies was 94.2-0% - making it the second most efficacious therapy after AS+MQ among the drugs we looked at.

Our results showed an average efficacy of 89.9% for AL. The cited paper found that AL, along with AS+MQ and DHA+PPQ, had the highest efficacy rates. While 89.9% is still quite high, AL's results were still on the lower end of all the therapies we analyzed.

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