A conversation with Professor Paul Milligan and Dr. Matt Cairns, August 30, 2018

Participants

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Note: These notes were compiled by GiveWell and give an overview of the major points made by Professor Milligan and Dr. Cairns.

Summary

GiveWell spoke with Professor Milligan and Dr. Cairns of LSHTM as part of its investigation into potential indirect effects of seasonal malaria chemoprevention (SMC), i.e. the reduction in malaria in untreated individuals resulting from SMC. SMC is one of GiveWell's priority programs. Conversation topics included the indirect effects of SMC observed in Cissé et al. 2016 (a randomized controlled trial measuring indirect effects of SMC in Senegal[1]), potential methods for estimating indirect effects of SMC in other areas and factors to take into account, and the general perspective in the global health sector on using SMC as a means of reducing transmission.

Indirect effects of SMC on the incidence of malaria

In areas where malaria transmission is highly seasonal, SMC generally covers most of the high-transmission time of year. SMC is effective at clearing parasites in the children treated, making mosquitoes who bite treated children far less likely to pick up infection and thereby potentially impacting overall transmission rates in the population, even among people who do not receive SMC.

In Cissé et al. 2016, SMC treatment was rolled out in stages, with some areas beginning SMC in 2008, others in 2009, and others in 2010. In 2008, SMC was given to children under five; in 2009 and 2010, treatment was expanded to children under ten.

The study found that SMC reduced the incidence of malaria in children by about 60%. In addition, there was a reduction in incidence in older age groups in the study areas where SMC was given to children. Areas that received SMC in 2010 but not 2008 saw a significantly reduced malaria rate in 2010 compared to 2008, with a reduction of about 26% in the rate of confirmed malaria cases in the 10-to-19 and over-20 age groups, which did not receive SMC treatment. Professor Milligan believes this is the only time that indirect effects from SMC have been measured in the field.

[1] https://dx.doi.org/10.1371/journal.pmed.1002175

Two potential metrics for measuring indirect effects of SMC are:

1. Change in malaria incidence in older age groups (as in the Cissé study), and
2. Change in parasite diversity; a reduction in parasite diversity can act as an indicator that transmission intensity is falling because weakly-transmitting strains tend to be eliminated first.

If SMC were going to be administered up to age ten or 12 in, e.g., Nigeria, it could be beneficial to roll that program out in a phased manner in order to be able to carefully measure impacts, including indirect effects on transmission, and incremental cost-effectiveness.

Estimating indirect effects

Imperial College London (ICL)'s malaria model

Dr. Matt Cairns and colleagues at Imperial College London have used ICL's malaria model to predict the effects of various SMC policies in different areas of Africa, including SMC's indirect effect on the incidence of malaria in individuals ages 15 and over. The model predicts that:

- Administering SMC to children up to age five (assuming no treatments are administered to six- and seven-year-olds in error, although this does happen in practice) would result in about a 5-10% reduction in malaria incidence in individuals 15 and over.
- Administering SMC to children up to age ten in the area of Senegal where the Cissé study was conducted (assuming no spillover treatment for 11- to 13-year-olds) would result in a 23% reduction in individuals 15 and over (which is close to the 26% reduction actually observed in Cissé et al. 2016).

In areas where transmission intensity is very high, it is more difficult to reduce transmission, and the predicted indirect effects are therefore somewhat smaller; for instance, the model predicts less proportional reduction in Burkina Faso and Guinea.

Overall, this model suggests that extending the upper age limit for SMC from 5 to 10 years of age could result in effects on transmission, which would increase the total number of cases averted by SMC by at least 20% in addition to the direct protection in the targeted age group. This may be attractive as part of a larger strategy to reduce transmission and ultimately eliminate malaria.

Disproportionate benefits from treating up to age ten due to gametocyte prevalence

During the Cissé study, children up to ten years old were treated. These children represented roughly 30% of the population but accounted for roughly 40% of malaria cases before SMC was introduced. In that case, treating children up to age ten was potentially able to directly prevent up to 40% of incident infections. In higher-transmission settings, this fraction would be greater. The reduction in

transmission from treating a particular age group would depend on gametocyte prevalence in that age group (among other things). A study in Gambia that looked at gametocyte prevalence relative to age showed prevalence peaking between ages five and ten, suggesting that SMC targeting only children under five would miss a sizeable proportion of gametocyte carriers; SMC administered up to age ten would catch markedly more; and SMC up to age 20 would reach a very large proportion (though there are carriers in much older age groups as well).

Modeling groups have investigated effects of malaria interventions in transmission.[2] Broadly, Professor Milligan thinks it is reasonable to estimate the potential for indirect effects based on the age pattern of gametocyte prevalence before SMC is introduced. (Overall parasite prevalence likely works fairly well as a proxy for gametocyte prevalence, though it is often difficult to get useful data on this since surveys of parasite prevalence are typically done in restricted age groups.)

Observations on treating up to age five vs. up to age ten

There appear to be significantly greater indirect effects from treating up to age ten than from treating up to age five. Cissé et al. 2016 found that treating up to age ten was associated with a 26% reduction in the malaria rate in older age groups. The ICL model estimates that the relative reduction in new cases with SMC in children under 10 years old only is approximately three-fold larger than SMC only in children under 5 years old. The model takes into account 1) that gametocyte prevalence is generally higher in five- to ten-year-olds than in children under five, and 2) that a higher proportion of the population being covered produces non-linear returns (see below).

Costs of treating older children

Some work has been done on costing and delivery of SMC for five- to ten-year-olds. Treating children up to age ten does not take much more time than treating only up to age five, because in many cases the older children are living in a household that is already being visited, so the cost of delivery is not significantly more. Treating older children does require buying more drugs, and those drugs are slightly more expensive because older children need higher doses.

There is considerable interest in SMC in older children. Another study that is currently underway in Mali, coordinated by the President's Malaria Initiative (PMI), is evaluating SMC for older children, with results expected in 2019.

Direct benefits from treating older children

To estimate the potential direct effects of treating older children (e.g. up to age 12) with SMC, it would be helpful to know the burden of severe malaria in those groups. However, it can be difficult to get that information from routine data at a sufficiently granular level because data is often aggregated into "children under five" and "five and above" (or in some countries, "under five," "five to 14," and "15 and above").

[2] https://malariamodelingconsortium.org/about/mmc-partners/

Modeling studies of the incidence among older children find that, in high-transmission countries like Mali and Burkina Faso, the malaria burden in the five-to-ten age group tends to be a lower proportion of the total malaria burden than the malaria burden in children under five, because children acquire immunity with repeated exposure to malaria. However, the absolute number of cases per child per year in the five-to-ten age group still tends to be similar to the number in low-transmission countries. It is therefore important to consider age-specific burden in terms of absolute numbers rather than proportions.

Non-linear returns on reducing transmission from increased coverage

The relationship between SMC coverage and effects on transmission is non-linear, for "herd immunity" reasons similar to those resulting in non-linear returns from immunizing an increasing proportion of a population for vaccine-preventable diseases. In order to observe significant effects on transmission, a fairly high percentage of the population needs to be treated. In many of the populations where SMC is administered, children under ten do comprise a fairly large fraction of the total population (e.g., roughly 18% of the population under five and 30% under ten), as well as disproportionately carrying infection.

Accounting for treating older children

The ICL model described above assumes that older children aren't treated by accident. In practice, Professor Milligan thinks that, in programs intended to only treat children under five, six- and seven-year-olds are often treated as well.

Six- and seven-year-olds who are treated by programs intended for children up to five are being under-dosed (since they ought to receive an appropriate dose for their age). This may be less of a problem for 11- or 12-year-olds who are treated by programs intended for children up to ten, since there is less difference in bodyweight in that age range, and treatments intended for 10-year-olds may be adequate to protect slightly older children.

For the Cissé et al. 2016 study, a census was conducted to establish children's dates of birth. This was then used to create printed lists for SMC administrators of whom to treat. That study probably restricted treatment to children ten and under more rigorously than is possible in routine programs.

Estimating the burden of malaria in SMC countries

Professor Milligan believes that estimates of the malaria burden in Chad, Niger, and North West Nigeria based on prevalence surveys have tended to under-estimate the true burden, as survey data that is available in these areas has been limited. When LSHTM was estimating the number of deaths and cases averted by ACCESS-SMC, it needed to adjust the burden estimates for those three countries to reflect data on malaria prevalence that was collected in large-scale, representative field surveys during the project.

Views on SMC as a strategy to reduce transmission

SMC is primarily viewed as a method for preventing severe malaria rather than for reducing transmission. SMC strategies have generally focused on children under five because that age range carries the most significant burden of severe disease. In Senegal, SMC is administered up to age ten in part because of data showing that severe malaria is also common in the five- to ten-year age range (though treating up to age ten also has the added benefit of treating a larger proportion of gametocyte carriers).

In many places, an argument could be made for treating up to age ten or 12 on the basis of the direct effects on disease burden in this population. Administering SMC up to age 15 is harder to justify on the basis of direct benefits, since children age ten to 15 typically have a lower malaria disease burden. Administering SMC up to, e.g., age 20 would likely not be worthwhile solely from the standpoint of reducing disease burden; many of the people treated in that case would not derive a personal health benefit.

A common view is that in high-transmission areas the focus should be on reducing disease burden and in low-transmission areas the focus should be on reducing transmission and/or eliminating the disease.

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