A conversation with Dr. Thomas Churcher and Professor Hilary Ranson, May 31, 2017

Participants

- Dr. Thomas Churcher – Lecturer in Infectious Disease Dynamics, Imperial College London
- Professor Hilary Ranson – Professor in Medical Entomology, Liverpool School of Tropical Medicine
- Josh Rosenberg – Senior Research Analyst, GiveWell
- Christian Smith – Research Analyst, GiveWell

Note: These notes were compiled by GiveWell and give an overview of the major points made by Dr. Thomas Churcher and Professor Hilary Ranson.

Summary

GiveWell spoke with Dr. Churcher of Imperial College London and Professor Ranson of the Liverpool School of Tropical Medicine as part of its investigation into adult malaria mortality and resistance to the insecticide used in insecticide-treated bed nets (ITNs). Conversation topics included the state of research on, and methods of estimating, insecticide resistance and the impact of ITNs on adult malaria mortality.

Adult malaria mortality

GiveWell: We have been unable to find much empirical research the impact of ITNs on adult malaria mortality. Is there substantial research that we have not seen, and why do you think we have not been able to find more research?

Dr. Churcher: It is true that there are not many clear estimates on these issues. This is largely because the complex nature of immunity makes impacts on adult malaria mortality very hard to estimate. Young children will have fairly similar responses to an anti-malaria intervention because they have not yet developed immunity. Adults are much more variable: in high transmission areas almost all have considerable immunity, which reduces the chance that a case of malaria will result in death. Therefore though ITNs would prevent cases in adults it might limit the impact of ITNs on adult case fatality. In comparison, in low transmission settings the case fatality rate would be higher due to lower immunity, so ITNs may be more effective at reducing the number of deaths. Due to the cost and difficulty of conducting trials, it would be very challenging to obtain good quality data.

GiveWell: The theoretical mechanism by which ITNs could reduce adult malaria mortality seems quite simple, and very similar to that for children: they sleep under nets, so they get bitten less, so they get less malaria, so they are less likely to die from malaria. Does this sound right, or are there factors that limit the comparison with children, such as different sleeping patterns?

Dr. Churcher: That sounds roughly correct, though the link between getting malaria and dying from it will depend heavily on their level of immunity and therefore vary from place to place. We investigated mosquito biting times and the times people are under a bed net, and generally did not find large differences between adults and children, though it did vary substantially from site to site.

Bed net usage rates among adults are quite good overall; they mostly share a sleeping place with young children. Again, there is very little research out there and quite a lot of variability. For example, one study found the lowest usage is often among teenagers as, unlike young children, adolescents often don't share sleeping spaces with their parents.

GiveWell: One way of roughly estimating the magnitude of the effect of ITNs on adult mortality is to infer from changes in incidence. For instance, if there is a 50% decrease in malaria cases, we can assume a 50% drop in mortality as well. Does this sound sensible?

Dr. Churcher: There are many issues with this approach, but I cannot think of a simple better way to do it. The appropriate figures will vary considerably among locations: in areas with large numbers of cases, there will likely be a proportionally smaller impact on malaria mortality, because this will be in areas of very high transmission. But as long as you are basing the estimates on data from areas with similar transmission rates to where the nets are being distributed, this seems like the best option.

It is also worth keeping in mind whether the malaria cases being studied are actually symptomatic. Some people have easily detectable levels of the parasite and are therefore likely to be symptomatic. Others have the parasite but it is not easily detectable and they do not show symptoms. If the latter are included, the reduction in clinically important cases could be exaggerated. This would best be investigated using a transmission dynamics model. A 2014 paper by Dr. Jamie Griffin and colleagues uses such a model to answer some related questions [https://www.nature.com/articles/ncomms4136], though only for clinical cases, not deaths, so some extrapolation would still be required. Similarly, a study in 2012 [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60034-8/fulltext] estimated changes in adult mortality across the world and predicted a substantial decline in adult deaths since 2004. Though they were unable to find a statistical association with this and ITN use, there are many reasons for this, and I expect much of the observed reduction was due to nets.

Insecticide resistance

GiveWell: You wrote a paper on the impact of insecticide resistance on the efficacy and effectiveness of bed nets for malaria control in Africa [https://elifesciences.org/articles/16090]. We have taken from that the mosquito mortality rates where our recommended charities work and used your estimates of the impact of resistance on the effectiveness of ITNs to come up with a number to put in our cost-effectiveness analysis. (We estimated that resistance reduces effectiveness by around a third in areas where our recommended charities work.) Do you think that is a reasonable method?

Dr. Churcher: Given the current state of knowledge in this area, that seems like a sensible approach. However, I should stress that these are predictions from a simulation model and there are various reasons why this might not be seen in reality. We really need good, well designed studies to see if these predictions are correct but unfortunately, this is very hard to do.

Professor Ranson: Note that most studies on the impact of resistance, including the WHO's, only take into account personal protection. Ours looks at the population as a whole and includes benefits for non-net users as well. It is primarily people *not* using nets who are likely to be at increased risk due to resistance, as there is no physical barrier to prevent bites.

GiveWell: Are there any other studies that provide explicit quantitative estimates of the impact of resistance that should inform our cost-effectiveness analysis?

Professor Ranson: Results from a five-country WHO study on this topic should be published within a year or so. However, we, and others, have some issues with the methodology used. Aside from that, I do not know of any other relevant papers.

Dr. Churcher: Not that I know of.

GiveWell: What exactly are your concerns with the methodology in the WHO study?

Professor Ranson: Firstly, I should say that it is incredibly hard to get good estimates because there are so many confounders. No single study was every going to be definitive.

One problem, as mentioned, is that the study looked only at personal protection, ignoring non-net users.

Another is the sites where the trials were conducted. Data presented at the 2016 meeting of the American Society of Tropical Medicine and Hygiene suggested there was a low prevalence of resistance in the mosquito population in the study areas, and one may not expect to see much impact of resistance on net effectiveness in such locations. There may be a greater impact in very high-resistance areas, such as Burkina Faso, Côte d'Ivoire, and eastern Uganda, and resistance is increasing rapidly across Africa. It is therefore important not to extrapolate too much from the WHO's findings.

GiveWell: The WHO study looked at high, medium and low resistance areas, classifying them according to mosquito mortality rates. Would you prefer to use mortality rates where mosquitoes are exposed to much larger quantities of insecticide, and other indicators of resistance intensity?

Professor Ranson: Ideally, yes, but there is not strong agreement on the best way to measure resistance. We employed the same methodology as the WHO, using the prevalence of resistance in the mosquito population as an indicator of the intensity of resistance. Dr. Churcher's work found a reasonably good correlation between tube bioassays and the more natural situation of experimental huts, so these estimates are probably not too far off. They can probably be improved upon, but there is no better metric currently available.

This is a major area that warrants a lot more research, not just on the intensity of resistance, but also on how good the resistant vectors are at transmitting malaria and whether they are compromised in any way by contact with insecticide. This is one reason why it is so difficult to make clear inferences from the level of resistance in tube bioassays to the level of malaria in a population.

Dr. Churcher: The main problem may not be the metric but the thresholds used. The WHO based its classification on the median resistance in the observed populations: everything above was "high resistance" and everything below was "low resistance." Since all its sites probably had relatively low resistance, it called levels "high" that we would call "low."

Obviously it is not possible to randomize by resistance level, which makes it very hard to conduct good studies. The WHO might be comparing areas with high resistance and low transmission to areas with low resistance and high transmission.

Different people use different definitions for when a mosquito is resistant, though we don't know which is best. I recommend GiveWell be careful when using these definitions as, though a mosquito might be resistant to some actions of the insecticide, it might not be sufficient to have a public health impact.